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Assessing, Managing and Monitoring Biologic Therapies for Inflammatory Arthritis

RCN Guidance for Rheumatology Practitioners (Fourth edition)

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Foreword

Welcome to this updated fourth 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 third edition of this guidance was published in 2014, significant developments have had an impact on this sphere of practice. These include:

- the availability of several new licensed treatments
- the development and availability 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 monitor the use and progress of patients taking biologic therapies and biosimilar therapies and the the long-term safety profile of for these agents
- NICE technology appraisal (see Table 1)

When updating this guidance Stop-think-best practice reflection opportunity notes have been added to help promote best practice, clinical excellence and provision of quality care and supporting, NMC (2015) Code and NMC (2016) Revalidation recommendations (See appendix 14).

Relevant for physicians, rheumatology specialist 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 (and non radiographic Spondyloarthritis) (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)
- local protocols, policies and guidelines for infusions, including sharps (RCN, 2013; HSE/EU, 2014)
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 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. See section below outlining the key issues regarding newer biosimilar therapies.

**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 conventional 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

A similar biological or ‘biosimilar’ medicine is a biological medicine that is similar to another biological medicine that has already been authorised for use in the European Community. The active substance of a biosimilar is a known biological active substance and similar to the one of the reference medicinal product. The biosimilar sponsor is to “generate evidence substantiating the similar nature, in terms of quality, safety and efficacy”. In the development of a biosimilar, there is no requirement to demonstrate clinical benefit to patients per se as this has been shown for the reference medicine. Instead, biosimilars undergo a comprehensive totality of evidence approach which demands extensive comparability studies that demonstrate similarity to the reference medicine. The benefits and risks are then inferred from the similarity of the biosimilar medicine to the reference medicine. Biosimilars are regulated in the same way by the European Medicines Agency (EMA). Therefore, from a scientific and regulatory point of view, the active substance of a biosimilar medicine has been shown to have no clinically meaningful differences compared to the active substance of the originator.

For more details see the NHS publication, Answers to commonly asked questions about biosimilar versions of infliximab and NHS England’s ‘What is a biosimilar medicine?’

The continuing development of biological medicines, including biosimilar medicines, creates increased choice for patients and clinicians, increased commercial competition and enhanced value propositions for individual medicines. Biosimilars have been available for some time and to date we haven’t seen the use of biosimilars result in additional patients being treated with other biologics.

The NICE position statement on evaluating biosimilars was published in January 2015. This states that biosimilars notified to the NICE topic selection process for referral to the technology appraisal programme will be considered in the context of a multiple technology appraisal, in parallel with their reference products. This enables NICE to decide to apply the same remit, and the resulting guidance, to relevant licensed biosimilar products which subsequently appear on the market. In other circumstances, where a review of the evidence for a biosimilar medicine is considered necessary, NICE will consider producing an evidence summary.

Biosimilar versions of several biologic drugs have been available for some time. As for all medicines, the safety of biosimilar medicines is continuously monitored after authorisation. Recently, biosimilar versions of infliximab (Inflectra and Remsima) and etanercept (Benepali) have been launched in the UK, and further biosimilar versions of adalimumab, flixabi, rituximab and truxima are expected to be available in the near future.

Because biosimilar and reference biological medicines that have the same international non-proprietary name (INN) are not presumed to be identical in the same way as generic non-biological medicines, brand name prescribing is recommend (MHRA February 2008 edition of Drug Safety Update). This ensures that the intended product is received by the patient. Products cannot be automatically substituted at the point of dispensing and the choice of whether a patient receives a biosimilar or originator biological medicine is decided between the clinician and the patient.

Pharmacovigilance is important for biosimilar medicines and every biosimilar authorised by the EMA will have a risk management plan in place (details of which will be in the European Public Assessment Report). Safe introduction and ongoing safe use of biosimilars requires practitioner, patient and manufacturer engagement with these processes.

The NICE adoption resource introducing biosimilar versions of infliximab: Inflectra and Remsima®, has been produced to help manage the introduction of biosimilar medicines into care pathways safely and effectively. Local organisations will need to assess the applicability of the learning from the examples provided of current practice, taking into consideration the time, resources and costs of an implementation programme.
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.

Tips for managing the introduction of biosimilar medicines

1. Identify clinical and pharmacy champions to take the lead in introducing biosimilars.

2. Educate all stakeholders (including patients) to provide them with information on what a biosimilar is, how it differs from a generic, the biosimilar regulatory process, the manufacturing process, indication extrapolation, to allow them to make an informed decision on their introduction.

3. Identify the potential cost-saving and re-investment opportunities.

4. Seek formal approval at the local formulary committee once there is clinical consensus to include biosimilars on the formulary.

5. Collect baseline data and agree metrics to be collected during and after the introduction of biosimilars.

6. Submit data to national audits and registries. For further information refer to NICE’s Biosimilar medicines key therapeutic topic (NICE, 2016). Available at: nice.org.uk/guidance/ktt15

*Technology appraisal guidance* (NICE, 2016). Available at: www.nice.org.uk

Stop-think-best practice reflection opportunity

Full patient monitoring at the time of switch should occur whether the patient is stable or whether the patient is being switched for medical reasons such as loss of efficacy. Pre-switch screening should take place. BSR guidance states:

“the decision to switch patients currently receiving a reference product to a biosimilar should be on a case-by-case basis until further data are available to support safe switching”
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

Shared decision making resources can be found at: http://personcentredcare.health.org.uk

Measuring shared decision making (sure score): www.england.nhs.uk/rightcare

Improving patient experience – ‘ask three questions’ available at the e-learning resource for shared decision making: Advancing Quality Alliance 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.

Stop-think-best practice reflection opportunity

Also reflect on your approach to shared decision making. What information do you need to know in order to advise your patients about biologics and biosimilars?

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

- promoting best practice in prescribing is essential. Repeat prescription management is often organised by rheumatology nurse and team administrators. In this setting it is essential that non medical prescribing roles are clearly defined. The NMC recommend separation of prescribing and administration roles as this poses a significant risk and formal policies need to be in place. (NMC 2011)

Transcribing of a prescription by a registered nurse who is not a prescriber should only happen in exceptional circumstances and should not be routine practice. The transcriber is responsible for any action resulting from their transcription. This must be covered by a medicines management policy and a robust agreed transcribing protocol.

- 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

- 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

The BSRBR-AS study team can be contacted at: bsrbr-as@abdn.ac.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
- GP s 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. The content of this section should be read in conjunction with the section on Biosimilars on page 10 of this document.

**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% of the population, have rheumatoid arthritis. Of these, approximately 15% 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% and 3%. 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% (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 0.05%-0.23% 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 (NICE TA383, 2016).

**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%, 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. For more information, see PART TWO: CHILDREN AND YOUNG PEOPLE of this document.

**Systemic Lupus erythematosus (SLE) and systemic Vasculitis (SV)** are 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-TNFα 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 licensed as an adjunctive therapy for SLE high disease activity, and is now NICE approved (NICE TA397, 2013).

