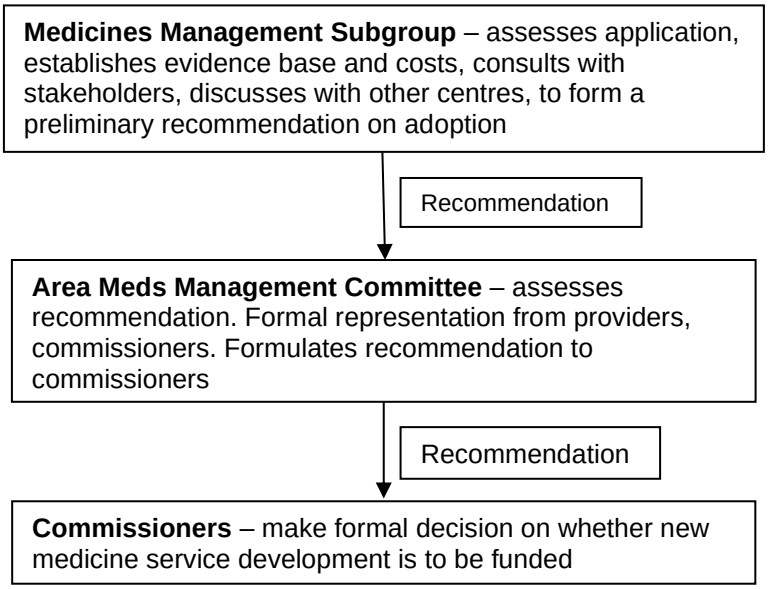
NHS
Pan Mersey
Area Prescribing Committee

Application and Case for Introduction of New Medicine Service Developments

Anti-TNF for managing planned conception in patients with active inflammatory arthritis

Purpose of this form: for providers to apply to commissioners for in-year funding of any new drug or extended use of an existing drug (e.g. new indication, new patient group) that will impact on prescribing costs in primary care. This includes where the prescribing will be passed on to primary care prescribers or where the drug is prescribed in hospital but generates additional PBR costs or is excluded from the Payment by Results Tariff and costs are passed on to commissioners. For simple new medicine service developments with no major funding implications please just complete the clinical section 1. and conflict of interest section 3.

Process:



Please complete this form as fully as possible. Please complete all relevant sections legibly. Any missing or illegible information will delay the application. You must discuss this application with the relevant Pharmacy Dept. / Medicines Management team. Applications completed by pharmaceutical companies are not acceptable.

Please submit completed form to your organisations representative on the Subgroup in your Pharmacy Dept / Medicines Management Team

Section 1 Clinical information

Name of medicine (generic and brand name):	**Anti-TNF therapy*** Adalimumab (Humira®) Certolizumab (Cimzia®) Etanercept (Enbrel®) Golimumab (Symponi®) Infliximab (Remicade®) *or biosimilar where available
Strength(s) and form(s) of preparation: Dose & schedule of administration	Adalimumab - SC injection 40mg/fortnight Certolizumab pegol - SC injection 200mg/fortnight or 400mg/month with a 6 week loading dose 400mg/fortnight Etanercept - SC injection 50mg/week Golimumab –50mg or 100mg/month Infliximab – 3mg/kg or 5mg/kg every 8 weeks
Licensed indication(s) :	Treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), non- radiographic axial spondyloarthritis (NR-axSpA), juvenile idiopathic arthritis (JIA) and adult onset Still's disease.
Proposed Indication (if different from or in addition to the above):	**Planned conception in patients with active inflammatory arthritis** Male and female patients with rheumatoid arthritis, psoriatic arthritis or active spondyloarthritis, where disease modifying anti rheumatic drugs(DMARDs) are contraindicated and need to be discontinued before conception is planned. DMARDs that need to be discontinued in females include methotrexate and leflunomide. DMARDs that need to be discontinued in male patients prior to conception include methotrexate, leflunomide and sulphasalazine.
Is this treatment instead of or in addition to any current treatment? Please give details:	This treatment is to be used instead of DMARD treatments: • In females - teratogenic DMARDs • In male patients - potentially teratogenic DMARDs and DMARDs that reduce male fertility The anti-TNF therapy will lead to reduced dependence on high dose corticosteroids in these patients