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 and biosimilar 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>
<thead>
<tr>
<th>International Non-proprietary name (INN) and (brand name)</th>
<th>Manufacturer</th>
<th>Mode of action</th>
<th>Current NICE approval (by condition)</th>
<th>Licence</th>
<th>Administration</th>
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<tbody>
<tr>
<td>Adalimumab (Humira®)</td>
<td>Abbvie</td>
<td>Anti-TNFα</td>
<td>Human monoclonal antibody RA TA195/ TA375 PsA TA199 AS TA383</td>
<td>RA, PsA Severe active AS or severe non-radiographic axial spondyloarthritis ie signs of inflammation (elevated CRP and/or MRI) ; after trying steroidal anti inflammatory drugs (NSAIDs), which have not worked. JIA Also: Psoriasis Crohn’s Disease Ulcerative colitis Psoriatic arthritis</td>
<td>40mg every other week by subcutaneous injection Prefilled pen or syringe</td>
</tr>
<tr>
<td>Certolizumab pegol (Cimzia®)</td>
<td>UCB Pharma</td>
<td>Anti-TNFα</td>
<td>PEGylated Fab’ fragment of a humanised monoclonal antibody RA TA375 AS TA383</td>
<td>RA AS (as above) PsA</td>
<td>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</td>
</tr>
<tr>
<td>Etanercept (Enbrel®)</td>
<td>Pfizer</td>
<td>Anti-TNFα</td>
<td>Human TNF receptor fusion protein and dimer of a chimeric protein RA TA195 / TA375 PsA TA199 AS TA383 JIA TA373</td>
<td>RA PsA AS (as above) JIA Also: Psoriasis</td>
<td>25mg twice a week, or 50mg weekly by subcutaneous injection Prefilled syringe or MyClic pen (50mg dose only) or vial and diluent</td>
</tr>
<tr>
<td>Etanercept (Benepali®) BIOSIMILAR</td>
<td>Biogen</td>
<td>Anti-TNFα</td>
<td>Human TNF receptor fusion protein is a dimer of chimeric protein As above (except JIA)</td>
<td>RA PsA AS (as above) JIA (please see Benepali) Also : Psoriasis</td>
<td>Pre-filled syringe 50mg once weekly &amp; pre-filled pen 50mg once weekly Benepali is currently only available as a 50mg pre-filled syringe or a 50mg pre-filled pen which are unsuitable for use in children and adolescents</td>
</tr>
<tr>
<td>Biologic Therapy</td>
<td>Manufacturer</td>
<td>Anti-TNFα</td>
<td>Indications</td>
<td>Dose and Administration</td>
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<tr>
<td><strong>Infliximab</strong> (Remicade®)</td>
<td>MSD (formerly Schering Plough)</td>
<td>Anti TNFα Chimeric human-murine IgG1 monoclonal antibody</td>
<td>RA TA195/ TA375 PsA TA199 AS TA383</td>
<td>RA (with MTX) PsA AS (as above) Also: Psoriasis Crohn’s Disease Ulcerative colitis 3mg (RA) &amp; 5mg (PsA, AS) 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)</td>
<td></td>
</tr>
<tr>
<td><strong>Infliximab</strong> (Inflectra®) BIOSIMILAR</td>
<td>Hospira</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
<td></td>
</tr>
<tr>
<td><strong>Infliximab</strong> (Remsima®) BIOSIMILAR</td>
<td>Celltrion/ Napp</td>
<td>As above</td>
<td>As above</td>
<td>As above</td>
<td></td>
</tr>
<tr>
<td><strong>Golimumab</strong> (Simponi®)</td>
<td>Schering Plough (MSD)</td>
<td>Anti TNFα Human monoclonal antibody</td>
<td>RA TA375 (partially updated TA225) PsA TA445 ASTA383</td>
<td>RA (with MTX) PsA AS (as above) 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</td>
<td></td>
</tr>
<tr>
<td><strong>Abatacept</strong> (Orencia®)</td>
<td>Bristol-Myers Squibb</td>
<td>T-Cell co-stimulation inhibitor Fusion protein</td>
<td>RA TA375</td>
<td>RA (with MTX) JIA 500mg, 750mg or 1000mg (depending on weight) at week 0, 2, 4 then monthly by intravenous infusion eg weight &lt;60kg = 500mg; ≥60kg = 750mg and ≥100kg = 1000mg OR 125mg weekly subcutaneously prefilled syringe (may be preceded by one infusion)</td>
<td></td>
</tr>
<tr>
<td><strong>Rituximab</strong> (MabThera®)</td>
<td>Roche Products Ltd</td>
<td>B-cell depletor Chimeric mouse/human antibody IgG1 monoclonal antibody</td>
<td>RA TA195</td>
<td>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)</td>
<td></td>
</tr>
<tr>
<td>Table 1: Biologic therapy (including Biosimilar therapy) options for adults* continued</td>
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<tr>
<td><strong>Tocilizumab (RoActemra®)</strong></td>
<td>Roche/Chugai Products Ltd</td>
<td>IL-6 receptor Humanised monoclonal antibody</td>
<td>RA TA347 (partially updated TA247)</td>
<td>RA sJIA pJIA</td>
<td>8mg per kilogram of body weight once every 4 weeks – by intravenous infusion (maximum dose 800mg) OR 162mg weekly subcutaneously prefilled syringe</td>
</tr>
</tbody>
</table>
| **Ustekinumab (Stelera®)** | Jansen | Human monoclonal antibody | PsA TA340 | PsA | 90mg dose for people who weigh more than 100kg at the same cost as the 45mg dose, as agreed in the patient access scheme
Initial dose 45mg followed by a dose 4/52s later and further dose every 12/52s thereafter. A dose of 90mg may be used in people with a body weight over 100kg |
| **Secukinumab (Cosentyx®)** | Novartis | Monoclonal antihuman antibody of the IgG1/kappa isotype that targets interleukin-17A | PsA TA445 AS (TA407) | PsA | Active AS & non-radiographic after treatment with NSAIDs or TNF-alpha inhibitors
150mg once weekly given by subcutaneous injection at weeks 0, 1, 2 and 3; followed by a maintenance dose once a month starting at week 4
The company has agreed a patient access scheme with the Department of Health |
| **Belimumab (Benlysta®)** | GlaxoSmithKline | Human monoclonal antibody that inhibits the activity of B-lymphocyte stimulator (BLyS) | SLE (TA397) Auto antibody positive | Add on therapy in adults with active autoantibody positive systemic lupus | 10mg/kg on days 0, 14, 28, and at 4 week intervals thereafter |

*Accurate as of October 2016*
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 patient’s 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 and 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-TNFα 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:

- significant haematological abnormalities, for example, reduced WBC, neutrophil or platelet count
- an absolute neutrophil count (ANC) below 2 x 10^9/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-TNFα 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)
- severe central nervous system Lupus, renal lupus, major organ or stem cell transplantation (Belimumab)
- all patients but in particular patients over 60 yrs of age patients with a medical history of prolonged immnosuppressant therapy or those with a history of PUVA treatment should be monitored for the appeabce of non-melanoma skin cancer (ustekinumab)
- both ustekinumab and secukinumab latex sensitivity – be aware that the needle cover of the prefilled syringe is manufactured from a derivative of latex.
1.1.2 Pre-treatment 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-TNFα. 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.


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-TNFα 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 – BSRBR; Ko et al., 2009)
- MS family history
- vaccination history – such as flu and pneumonia and chicken pox and 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 – aPTT)
- sodium controlled diet as tocilizumab (IV only), abatacept and infliximab all contain sodium
- exercise caution with patients with Crohn’s prescribed secukinumab as activation of this condition has been observed.

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
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).

1.1.3 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, only adults are 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 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.

The following individuals should not receive live vaccines:

- patients receiving systemic high-dose steroids, until at least three months after treatment has stopped. This would include children who receive prednisolone, orally or rectally, at a daily dose (or its equivalent) of 2mg/kg/day for at least one week, or 1mg/kg/day for one month. For adults, an equivalent dose is harder to define but immunosuppression should be considered in those who receive at least 40mg of prednisolone per day for more than one week. Occasionally, individuals on lower doses of steroids may be immunosuppressed and at increased risk from infections. In those cases, live vaccines could be considered with caution, in discussion with a relevant specialist physician
- patients receiving other types of immunosuppressive drugs (e.g. azathioprine, cyclosporin, methotrexate, cyclophosphamide, leflunomide and the newer biologics) alone or in combination with lower doses of steroids, until at least six months after terminating such treatment. The advice of the physician in charge or immunologist should be sought
- patients with immunosuppression due to human immunodeficiency virus (HIV) infection (see section below).

Please refer to specific vaccine chapters of The Green Book and for specific immunocompromised states not covered here.

Immunocompromised status:

- receiving systemic high dose steroids (>40mg/day) for more than one week
- treated with a combination of DMARDs 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.

### Varicella zoster immune status/vaccination

Chickenpox infection is a concern in any non-immune immunosuppressed patient with a significant contact to either chickenpox or exposed shingles. Checking varicella immune status (VZV IgG) prior to starting immunosuppression has been identified as an important aspect of patient care if there is no history of chickenpox/shingles.

Consideration can be given to providing two doses of varicella vaccine (four weeks apart) to immunocompetent, eligible patients if VZV IgG negative on a qualitative assay or <150mIU/ml on a quantitative assay. If VZV IgG is equivocal on the qualitative assay, then test on a quantitative assay. However, immunosuppression should not be initiated until four weeks after the final vaccine dose has been given. Please refer to your local policy.

If significant exposure occurs to either chickenpox or exposed shingles then VZV IgG testing should be urgently performed within seven days of the contact (even if prior immunity has been established or there is a past history of chickenpox/shingles) for all patients receiving biological therapies alone or in combination with steroids until at least six months after treatment. Varicella zoster immunoglobulin (VZIG) administration should not be delayed past 7 days after initial contact while an antibody test is being performed. For those patients where exposure is recognised late, VZIG can be given for up to 10 days post exposure. When VZV IgG testing has been performed then VZIG should be issued if VZV IgG is negative on a qualitative assay or <150mIU/ml on a quantitative assay. If VZV IgG is equivocal on the qualitative assay, then test on a quantitative assay if time permits. Please refer to your local policy or the Green Book. [https://www.gov.uk/government/publications/varicella-the-green-book-chapter-34](https://www.gov.uk/government/publications/varicella-the-green-book-chapter-34)

For those non immune contacts where prophylaxis with a blood product is not acceptable, then oral aciclovir at 10mg/kg four times a day can be considered from days 7 to 14 after exposure. Please refer to your local policy.

If chickenpox develops then the patient should be urgently assessed for aciclovir treatment; immunosuppression should be discontinued until the last spot has crusted over and the patient is clinically well.

In addition, consideration can be given to providing varicella vaccine to immunocompetent, healthy susceptible close household contacts of immunocompromised patients to prevent exposure situations ([https://www.gov.uk/government/publications/varicella-the-green-book-chapter-34](https://www.gov.uk/government/publications/varicella-the-green-book-chapter-34)).

The risk and severity of shingles is higher amongst immunosuppressed individuals, and individuals should be assessed for shingles vaccine eligibility (based on age) prior to starting treatment. At least 14 days, preferably one month, is required prior to starting immunosuppression ([https://www.gov.uk/government/publications/rubella-the-green-book-chapter-28](https://www.gov.uk/government/publications/rubella-the-green-book-chapter-28)).

If the patient is eligible for the shingles vaccine while on immunosuppressive therapy, the vaccine should NOT be given to those who are receiving or have received in the past 12 months biological therapy (for example, anti-TNF therapy, alemtuzumab,
ofatumumab and rituximab) unless otherwise directed by a specialist, or to those receiving or have received in the last three months high dose corticosteroids (>40mg prednisolone daily for more than one week), long term lower dose corticosteroids (>20mg prednisolone daily for more than 14 days), non-biological oral immune modulating drugs (methotrexate>25mg weekly, azathioprine >3.0mg/kg/day or 6-mercaptopurine >1.5mg/kg/day). The vaccine can ONLY be given in the following circumstances: patients on long term stable low dose corticosteroid therapy (defined as ≤ 20mg prednisolone per day for more than 14 days) either alone or in combination with low dose non-biological oral immune modulating drugs (e.g. methotrexate ≤ 25mg per week, azathioprine ≤3.0 mg/kg/day or 6-mercaptopurine ≤1.5 mg/kg/day). These drug doses are not considered to be sufficiently immunosuppressive and these patients can receive the vaccine. Specialist advice should be sought for other treatment regimens. Immunosuppressed patients who develop a shingles vaccine rash should be urgently assessed and offered aciclovir (https://www.gov.uk/government/publications/rubella-the-green-book-chapter-28).

It is suggested that most rheumatology teams will be aware that the use of biologic drugs and other powerful immunosuppressants is not always documented appropriately in primary care medical records, since these drugs are invariably prescribed in secondary care. The rheumatology community therefore needs to be aware that the shingles vaccine (zostervax) may be offered by GPs to patients on biologic drugs and other potent immunosuppressants, and that it may be appropriate to contact patients aged 70 and over (and/or their GPs) on biologic drugs and other potent immunosuppressants to advise them that they should not receive the shingles vaccine (zostervax) (BSR 2013). 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) (BSR 2013).

### Measles, mumps and rubella (MMR) immune status/vaccination

In the pre-immunosuppression assessment process, the history of a completed MMR vaccination schedule or previous measles infection would be helpful. If a patient has no history of MMR or measles infection and is currently immunocompetent, then they can receive two doses of MMR (providing they are eligible to receive the vaccine). However, a period of four weeks should occur prior to initiating immunosuppression following the second dose of MMR vaccine. (BSR 2002 at www.rheumatology.org.uk). Measles IgG should be tested in all patients (if they have received MMR then test 4-8 weeks after the second dose) to help inform post exposure prophylaxis.


This guidance states that those in Group A would be patients receiving high dose steroids (40mg daily for more than one week) until three months post treatment or other types of immunosuppressive drugs (e.g. azathioprine, cyclosporin, methotrexate, cyclophosphamide, leflunomide, anti-TNF alpha and biologic therapies alone or in combination with steroids, until at least six months after terminating such treatment. This group should be capable of maintaining a previous antibody response to either natural infection or vaccination, thus if the prior measles IgG was positive then this would indicate that Human Normal Immunoglobulin (HNIG) was not required. If the prior measles IgG was negative or equivocal then HNIG would be required within three days of exposure if possible. For those with unknown status at the time of exposure, management on the basis of history and, where possible, rapid antibody testing is recommended and Human Normal Immunoglobulin (HNIG) given. Patients receiving rituximab would fall into Group B of this guidance and should be tested urgently at the time of exposure if their antibody status is unknown or previously positive and HNIG issued according to the table “Algorithm for
assessing susceptibility in pregnant women and immunosuppressed contacts of measles” in the HPA’s Post Exposure Prophylaxis for Measles: revised guidance (May 2009).


HNIG can be given up to six days post exposure, but should be given within three days (if testing is not available in the time-frame) either if the patient was born after 1990 and a prior measles IgG result is not available or if the patient is in Group B. Where exposure is recognised late or who are found to be antibody negative or equivocal between six and eighteen days after exposure, discussion with the specialist caring for the individual should take place, and IVIG may be considered in order to attenuate infection. Where a second exposure occurs more than three weeks after a first dose of immunoglobulin, a further dose of immunoglobulin will need to be considered.

If measles develops, the patient should be urgently assessed by their GP and rheumatology team as it is a serious reportable infection, and the patient should be advised to discontinue the immunosuppression if possible. The immunosuppressive agent should not be restarted until the patient has recovered fully, is clinically well and has been re-assessed by their medical team.

**Inactivated vaccines**

Although influenza and pneumococcal vaccines do not offer complete protection (70-80% influenza and 50-70% 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% 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 and infant exposure to vaccinations**

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 patient’s (and infant’s) GP is essential and the relevant risks to the infant highlighted.

<table>
<thead>
<tr>
<th>Table 2. Time elapsed before giving live vaccines to infants exposed to biologic therapy in utero</th>
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<tbody>
<tr>
<td>Abatacept</td>
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<tr>
<td>Adalimumab</td>
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<tr>
<td>Etanercept (including biosimilars)</td>
</tr>
<tr>
<td>Infliximab (including biosimilars)</td>
</tr>
<tr>
<td>Rituximab</td>
</tr>
<tr>
<td>Tocilizumab</td>
</tr>
<tr>
<td>Golimumab</td>
</tr>
<tr>
<td>Certolizumab pegol</td>
</tr>
<tr>
<td>Ustekinumab</td>
</tr>
<tr>
<td>Secukinumab</td>
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<tr>
<td>Belimumab</td>
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</tbody>
</table>
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).
- 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.
Patient and carer fact sheets and booklets can be found at many websites, including:

- www.arthritiscare.org.uk (includes information in different languages)
- www.nras.org.uk (RA specific information on biologics including ‘the story so far’ published in April 2014)
- www.arthritisresearchuk.org (a broad range of condition specific leaflets).

Stop-think-best practice opportunity
Consider what specific advice you would give to a patient starting a biologic regarding vaccinations and why.

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.

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

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% 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.

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

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.
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.

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).
**Ankylosing spondylitis (and non radiographic Spondyloarthritis) (AS)**

Response criteria to biologic therapies for patients with AS includes:

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

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 is defined as:

- a reduction of BASDAI to 50% of the pre-treatment value or by $\geq 2$ units

AND

- a 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.

Treatment should only be continued if there is clear evidence of response as defined above.

Treatment with another anti-TNFα is recommended in patients who cannot tolerate or have not responded to treatment with the first TNF inhibitor, or whose disease has stopped responding after intimal response.

Please refer to appropriate NICE technology appraisals as outlined in Table 1. 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)
- Safety of Estrogen in Lupus National Assessment – Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI). This is a validated model of experienced clinicians’ global assessments of disease activity in lupus. It represents the consensus of a group of experts in the field of lupus research.
### 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.

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. If VZIG has been given as prophylaxis then the incubation period increases and is 8-28 days.

---

**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)
- shingles with facial nerve involvement (uncovered lesions, for example, facial shingles)
- disseminated shingles (> 1 dermatome involved)
- if the source is also immunosuppressed.

Source: The Green Book (DH)

Chickenpox or disseminated shingles infectivity is from two days prior to the rash until all 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.

Consideration can be given to providing varicella vaccine to immunocompetent, healthy susceptible close household contacts of immunocompromised patients to prevent exposure situations. Please refer to the Department of Health’s Green Book, Chapter 34 for further Information.

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

If a patient taking biologic therapy has a VZV exposure (see box above) and is not immune by testing at the time of exposure, then VZIG is indicated within seven days of exposure. If it is not possible to test within seven days of exposure then administer VZIG. For those patients where exposure is recognised late, VZIG can be given for up to 10 days post exposure. When VZV IgG testing has been performed then VZIG should be issued if VZV IgG is negative on a qualitative assay or <150mIU/ml on a quantitative assay. If VZV IgG is equivocal on the qualitative assay, then test on a quantitative assay if time permits. Please refer to your local policy or the Green Book. www.gov.uk/government/uploads/system/uploads/attachment_data/file/456562/Green_Book_Chapter_34_v3_0.pdf

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.

If naïve to varicella zoster then 50% may develop chicken pox despite VZIG; infection may be subclinical in 15% of cases.

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.


Measles infection

If measles develop, the patient should be advised to discontinue biologic therapy and report this immediately to their GP and rheumatology team, where further medical advice and treatment can be given, as measles is a serious reportable infection.