Reason for proposed change If replacing current treatment please state how it compares regarding efficacy and safety / tolerability	See above **Safety in preconception period** **Male patients** There is no evidence from randomised control trials to demonstrate safety of anti-tnf drugs for the treatment of male partners prior to conception. However case series and observational studies have provided some evidence of safety with regard to male fertility. Fertility and Reproduction in Male Patients with Ankylosing Spondylitis Treated with infliximab. J Rheumatol 2009;36;351-354 Infliximab and Semen Quality in Men with Inflammatory Bowel Disease. Inflamm Bowel Dis 2005;11:395–399 **Sperm count and sperm quality do not appear to be affected by use of antiTNF therapy in inflammatory arthritis** Effects of Tumour Necrosis Factor-α on Human Sperm Motility and Apoptosis. Journal of Clinical Immunology, Vol. 27, No. 2, March 2007 Effects of TNF antagonists on sperm characteristics in patients with spondyloarthritis. Ann Rheum Dis 2010;**69**:1842–1844 **Female Patients** Again data is derived from case reports and observational studies. There may be a potential signal of an increased spontaneous abortion rate in women exposed to anti-TNF therapies at conception but this may reflect concomitant methotrexate use and leflunomide use as well as the confounding effects of higher RA disease severity. To date collected reports have not indicated that anti-TNF therapy is associated with an increased risk of congenital malformations in offspring. However the numbers of patients treated is too small to draw firm conclusions Anti-TNF therapies and pregnancy: outcome of 130 pregnancies in the British Society for Rheumatology Biologics Register. Ann Rheum Dis 2011;**70**:823–826 Pregnancy outcome in women who were exposed to anti-tumor necrosis factor agents: results from a national population register. Arthritis Rheum 2006; **54**: 2701 – 2. A review article states that the currently available data does not support a large excess risk of adverse pregnancy outcome in patients who have been exposed to anti-TNF therapy at some point during the pregnancy or in the preconception period. Anti-TNF therapy and pregnancy outcomes in women with inflammatory arthritis. Expert Rev 2009. 5 (1),27-34

	However, some anti-TNF drugs can cross the placenta from the latter part of the second trimester and there are some concerns raised over infection risk and the effect of anti-TNF therapy on the infant's developing immune system. In particular, those drugs with an fc piece of the IgG molecule will be actively transported across the placenta. Certolizumab is a pegolated molecule and lacks the fc fragment and therefore does not cross the placenta. This drug appears not to be detected in infants born after maternal exposures during the later trimesters of pregnancy. Safety of anti-TNF agents during pregnancy and breastfeeding in women with inflammatory bowel disease Am J Gastroenterol. 2013 Sep;108(9):1426-38
Proposed place in therapy relative to other therapies (include protocol for use if available)	**Use of anti-TNF therapy as DMARD replacement** This would only be considered where couples meet the Cheshire & Merseyside NHS Funded Treatment for Subfertility Policy. http://www.panmerseyapc.nhs.uk/guidelines/documents/subfertility_20151021.pdf The policy is set by 12 local Clinical Commissioning Groups (CCGs) including those under the Pan Mersey APC. To qualify for 'NHS funded' assisted conception treatment the following criteria must be met: **Age** The female partner must be aged < 42 years at start of treatment period. **Female Body Mass Index (BMI)** Women will be required to achieve a BMI of 19-29.9 before treatment begins **Smoking** Patients should be confirmed non-smokers in order to access treatment **Drugs & Alcohol** Patients will be asked to give an assurance that their alcohol intake is within Department of Health guidelines and they are not using recreational drugs. Any evidence to the contrary will result in the cessation of treatment. **Definition of Childlessness** Funding will only be made available where a couple have no living children from a current or any previous relationship • If previous living child from current or previous relationship then excluded from treatment. • A child adopted by a patient or adopted in a previous relationship is considered to have the same status as a biological child. **Subfertility definition** Sub-fertility must not be the direct result of a sterilisation. Couples who have undertaken a reversal of their sterilisation procedure are not eligible for treatment.

Female patients
Female patients, with active inflammatory arthritis currently treated with DMARD therapy, who are considering pregnancy, should be referred for preconception counselling before starting therapy.

The time scale for DMARD withdrawal and risks associated with alternative DMARD, corticosteroid or anti-TNF therapy will be discussed during this consultation.

If the patients clinical condition is not adequately managed with sulphasalazine or hydroxy-chloroquine or low dose oral prednisolone or intermittent intramuscular depomedrone during the preconception period, the treating clinical team would suggest use of anti-TNF therapy for a period of up to 12 months preconception with the option of continuing anti-TNF therapy throughout pregnancy if disease does not improve during the pregnancy. This would be under the joint supervision of the obstetric and rheumatology teams.

Between 50-70% of RA patients report a marked improvement in rheumatological symptoms when pregnant and it would only be the minority that will require ongoing treatment with anti-TNF therapies after conception.

If conception does not occur after 12 months of anti-TNF therapy, the treating physician should write for exceptional funding approval to continue treatment for a further 6 months.