Biologic therapy should not be restarted until the patient has recovered fully, is clinically well and has been re-assessed by their GP and/or rheumatology specialist team.

In an outbreak scenario, patients receiving biologic therapy would require immunoglobulin if they were measles IgG negative or equivocal and had contact with an individual who had measles.

Also refer to:


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 (along with other infectious aetiologies) 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 sulphasalazinle 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-TNFα 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-TNFα therapy, despite the fact that anti-TNFα 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).
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 should include testing for hepatitis B surface antigen and hepatitis B total core antibody in all patients who will receive biological therapies.

For those who are hepatitis B surface antigen (HBsAg) positive, then advice should be sought from a physician with expertise in hepatitis B.

For those who are negative for hepatitis B surface antigen (HBsAg), but are positive for hepatitis B total core antibody (HBcAb), then EDTA blood should be sent for HBV PCR. If the HBV PCR shows detection of HBV DNA, then advice should be sought from a physician with expertise in hepatitis B. If the HBV PCR is not detected, then HBV prophylaxis with lamivudine should be considered for those undergoing B cell depletion, and continued for 12 months post cessation of immunosuppression. For patients receiving other biological therapies then monitoring with HBV PCR is required during immunosuppression and for six months after cessation – if the HBV PCR becomes detectable then urgent referral should be made to a physician with expertise in HBV management. (see NICE guidance CG165 www.nice.org.uk/Guidance/cg165).

<table>
<thead>
<tr>
<th>Reactivation risk</th>
<th>HBsAg negative and HBcAb positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10% (High)</td>
<td>B cell depleting agent (rituximab, ofatumumab, alemtuzumab, etc)</td>
</tr>
<tr>
<td></td>
<td>BMT</td>
</tr>
<tr>
<td>1-10% (Moderate)</td>
<td>TNFα inhibitors (etanercept, Thalidomide, adalimumab, certolizumab, infliximab, etc)</td>
</tr>
<tr>
<td></td>
<td>Other cytokine or integrin inhibitors (abatacept, ustekinumab, natalizumab, vedolizumab, etc)</td>
</tr>
<tr>
<td></td>
<td>Tyrosine kinase inhibitors (imatinib, nilotinib, idelalisib, etc)</td>
</tr>
<tr>
<td></td>
<td>Moderate/high dose corticosteroids (prednisolone &gt;10mg daily for 24 weeks)</td>
</tr>
<tr>
<td></td>
<td>Anthracyclines (doxorubicin, epirubicin, etc)</td>
</tr>
<tr>
<td>&lt;1% (Low)</td>
<td>Traditional agents (azathioprine, 6-mercaptopurine, methotrexate)</td>
</tr>
</tbody>
</table>

> Low dose corticosteroids (prednisolone <10mg daily for 24 weeks)
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-TNFα therapy including the new biologics and biosimilars; consequently, on-going vigilance is required. Preventative skin care and skin surveillance is also recommended (BSR/BHPR, 2010). Please refer to SPCs for individual drugs.

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 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 (½) 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>
<thead>
<tr>
<th>Name</th>
<th>Usual dosing interval</th>
<th>Suggested period to stop before surgery</th>
<th>Half life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept (Enbrel®) SC</td>
<td>25mg dose twice weekly 50mg dose once weekly</td>
<td>2 weeks</td>
<td>70 hours</td>
</tr>
<tr>
<td>Etanercept (Benepali®)SC BIOSIMILAR</td>
<td>50mg dose once weekly</td>
<td>2 weeks</td>
<td>70 hours</td>
</tr>
<tr>
<td>Adalimumab (Humira®) SC</td>
<td>Fortnightly</td>
<td>70 days (2½ months)</td>
<td>14 days</td>
</tr>
<tr>
<td>Certolizumab pegol (Cimzia®) SC</td>
<td>Fortnightly</td>
<td>70 days (2½ months)</td>
<td>14 days</td>
</tr>
<tr>
<td>Golimumab (Simponi®) SC</td>
<td>Once a month</td>
<td>70 days (2½ months)</td>
<td>9-15 days</td>
</tr>
<tr>
<td>Infliximab (Remicade®) IV</td>
<td>Every 4-8 weeks</td>
<td>42 days (1½ months)</td>
<td>8-9.5 days</td>
</tr>
<tr>
<td>Infliximab (Inflectra®) IV BIOSIMILAR</td>
<td>Every 8 weeks</td>
<td>8 weeks</td>
<td>8-9.5 days</td>
</tr>
<tr>
<td>Infliximab (Remsima®) IV BIOSIMILAR</td>
<td>Every 8 weeks</td>
<td>8 weeks</td>
<td>8-9.5 days</td>
</tr>
<tr>
<td>Abatacept (Orencia®) IV</td>
<td>Every 4 weeks</td>
<td>70 days (2½ months)</td>
<td>Half-life = 14.3 days (Range = 8-25 days)</td>
</tr>
<tr>
<td>Abatacept (Orencia®) SC</td>
<td>Weekly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituximab (MabThera®) IV</td>
<td>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)</td>
<td>98 days (3½ months)</td>
<td>Half-life = 20.8 days (Range = 8.58 -35.9 days)</td>
</tr>
<tr>
<td>Tocilizumab (RoActemra®) IV and SC</td>
<td>Every 4 weeks (IV) Weekly (SC)</td>
<td>56 days (2 months)</td>
<td>8-14 days</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>45mg every 4 weeks</td>
<td>4 months</td>
<td>15-32 days</td>
</tr>
<tr>
<td>Secukinumab SC</td>
<td>150-300mg every 4 weeks</td>
<td>No data</td>
<td>18-46 days</td>
</tr>
<tr>
<td>Belimumab IV</td>
<td>10mg/kg every 4 weeks</td>
<td>No data</td>
<td>19.4 days</td>
</tr>
</tbody>
</table>

*For the most up-to-date information you should always refer to the full SPC of an individual drug – see 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).

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.uk and refer to SPCs, and BSR/BHPR (2011).

1.1.12 Reducing or stopping TNF-alpha inhibitors in patients with RA

The evidence base for tapering and withdrawal of biologic drugs is increasing, and EULAR included a recommendation in their 2013 management guidelines: “If a patient is in persistent remission after having tapered glucocorticoids, one can consider tapering biologic DMARDs, especially if this treatment is combined with a conventional synthetic DMARD”. In addition, EULAR recommendations note “reinstitution of biologic DMARDs appears to allow the good outcome to be recaptured”.

The adverse effect profile of biologic DMARDs is such that it is appropriate to utilise the lowest dose that will achieve clinical remission for the patient. The majority of patients are maintained on a standard dose of biologic DMARD; however, a number of papers have proposed a lower dosage regimen (achieved through dose tapering) in patients with low disease activity scores, which still preserves an excellent clinical outcome (Medicines Evidence Commentary, NICE, 2014 and Van Herwaarden et al, 2014).

It is recognised that this would be outside of licensed dose recommendation within the Summary of Product Characteristics for these drugs; however, it is also in keeping with established prescribing practice for DMARDs to maintain the patient on the lowest dose that maintains clinical remission and avoids unnecessary dose-related adverse events.
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
- ustekinumab
- secukinumab.

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 and biosimilars 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
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.

Stop-think-best practice opportunity
Safe home administration of subcutaneous biologics. What information do you need to know, ask or advise your patients?

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 circumstances, and with the patient’s 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:

• want to proceed with home administration and be able to carry this out
• have 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 and risk assessment
• agree a back-up plan in the event of being unable to self-administer.
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
- belimumab.

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 handing 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
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 childbearing age should be counselled regarding the nature of the risks to pregnancy with certain biologic drugs and advised accordingly (BSR/BHPR 2016).

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 O₂ saturation levels if indicated
   - urinalysis – request MSU if infection suspected and consider if infusion should be administered.

Stop-think-best practice opportunity

Consider the circumstances where an infusion should be withheld and why.
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 1,000 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 10mg IV tds (or other appropriate antihistamine)
- hydrocortisone 100mg IV tds
- metoclopramide 10mg IV tds
- paracetamol 1g orally qds (maximum 4g in 24 hours).

Refer to your local policy for infusion reaction management.

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 100ml with sodium chloride 9mg/ml (0.9%) solution for injection. The final concentration will be no more than 10mg/ml. Dose of infusion is 500mg, 750mg or 1,000mg (depending on weight) at week 0, 2, 4 then monthly by...

---

**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
intravenous infusion. See table below.

<table>
<thead>
<tr>
<th>Body weight of patient</th>
<th>Dose</th>
<th>Number of vials</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 60kg</td>
<td>500mg</td>
<td>2</td>
</tr>
<tr>
<td>≥ 60kg to ≤ 100kg</td>
<td>750mg</td>
<td>3</td>
</tr>
<tr>
<td>&gt; 100kg</td>
<td>1,000mg</td>
<td>4</td>
</tr>
</tbody>
</table>

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 (≥1/10 patients). Dizziness and hypertension may also occur. Seek medical advice in the case of hypertension.

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 10ml of water for injections, using a syringe equipped with a 21-gauge (0.8mm) or smaller needle.

The reconstituted solution dose is further diluted to 250ml 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 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.

**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.

For biosimilars Remsima® and Inflectra please see SPC and local guidelines for administration as these
cannot be given over an hour. This has potential cost implications whilst also impacting practical provision.

### 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 10mg 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

<table>
<thead>
<tr>
<th>Concentration</th>
<th>1mg/ml</th>
<th>2mgs/ml</th>
<th>4mgs/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Volume of fluid</td>
<td>1,000mls</td>
<td>500mls</td>
<td>250mls</td>
</tr>
</tbody>
</table>

#### 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

<table>
<thead>
<tr>
<th>Time</th>
<th>mgs/hour</th>
<th>mls/hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st 30 minutes</td>
<td>50mg/hour</td>
<td>25mls/hour</td>
</tr>
<tr>
<td>2nd 30 minutes</td>
<td>100mg/hour</td>
<td>50mls/hour</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Time</th>
<th>mgs/hour</th>
<th>mls/hour</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st 30 minutes</td>
<td>100mg/hour</td>
<td>50mls/hour</td>
</tr>
<tr>
<td>2nd 30 minutes</td>
<td>200mg/hour</td>
<td>100mls/hour</td>
</tr>
</tbody>
</table>

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 licence for a faster infusion rate up to 600mg/hr (RA only). See [www.medicines.org.uk](http://www.medicines.org.uk)

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
• \(O_2\) 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

### 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 4ml (80mg), 10ml (200mg) or 20ml (400mg) concentrate. The recommended posology is 8mg/kg body weight, given once every four weeks.

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

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

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 every four weeks.

**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 Belimumab administration

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

**Preparation of infusion**
Belimumab must be reconstituted before administration. Prepare the infusion according to manufacturer’s guidelines. Belimumab is supplied in vials containing either 5ml vial (120mg) or 20ml vial (400mg) concentrate.

Reconstitution and dilution must be carried out under aseptic conditions.

Allow 10-15 minutes for the vial to warm to room temperature (15°C - 25°C).

It is recommended that a 21-25 gauge needle be used when piercing the vial stopper for reconstitution and dilution.

The recommended posology is 10mg/kg

No dose adjustment is recommended for underweight or obese subjects.

Calculate the withdrawal volume of sterile, non-pyrogenic sodium chloride 9mg/ml (0.9%) solution for injection from a 250ml infusion bag, equal to the volume of concentrate required for the patient’s dose,
under aseptic conditions. To mix the solution, gently invert the infusion bag to avoid foaming.

**Administering infusion**

Belimumab is administered intravenously by infusion, and should be infused over a 1-hour period and must not be administered as an intravenous bolus. The infusion is given every 4 weeks.

The infusion rate may be slowed or interrupted if the patient develops an infusion reaction. The infusion must be discontinued immediately if the patient experiences a potentially life-threatening adverse reactions.

**Clinical observation during infusion**

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.

For a full list information regarding administration of intravenous biologic and biosimilar drugs, see the drug’s SPC (available at: www.emc.medicines.org.uk) and your local protocols.

**2.2.8 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 (for example 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.arthritisresearchuk.org).

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

**Stop-think-best practice opportunity**

Consider what information a patient needs to understand and how you would ensure they have access to this.
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.

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%, 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.


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

In December 2015, new NICE guidance was published entitled *Abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis* (TA373). In short this means that:

- abatacept, adalimumab etanercept and tocilizumab are recommended as possible treatments for children and young people with polyarticular juvenile idiopathic arthritis
- adalimumab and etanercept are recommended as possible treatments for people with enthesitis-related juvenile idiopathic arthritis
- etanercept is recommended as a possible treatment for children and young people with psoriatic juvenile idiopathic arthritis.

This means that these biological medications can now be given to children and young people without as many problems as previously experienced.

New biosimilars are currently being used in children throughout the United Kingdom and the data is being reviewed by the Registries.

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 53.
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 http://80.87.12.43/BSPAR/.
<table>
<thead>
<tr>
<th>Generic name</th>
<th>Adalimumab</th>
<th>Etanercept</th>
<th>Infliximab</th>
<th>Tocilizumab</th>
<th>Abatacept</th>
<th>Anakinra</th>
<th>Canakinumab</th>
</tr>
</thead>
<tbody>
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<td>Humira®</td>
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<td>Remicade®</td>
<td>RoActemra®</td>
<td>Oencia®</td>
<td>Kineret®</td>
<td>Ilaris – Canakinumab®</td>
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<tr>
<td>Inhibits what?</td>
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<td>TNF</td>
<td>TNF</td>
<td>IL6</td>
<td>T- cell</td>
<td>IL-1</td>
<td>IL6</td>
</tr>
<tr>
<td>Type of biologic</td>
<td>Humanised soluble anti-TNF monoclonal antibody</td>
<td>Soluble TNF receptor fusion protein</td>
<td>Chimeric human murine anti-TNF monoclonal antibody</td>
<td>Humanised anti-IL6 receptor monoclonal antibody</td>
<td>Humanised selective T cell co-stimulatory modulator</td>
<td>Humanised anti-IL1 Receptor antagonist</td>
<td>Humanised Anti-IL-1β monoclonal antibody</td>
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<tr>
<td>Licensed</td>
<td>Yes – Polyarticular JIA 4 to 17 yrs</td>
<td>Yes – Poly articular JIA</td>
<td>Off label</td>
<td>Yes – Systemic JIA</td>
<td>Yes – Poly JIA</td>
<td>Off label</td>
<td>For CAPS</td>
</tr>
<tr>
<td>NICE approval</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Dose</td>
<td>24mg/m² up to 40 mgs</td>
<td>0.4mg/kg twice wkly or 0.8mg/kg wkly</td>
<td>6mg/kg</td>
<td>&lt; 30kg’s 12mg/kg &gt;30kg’s 8mg/kg</td>
<td>10mg/kg</td>
<td>2mgs/kg Max 100 mgs</td>
<td>2-4mgs/kg</td>
</tr>
<tr>
<td>Given how often</td>
<td>Fortnightly</td>
<td>Every week or twice weekly</td>
<td>At 0, 2, &amp; 6 weeks, then 4 to 6 weeks</td>
<td>Fortnightly for sJIA, 4 wkly for Poly JIA</td>
<td>At 0, 2, 4 weeks, then 4 weekly</td>
<td>Daily</td>
<td>8 weekly</td>
</tr>
<tr>
<td>Drug half-life</td>
<td>12-14 days</td>
<td>5 days</td>
<td>9 days</td>
<td>23 days</td>
<td>8 to 25 days</td>
<td>6 hours</td>
<td>22.9 to 25.7 days</td>
</tr>
<tr>
<td>How given</td>
<td>SC</td>
<td>SC</td>
<td>IVI</td>
<td>IVI</td>
<td>IVI</td>
<td>SC</td>
<td>SC</td>
</tr>
<tr>
<td>Onset of benefit</td>
<td>2 -12 weeks</td>
<td>2-12 weeks</td>
<td>2-12 weeks</td>
<td>2-12 weeks</td>
<td>2-12 weeks</td>
<td>4-12 weeks</td>
<td>2-12 weeks</td>
</tr>
<tr>
<td>Methotrexate needed?</td>
<td>Suggested, not required</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>
### Table 5. Biologic therapy options for children and young people continued

<table>
<thead>
<tr>
<th>Generic name</th>
<th>Adalimumab</th>
<th>Etanercept</th>
<th>Infliximab</th>
<th>Tocilizumab</th>
<th>Abatacept</th>
<th>Anakinra</th>
<th>Canakinumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand name</td>
<td>Humira®</td>
<td>Enbrel®</td>
<td>Remicade®</td>
<td>RoActemra®</td>
<td>Orencia®</td>
<td>Kineret®</td>
<td>Ilaris – Canakinumab®</td>
</tr>
</tbody>
</table>

**Common adverse events**
- Injection site reactions, upper respiratory infections
- Infusion reactions, upper respiratory infections
- Infusion reactions, upper respiratory infections, changes in blood parameters; especially neutrophils, LFTs & platelets. Normalises ESR & CRP & masks fever, so be alert for covert signs of infection
- Neutropenia
- Localised injection site reactions

**Special instructions**
- Can sting when given as has high PH value
- Add reconstitution fluid slowly, best used when removed from fridge for 15 mins before use
- Must use 0.4micron filter for administration. Infuse over 2 hours
- Use 50ml or 100ml bag of saline depending on which dose bracket used. Infuse over 1 hour
- Must use 0.4micron filter and silicone free syringes. Infuse over 30mins
- Should be given at same time daily
- Vials have special instructions on how to prepare, see package leaflet

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 required 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

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>
<thead>
<tr>
<th>Table 6. Assessment check list prior to starting any biologic therapy for children and young people</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Education for family and child/young people</strong></td>
</tr>
<tr>
<td><strong>Lifestyle issues</strong></td>
</tr>
<tr>
<td><strong>Blood screening</strong></td>
</tr>
<tr>
<td><strong>TB screening</strong></td>
</tr>
<tr>
<td><strong>Measurements</strong></td>
</tr>
<tr>
<td><strong>Psychological support</strong></td>
</tr>
<tr>
<td><strong>Training for S/C administration</strong></td>
</tr>
</tbody>
</table>
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 immuno-compromised child best practice statement* available at www.rcpch.ac.uk and also Appendix 12).