If conception does not occur after 18 months of anti-TNF treatment, consideration should be given to seeking assisted conception interventions.

Funding for continued anti TNF usage beyond 18 months would need to be applied for on an exceptional circumstances request via an IFR.

After delivery previously effective DMARD therapy will be reinstated and anti-TNF will not be continued.

Male patients
Male patients who have active inflammatory joint disease currently treated with leflunomide, methotrexate or sulphasalazine and are planning to father a child will be advised to discontinue these treatments.

If the patients clinical condition is not adequately managed with hydroxychloroquine or low dose oral prednisolone or intermittent intramuscular Depomedrone® during the preconception period, the treating clinical team would suggest use of anti-TNF therapy for a period of up to 12 months preconception and continuing anti-TNF therapy for the first 12 weeks of any pregnancy. If a pregnancy continues to 12 weeks the anti-TNF therapy will be withdrawn from the male partner and previously effective DMARD therapy will be reinstated.

References:

Barrett JH, Brennan P, Fiddler M, Silman AJ. Does rheumatoid arthritis remit during pregnancy and relapse postpartum? Results from a nationwide study

	in the United Kingdom performed prospectively from late pregnancy. *Arthritis Rheum*. Jun 1999;42(6):1219-27 de Man YA, Dolhain RJ, van de Geijn FE, Willemsen SP, Hazes JM. Disease activity of rheumatoid arthritis during pregnancy: results from a nationwide prospective study. *Arthritis Rheum*. Sep 15 2008; 59(9):1241-8.
Predicted clinical impact on Primary Care e.g. will it be initiated in hospital only but then prescribed in primary care, or may it be initiated in primary care? Will it require shared care? Please describe:	Cost implications for funding anti-TNF therapy. Monitoring according to the shared care agreement is less intensive for antiTNF monotherapy than for methotrexate, leflunomide and sulphasalazine. 3 monthly full blood count and liver function tests are recommended these will be conducted in secondary care.
Monitoring requirements (e.g. for efficacy, side-effects) – if any? Do these differ from current situation?	Monitoring requirements will be unchanged i.e. will be done by secondary care.
Brief summary of evidence in support of requested medicine / additional use Meta-analyses, systematic reviews, double-blind	See evidence above (included in section on proposed change) covering evidence for intervention efficacy, safety and tolerability of anti-TNF therapy. Reasons for DMARD withdrawal in males and females treated with leflunomide and methotrexate include concerns about teratogenicity of these therapies (1,2) and reduced semen quality associated with use of sulphasalazine in males (3). Whilst many patients with inflammatory arthritis can manage after temporary withdrawal of their DMARD therapy in the preconception period, some patients with active disease require additional treatment. Up until now the mainstay of additional treatment in this situation has been use of moderate doses of oral prednisolone or intermittent doses of intramuscular methyl

randomised controlled trials in peer-reviewed journals. Ensure that evidence to support advantages / benefits of the new medicine over existing treatments is included where appropriate. Include any relevant morbidity, mortality, health economic and quality of life benefits.	prednisolone. In many situations the glucocorticoid therapy is not sufficient to control the active joint disease putting the patient at risk of progressive joint damage and disability as well as exposing young patients to unacceptable glucocorticoid related side effects. In addition levels of fertility may be reduced in patients with uncontrolled systemic inflammatory joint disease (4). Accumulating evidence from observational studies looking at pregnancy outcomes in patients treated with anti-TNF therapies has not demonstrated any teratogenic effects associated with use of etanercept, adalimumab, golimumab and certolizumab. The US Food and Drug Administration (FDA) currently rates these therapies as category B drugs for drug safety during pregnancy (5). Animal studies have shown no harm to the foetus, but, no randomized, blinded, placebo-controlled trials on potential teratogenicity in humans have been completed. Numerous case reports have shown positive outcomes with anti–TNF-alpha use in pregnancy, with an incidence of spontaneous abortion and birth defects similar to that in the general population (6,7,8,9).
References Please list and include copies or internet links with the application	1. Teratogen Update: Reproductive Risks of Leflunomide (Arava™); A Pyrimidine Synthesis Inhibitor: Counseling WomenTaking Leflunomide Before or During Pregnancy and Men Taking Leflunomide Who Are contemplating Fathering a Child TERATOLOGY 2001. 63:106–112 2. The effects of methotrexate on pregnancy, fertility and lactation. QJM (1999) 92 (10): 551-563 3. Sulphasalazine and male infertility: reversibility and possible mechanism. Gut. 1981 Jun;22(6):445-51. 4. Katz PP (2006) Childbearing decisions and family size among women with rheumatoid arthritis. Arthritis Rheum 2006 Apr 15; 55(2):217-23. 5. Rheumatoid arthritis and pregnancy: evolution of disease activity and pathophysiological considerations for drug use. 6. de Man YA, Dolhain RJ, van de Geijn FE, Willemsen SP, Hazes JM. Disease activity of rheumatoid arthritis during pregnancy: results from a nationwide prospective study. *Arthritis Rheum*. Sep 15 2008;59(9):1241-8. [Medline]. 7. Wegmann TG, Lin H, Guilbert L, Mosmann TR. Bidirectional cytokine interactions in the maternal-fetal relationship: is successful pregnancy a TH2 phenomenon?. *Immunol Today*. Jul 1993;14(7):353-6. [Medline].

	8. Østensen M, Förger F, Nelson JL, Schuhmacher A, Hebisch G, Villiger PM. Pregnancy in patients with rheumatic disease: anti-inflammatory cytokines increase in pregnancy and decrease post partum. *Ann Rheum Dis*. Jun 2005;64(6):839-44. [Medline]. [Full Text]. 9. Unger A, Kay A, Griffin AJ, Panayi GS. Disease activity and pregnancy associated alpha 2-glycoprotein in rheumatoid arthritis during pregnancy. *Br Med J (Clin Res Ed)*. Mar 5 1983;286(6367):750-2. [Medline]. [Full Text]. 10. Safety of anti-TNF agents during pregnancy and breastfeeding in women with inflammatory bowel disease Am J Gastroenterol. 2013 Sep;108(9):1426-38

Section 2 Financial information

Costs: (excluding VAT) Cost per patient per year of medicine:	Anticipated average 6 months anti-TNF treatment per patient is £4750, some patients would be on therapy for 12 months or more (use of biosimilar versions will be less costly).
Number of patients per year to be treated for the whole organisation:	10 patients/ year estimated across the Pan Mersey APC, please note that some of these patients are already being funded via IFR route.
Additional costs e.g. day case tariff, tests per patient per year:	• Additional TB screening tests prior to starting treatment • Chest X-ray £60 • Interferon-gamma release assay testing for latent TB £64.00 per patient.
Any impact on PBR activity? Please give details:	These therapies are PBR excluded . No additional appointment activity anticipated.
Overall financial impact:	Over a year treating 10 patients for an average of 6 months would cost £47,500 (use of biosimilar versions will be less costly).
Current treatment(s) usually used (if any):	In situations where DMARDs are withdrawn during preconception periodic glucocorticoid therapies either as oral prednisolone 10mg-30mg /day or as monthly intramuscular Depomedrone® injections have been used to try and maintain control of active inflammatory rheumatic disease.
Cost per patient per year currently treated (excluding VAT):	Oral prednisolone average dose 15mg/day for 6 months cost £103.14 Intramuscular methylprednisolone average of 6 injections

	of 120mg cost £56
Number of patients per year currently treated:	Additional costs for IM injection tariff
Current additional costs e.g. day case tariff, tests per patient per year:	None significant.
Predicted financial impact on Primary Care e.g. Is the medicine hospital only but PBR excluded, will it be initiated in hospital only but then prescribed in primary care, or may it be initiated in primary care? Please describe:	The therapy is PBR excluded and will be prescribed by secondary care rheumatology teams

Section 3 Conflicts of Interest

Please state any potential conflicts of interest e.g. funding of research, equipment, consulting or speaking fees etc. in relation to this request:	No conflict of interests.

Name of Applicant: Dr Nicola Goodson

Role: Senior Lecturer in Rheumatology, Consultant Rheumatologist (Honorary)

Organisation name: Aintree University Hospital Foundation NHS Trust
This form is submitted on behalf of the Mersey regional rheumatologists with the aim of seeking approval for use of these drugs for this indication, across
Pan Mersey APC

I confirm I have sent a copy of this form to my organisations Drug & Therapeutics Committee / Medicines Management Committee or equivalent, and it has been approved following the appropriate procedure within my organisation.

Signature of Applicant:

Dr N J Goodson
29/09/2015

Name of Clinical Director / CCG Prescribing Lead:……..

Signature Clinical Director / Prescribing Lead:……

Name of Chief Pharmacist / Head of Medicines Management: Mrs M Norval (Chief Pharmacist, Aintree University Hospital NHS Trust)…….
Signature of Chief Pharmacist / Head of Medicines Management:……..

Please note that the application will not be considered unless the Chief Pharmacist / Clinical Director / Prescribing Lead / Head of Medicines Management in your organisation have signed this form.