As with any immune-suppressant therapy, guidelines on immunisation in the immuno-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

Chickenpox infection is a concern in any non-immune immunosuppressed patient with a significant contact to either chickenpox or exposed shingles. Checking varicella immune status (VZV IgG) prior to starting immunosuppression has been identified as an important aspect of patient care if there is no history of chickenpox/shingles.

Consideration can be given to providing two doses of varicella vaccine (four weeks apart) to immunocompetent, eligible patients if VZV IgG negative on a qualitative assay or <150mIU/ml on a quantitative assay. If VZV IgG is equivocal on the qualitative assay, then test on a quantitative assay. However, immunosuppression should not be initiated until four weeks after the final vaccine dose has been given. Please refer to your local policy.

If significant exposure occurs to either chickenpox or exposed shingles then VZV IgG testing should be urgently performed within seven days of the contact (even if prior immunity has been established or there is a past history of chickenpox/shingles) for those patients receiving biological therapies alone or in combination with steroids until at least six months after treatment. Varicella zoster immunoglobulin (VZIG) administration should not be delayed past seven days after initial contact while an antibody test is being performed. For those patients where exposure is recognised late, VZIG can be given for up to ten days post exposure. When VZV IgG testing has been performed then VZIG should be issued if VZV IgG is negative on a qualitative assay or <150mIU/ml on a quantitative assay. If VZV IgG is equivocal on the qualitative assay, then test on a quantitative assay if time permits. Please refer to your local policy or the Green Book, especially for VZIG dose in children.


Children are often exposed multiple times and prophylactic oral aciclovir 10mg/kg four times a day can be considered, from days 7-14 post exposure, for those in whom prophylaxis with a blood product is not acceptable. Please refer to your local policy.

If chickenpox develops then the child should be urgently assessed for aciclovir treatment by the local paediatrician; immunosuppression should be discontinued until the last spot has crusted over and the patient is clinically well.

In addition, consideration can be given to providing varicella vaccine to immunocompetent, healthy susceptible close household contacts of immunocompromised patients to prevent exposure situations (www.gov.uk/government/uploads/system/uploads/attachment_data/file/456562/Green_Book_Chapter_34_v3_0.pdf).

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).
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 an 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

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 ).

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

• 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 (2013) Use of IV Tocilizumab in the treatment of adults with RA
• 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-TNFα therapies
• BSR/BHPR (2011) Guidelines on MabThera®
• BSR and BHPR (2011) Guidelines on the use of rituximab in rheumatoid arthritis
• BSR and BHPR (2016) Guideline for the treatment of axial spondyloarthritis (including ankylosing spondylitis) with biologics
• BSR BHPR (2016) Prescribing for rheumatological conditions in pregnancy and breastfeeding Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids
• EULAR (2010) Update of the ASAS/EULAR recommendations for the management of ankylosing spondylitis. Available at 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

Guidance documents:
• 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 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 TA340 Ustekinumab for treating active psoriatic arthritis (June 2015)
• NICE TA373 Abatacept, adalimumab, etanercept and tocilizumab for treating juvenile idiopathic arthritis (December 2015)

• NICE TA375 Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed (January 2016)

• NICE TA397 Belimumab for treating active autoantibody-positive systemic lupus erythematosus (June 2016)

• NICE TA 407 Secukinumab for active ankylosing spondylitis after treatment with non-steroidal anti-inflammatory drugs or TNF-alpha inhibitors (September 2016)

• NICE TA 445 Certolizumab pegol and secukinumab for treating active psoriatic arthritis after inadequate response to DMARDs (May 2017)

• 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 QS33 Rheumatoid arthritis (August 2013)

• NICE QS40 Psoriasis (2013)

• 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.

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 or 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

• 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

• Arthritis Research (www.arthritisresearchuk.org) and Skills for Health competency frameworks (www.skillsforhealth.org.uk)

• Yellow card scheme, see 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

• Quality, innovation, productivity and prevention (QIPP). See NICE website www.nice.org.uk and 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

<table>
<thead>
<tr>
<th>Element of competence to be achieved</th>
<th>Date of achievement</th>
<th>Practitioner signature</th>
<th>Supervisor signature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discuss the rationale for the use of subcutaneous biologic therapy in rheumatic conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discuss potential issues related to treatment including:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• screening of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• possible side effects or adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• drug interactions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• contra-indications to therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discuss the circumstances when subcutaneous biologic therapy should not be administered</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Describe interventions to alleviate side effects</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Demonstrate the ability to teach a patient/carer how to administer subcutaneous biologic therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demonstrate the ability to assess a patient’s/carer’s suitability for home administration of subcutaneous biologic therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• storage, handling and hygiene prep (hand washing/clean working area)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• safe use and disposal of equipment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• ensuring a quiet and safe environment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• travelling and transporting biologic therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Task</td>
<td>Status</td>
<td></td>
<td></td>
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<tr>
<td>----------------------------------------------------------------------</td>
<td>--------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demonstrate the ability to discuss the information/educational needs of the patient/carer in relation to home administration of subcutaneous biologic therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>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)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demonstrate adherence to information governance policy and procedures, in relation to record sharing and confidentiality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Describe sites on the body that would be appropriate for subcutaneous injection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Demonstrate the ability to maintain concise and accurate patient documentation and audit</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Describe the local monitoring requirements and follow up arrangements for subcutaneous biologic therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Identify the ways of maintaining current competency</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Identified areas for further learning:**

**Date of review:**


### Appendix 3

#### Diagnostic criteria

<table>
<thead>
<tr>
<th>Rheumatoid arthritis (RA)</th>
<th>Psoriatic arthritis (PsA)</th>
<th>Ankylosing spondylitis (AS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Classification criteria:</strong></td>
<td>To meet the CASPAR criteria:</td>
<td>Modified New York criteria for diagnosis of AS:</td>
</tr>
<tr>
<td>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</td>
<td>Presence of inflammatory articular disease (joint, spine, or enthesal) with ≥3 points from the following five categories:</td>
<td><strong>Radiographic criterion:</strong></td>
</tr>
<tr>
<td><strong>A. Joint involvement</strong></td>
<td>1. Current psoriasis OR history of psoriasis, OR family history of psoriasis.</td>
<td>Sacroiliitis at least grade 2 bilaterally or grade 3 or 4 unilaterally</td>
</tr>
<tr>
<td>1 large joint</td>
<td>2. Rheumatoid negative (usually).</td>
<td><strong>Clinical criteria:</strong></td>
</tr>
<tr>
<td>0</td>
<td>3. Current dactylitis OR a history of dactylitis.</td>
<td>• low back pain and stiffness &gt; 3/12s that improves with exercise but is not relieved by rest</td>
</tr>
<tr>
<td>2–10 large joints</td>
<td>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.</td>
<td>• limitation of the lumbar spine in both the sagittal and frontal planes</td>
</tr>
<tr>
<td>1</td>
<td>Current psoriasis is assigned a score of 2; all other features are assigned a score of 1.</td>
<td>• limitation of chest expansion relative to normal values correlated for age and sex.</td>
</tr>
<tr>
<td>2–10 small joints (with/without involvement of large joints)</td>
<td></td>
<td>Definite ankylosing spondylitis if radiological criterion is present, including at least one clinical criterion.</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Probable ankylosing spondylitis if three clinical criteria are present, or if the radiological criterion is present, but there are no clinical signs of disease.</td>
</tr>
<tr>
<td>3–10 small joints (with/without involvement of large joints)</td>
<td></td>
<td>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.</td>
</tr>
<tr>
<td>&gt;10 joints (at least one small joint)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>B. Serology (at least 1 test result is needed for classification)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative RF and negative ACPA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-positive RF/low-positive ACPA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High-positive RF or positive ACPA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>C. Acute-phase reactants (at least 1 test result is needed for classification)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal CRP and normal ESR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal CRP or abnormal ESR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>D. Duration of symptoms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥6 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A score of ≥6/10 is needed for classification of a patient as having definite RA.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Source documents**

[Modified New York criteria for diagnosis of AS](#)

**Radiographic criterion:**

Sacroiliitis at least grade 2 bilaterally or grade 3 or 4 unilaterally

**Clinical criteria:**

- low back pain and stiffness > 3/12s that improves with exercise but is not relieved by rest
- limitation of the lumbar spine in both the sagittal and frontal planes
- limitation of chest expansion relative to normal values correlated for age and sex.

Definite ankylosing spondylitis if radiological criterion is present, including at least one clinical criterion.

Probable ankylosing spondylitis if three clinical criteria are present, or if the radiological criterion is present, but there are no clinical signs of disease.

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.
ACR-EULAR (2010) revised RA classification criteria:  
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  
NICE (2013) CG79 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

The Classification criteria for Psoriatic Arthritis (CASPAR criteria) Taylor et al (2006)  

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


Assessment of Spondyloarthritis international Society (ASAS) criteria Rudwaleit et al (2009)  


## Appendix 4

Current live vaccines available in the UK

<table>
<thead>
<tr>
<th>Live vaccine</th>
<th>Brand name</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG</td>
<td>Bacillus Calmette-Guerin Vaccine</td>
</tr>
<tr>
<td>Measles, mumps and rubella combined vaccine (MMR)</td>
<td>MMRvaxPRO®, Priorix®</td>
</tr>
<tr>
<td>Poliomyelitis (live oral vaccine)</td>
<td>Poliomyelitis Vaccine, live (oral) GSK OPV</td>
</tr>
<tr>
<td>Rotavirus (live oral vaccine)</td>
<td>Rotarix®</td>
</tr>
<tr>
<td>Typhoid (live oral vaccine)</td>
<td>Vivotif®</td>
</tr>
<tr>
<td>Varicella-Zoster Vaccine</td>
<td>Varilrix®, Varivax®</td>
</tr>
<tr>
<td>Shingles</td>
<td>Zostavax®</td>
</tr>
<tr>
<td>Yellow fever</td>
<td>Arilvax®, Stamaril®</td>
</tr>
<tr>
<td>Nasal influenza vaccine</td>
<td>Flumist®</td>
</tr>
</tbody>
</table>

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

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

**Home care contact number:**
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:**

**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 alcohol wipes and cotton wool swabs, 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.

| Infections | Patients 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. **Practitioners** 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.

| Hepatitis B and C reactivation | 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. **Specialist physician input is recommended.** 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).

| Allergic reactions | Injection site 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%, of those receiving subcutaneous biologic injections report these. **Allergic reactions** have been reported to include pruritus, though some serious anaphylactic reactions have also been reported with adalimumab and golimumab. Infusion reactions: serious hypersensitivity reactions have been reported in association with:
  - **Tocilizumab** – 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.
  - **Infliximab** – acute infusion reactions including anaphylactic shock and delayed hypersensitivity reactions have been reported. **Treatment should be stopped immediately and emergency treatment given.**
  - **Rituximab** – 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.

| Active hepatic disease/hepatic impairment | Have been reported with tocilizumab and infliximab: Monitoring recommendations include:
  - 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).
### Haematological disorders

All patients on anti-TNFα therapy, including those not on concomitant DMARDs, FBCs should be monitored regularly.

- **Tocilizumab** monitoring recommendations include: FBC: 4-8 weeks after treatment initiation and thereafter, according to standard practice.
- **Golimumab** has been very rarely associated with disorders, cytopenias and malignancies, including lymphomas.

In practice FBC is repeated every six months, or according to DMARDs and remind patients to report signs of haematological disorders—sashes bruising bleeding tiredness or pallor.

### Glycaemic control and sodium levels

- **Tocilizumab** and **infliximab**: caution in those patients who are on a controlled sodium diet, as both of these contain sodium.
- **Etanercept**: hypoglycaemia (in diabetic patients) has been reported therefore patient education and monitoring needs to be considered, as clinically indicated.

### Neurological disorders

Symptoms potentially indicative of new/worsening demyelinating disorders. Cases of PML have been reported with **rituximab** (and other biologics) and so patients and practitioners need to be vigilant regarding this.

### Auto-antibody formation

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 HAHA (human antihuman antibodies) may be associated with a greater risk of infusion/allergic reactions or a reduced treatment benefit.

The potential for the HAHA anti-bodies to develop must be considered in all treatments that have a chimeric monoclonal antibodies component – in other words **infliximab** and **rituximab**. The co-prescription of MTX can significantly reduce the incidence of antibodies developing.

### Malignancies

Monitor and exercise vigilance for any possible signs of malignancies during biologic therapy. Appropriate skin protection and periodic skin examination is recommended.

### Cardiac Disorders

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 **tocilizumab**: Lipid parameters: 4-8 weeks after treatment initiation. (Patients should be managed according to local clinical guidance for management of hyperlipidaemia).

### Pulmonary symptoms

- **Patients** should be monitored (lung function tests) for any new or any worsening of pre-existing pulmonary symptoms (**interstitial lung disease** (ILD)) and encouraged to promptly report these to their **GP** and **specialist practitioners** – so that appropriate assessment, **investigations** and advice can be given – which may include the cessation of the therapy, until full investigations have been completed.

### Skin rashes

Practitioners should monitor and be observant and vigilant regarding the development of any skin rashes whilst receiving any biologic therapy. Be aware of **lupus-like syndrome** or other significant autoimmune disease or psoriasis.

### Uveitis

Monitor for the development of any uveitis type symptoms that patients may develop whilst receiving any biologic therapy. An **alternative anti-TNFα** agent could be considered.

### Surgery

Monitor patient’s post-operative surgery progress and provide appropriate advice, as and when required.
<table>
<thead>
<tr>
<th>Pregnancy breastfeeding and contraception</th>
<th>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. There is at present no evidence to the contrary of this advice however, the continuation of anti-TNFα 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. The pros and cons of breastfeeding in patients treated with anti-TNFα therapies should be considered on an individual basis.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post treatment monitoring</td>
<td>Infliximab the elimination of infliximab may take up to six months – monitoring once treatment has been stopped monitoring should continue accordingly.</td>
</tr>
</tbody>
</table>
Appendix 8
Example of a standardised assessment and management template for inclusion in patient records

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

<table>
<thead>
<tr>
<th>Known sensitivity to therapy or component parts (for example, murine products)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnant or breastfeeding (effective contraception must be used)</td>
<td></td>
</tr>
<tr>
<td>History of or suspicion of malignancy – requires further investigation</td>
<td></td>
</tr>
<tr>
<td><strong>Type:</strong></td>
<td><strong>Date:</strong></td>
</tr>
<tr>
<td>Moderate or severe congestive heart failure (New York Heart Classification (NYH) III or IV)</td>
<td></td>
</tr>
<tr>
<td>Family history or previous diagnosis or suspicion of demyelination (for example, MS)</td>
<td></td>
</tr>
<tr>
<td>Active infection of patients at high risk of infection. Examples include:</td>
<td></td>
</tr>
<tr>
<td>• chronic leg ulcers</td>
<td></td>
</tr>
<tr>
<td>• previous tuberculosis or risk factors or suspicion of TB (see section below, TB assessment)</td>
<td></td>
</tr>
<tr>
<td>• septic arthritis of a native joint within the last 12 months or sepsis</td>
<td></td>
</tr>
<tr>
<td>• prosthetic joint within the last 12 months: excluded indefinitely if the joint remains in situ</td>
<td></td>
</tr>
<tr>
<td>• persistent or recurrent chest infections</td>
<td></td>
</tr>
<tr>
<td>• other infections: acute or chronic hepatitis B or C, or HIV</td>
<td></td>
</tr>
<tr>
<td>• Chronic respiratory conditions including: interstitial lung disease, chronic obstructive pulmonary disease (COPD) or abnormal chest x-ray</td>
<td></td>
</tr>
<tr>
<td>• History of pneumocystis pneumonia (PCP) and taking high dose steroids</td>
<td></td>
</tr>
</tbody>
</table>

**Cautions:** Evidence of any pre-malignant conditions including: Barrett’s oesophagus, cervical dysplasia, large bowel polyps, non-melanoma skin cancer; signs of heart failure (CCF)

<table>
<thead>
<tr>
<th>Patient eligible for treatment?</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

If NO, state reason for exclusion:

If YES complete all screening below before continuing
# Section 3: Screening prior to treatment

<table>
<thead>
<tr>
<th>Tuberculosis assessment of immunity/risk</th>
<th>Tick box</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG scar</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>NO</td>
</tr>
<tr>
<td>Mantoux</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>NO</td>
</tr>
<tr>
<td>Quantiferon or T-Spot test</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>NO</td>
</tr>
<tr>
<td>Chest x ray</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Results:</th>
<th>Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Signature:</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: chest x-ray should be taken as close as possible to the time before starting treatment

## Tuberculosis risk factors/additional respiratory factors to consider

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

<table>
<thead>
<tr>
<th>Referred to TB clinic</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Result:</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Check result of TB testing before proceeding

## Immunisation

<table>
<thead>
<tr>
<th>Influenza vaccination</th>
<th>YES</th>
<th>NO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumovax immunisation</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Varicella zoster status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exposure to recent infections (shingles/chicken pox)</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Hepatitis B assessment required</td>
<td>YES</td>
<td>NO</td>
</tr>
<tr>
<td>Hepatitis C assessment required</td>
<td>YES</td>
<td>NO</td>
</tr>
</tbody>
</table>

## Other:

- 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

Specify further investigations required:

## Review date:

Review of infection:

Type:
Date of last infective episode:  
Treatment:  
(Review with prescribing practitioner)

**Section 4: Patient guidance and shared decision making:**  
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

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

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Oligoarticular onset Four or fewer joints involved.</td>
</tr>
<tr>
<td></td>
<td>Extended oligoarticular More than four joints involved after the first six months of disease.</td>
</tr>
<tr>
<td>2</td>
<td>Polyarticular onset Rheumatoid factor –ve Five or more joints during the first six months of disease with no detectable rheumatoid factor.</td>
</tr>
<tr>
<td>3</td>
<td>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.</td>
</tr>
<tr>
<td>4</td>
<td>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: • transient episodic erythematous rash • enlargement of liver or spleen • serositis.</td>
</tr>
<tr>
<td>5</td>
<td>Psoriatic arthritis Arthritis and psoriasis or arthritis and at least two of the following: • dactylitis • nail abnormalities (pitting) • family history of psoriasis confirmed by a dermatologist in at least one first-degree relative.</td>
</tr>
<tr>
<td>6</td>
<td>Enthesitis-related arthritis Previously known as juvenile spondyloarthropathy. 1) Arthritis and enthesitis, or 2) Arthritis or enthesitis plus two of the following: • sacroiliac joint tenderness, inflammatory spinal pain, or both • HLA-B27 • family history in first-, or second-degree relative of medically confirmed HLA B27+ve associated disease • acute anterior uveitis • onset of arthritis in a boy after the age of eight years.</td>
</tr>
<tr>
<td>7</td>
<td>Other arthritis Any form of idiopathic chronic arthritis which does not fit into the above categories.</td>
</tr>
</tbody>
</table>

(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 15mg/m² 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 ($>0.25\text{mg/kg daily}$) 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 immuno-suppressive therapy. This does not always give full immunity and may need to be repeated.

If an immunosuppressed child currently receiving biological therapies (or within six months of stopping) is exposed to VZV then urgent VZV IgG antibody testing is recommended. Varicella zoster immunoglobulin (VZIG) administration should not be delayed past seven days after initial contact while an antibody test is being performed. For those patients where exposure is recognised late, VZIG can be given for up to ten days post exposure. When VZV IgG testing has been performed then VZIG should be issued if VZV IgG is negative on a qualitative assay or <150mIU/ml on a quantitative assay. If VZV IgG is equivocal on the qualitative assay, then test on a quantitative assay if time permits. Please refer to your local policy or the Green Book, especially for VZIG dose.

Appendix 13
Reflection exercise for CPD and NMC revalidation

Self-reflection exercise: To illustrate understanding behind the changes presented in this updated (fourth edition)
In line with the Nursing and Midwifery Council (NMC, 2016) Revalidation, each practitioner is required to record a minimum of five written reflections relevant to their experience over the three years prior to the renewal of their registration. This reflection can be on a continuing professional development (CPD) activity, reflection of an event or experience.

Based on the NMC Reflective Accounts Form (at time of publication), the template below can be used to record your thoughts on reading this document, which can then serve as one of the compulsory five written reflections. Any reflective account needs to explain what you have learnt for the CPD activity, how you have changed or improved your work as a result and how this is relevant to the code. Please ensure you visit the NMC revalidation website for the latest and most up-to-date version of the NMC Reflective Accounts Form.

Once you have read this document, spend some time considering what you have learnt and how this will inform and change your future practice. Once you have written in the table below you can show this to your confirmer and discuss with them what you have written.

The questions that follow will assist you when writing the reflective account, but if they do not meet your individual learning needs, please feel free to develop your questions to assist your reflective learning.

Consider the following questions:

• Think of the last patient you put on a biologic drug, was there anything you would like to do differently which would ensure a more efficient process for the patient?

• What else do I need to do/know to extend my professional development in this area?

• Is there anything I’ve read in the document that I would like to understand better and need to read about further to clarify my understanding?.

• What have I learnt from reading this updated (2017) edition? and how does this relate to my practice?

• What information do I need to know and provide patients, administering subcutaneous Biologic therapies when travelling abroad?

• What advice do I need to know and provide patients regarding Biologic therapies, pregnancy and breastfeeding?

• What knowledge/skills have I acquired whilst reading this updated document and how will it relate to and/or change my clinical practice?

• Is there anything that I did not understand, need to explore or read about further to clarify my understanding?
### Example of NMC (2016) Revalidation Reflective Accounts Form

PLEASE NOTE: This is an example form only. For revalidation, please ensure you visit the NMC revalidation website for the latest and most up-to-date version of the NMC Reflective Form: [http://revalidation.nmc.org.uk/download-resources/forms-and-templates](http://revalidation.nmc.org.uk/download-resources/forms-and-templates)

<table>
<thead>
<tr>
<th>What was the nature of this CPD activity?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reading the Assessing, managing and monitoring biologic therapies for inflammatory arthritis, RCN (2017 updated fourth edition)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>What did you learn from reading this best practice document?</th>
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</table>

<table>
<thead>
<tr>
<th>How did you change your practice from reading this best practice document?</th>
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</table>

<table>
<thead>
<tr>
<th>How is this relevant to the Code? (select either: Prioritise people, practice effectively, preserve safety, promote professionalism and trust)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
</tbody>
</table>

Royal College of Nursing (RCN) (2016) Revalidation. Available at: [www.rcn.org.uk/professional-development/revalidation](http://www.rcn.org.uk/professional-development/revalidation)
Appendix 14
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

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

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: Helpline/The Source, Arthritis Care, Floor 4, Linen Court, 10 East Road, London, N1 6AD.

**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 020 8741 1515.

Email: admin@nass.co.uk

Write to: NASS, 4 Albion Court, Hammersmith, London, W6 0QT.

**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

Write to: NRAS, Ground Floor, 4 Switchback Office Park, Gardner Road, Maidenhead, Berkshire, SL6 7RJ.

**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.nrars.org.uk](http://www.nrars.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)
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.nrars.org.uk](http://www.nrars.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 nursing 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
Humira® (adalimumab)
Cimzia® (certolizumab pegol)
Enbrel® (etanercept)
Benepali® (etanercept)
Remicade® (infliximab)
Inflectra® (infliximab)
Remsima® (infliximab)
Simponi® (golimumab)
Orencia® (abatacept)
MabThera® (rituximab)
Roactemra® (tocilizumab)
Stelera® (usekinumab)
Cosentyx® (secukinumab)
Benlysta® (belimumab)


Arthritis Research UK patient information leaflets available from: www.arthritisresearchuk.org


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: AWMSG.


References

PART ONE: Adult patients


Galloway J, Moseley A, Mercer L, Dixon W, Fu B, Ustianowski A et al., (2010) Varicella zoster virus (VZV) infections are increased in patients with rheumatoid arthritis (RA) treated with anti-TNFα therapy; results from the British Society for Rheumatology Biologics Register (BSRBR) [abstract], *Arthritis and Rheumatology*, 62 (suppl. 10), 421 DOI: 10.1002/art.28190.


Galloway et al., (2011) (b) Drug specific risk of tuberculosis in patients with RA treated with anti-TNFα therapy. Conclusion: the rate of TB in patients with RA treated with anti-TNFα therapy was three-to-four fold higher in patients receiving infliximab and adalimumab than those receiving etanercept, *Annals of Rheumatic Diseases*, 69, pp.522-528.


Lok et al (2016) (UpToDate article) www.uptodate.com/content/hepatitis-b-virus-reactivation-associated-with-immunosuppressive-therapy


National Institute for Health and Care Excellence (2016) Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed. Technology appraisal guidance, London: NICE. Available from: www.nice.org.uk/guidance/ta375


Royal College of Nursing (2013) Sharps safety RCN guidance to support the implementation of the Health and Safety (sharp instruments in health care Regulations), London: RCN. Available from: www.rcn.org.uk


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Saad et al., (2009) Efficacy and safety of anti-TNFα therapies in Psoriatic Arthritis (PsA): an observational study; results from the BSRBR, Rheumatology, 49, pp.697-705.


Soliman et al., (2012) Rituximab or a second anti-TNFα necrosis factor therapy for RA patients who have failed their first anti-tumour necrosis factor therapy? Comparative analysis from the BSRBR, *Arthritis Care and Research*, 64(8), pp.1108-1115.


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PART TWO: Children and young people


Royal College of Nursing (2013) *Lost in transition: moving young people between child and adult health services*, London: RCN.


**Further reading**


The RCN represents nurses and nursing, promotes excellence in practice and shapes health policies.

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RCN Online
www.rcn.org.uk

RCN Direct
www.rcn.org.uk/direct
0345 772 6100

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