NHS
Pan Mersey
Area Prescribing Committee

Application and Case for Introduction of New Medicine Service Developments

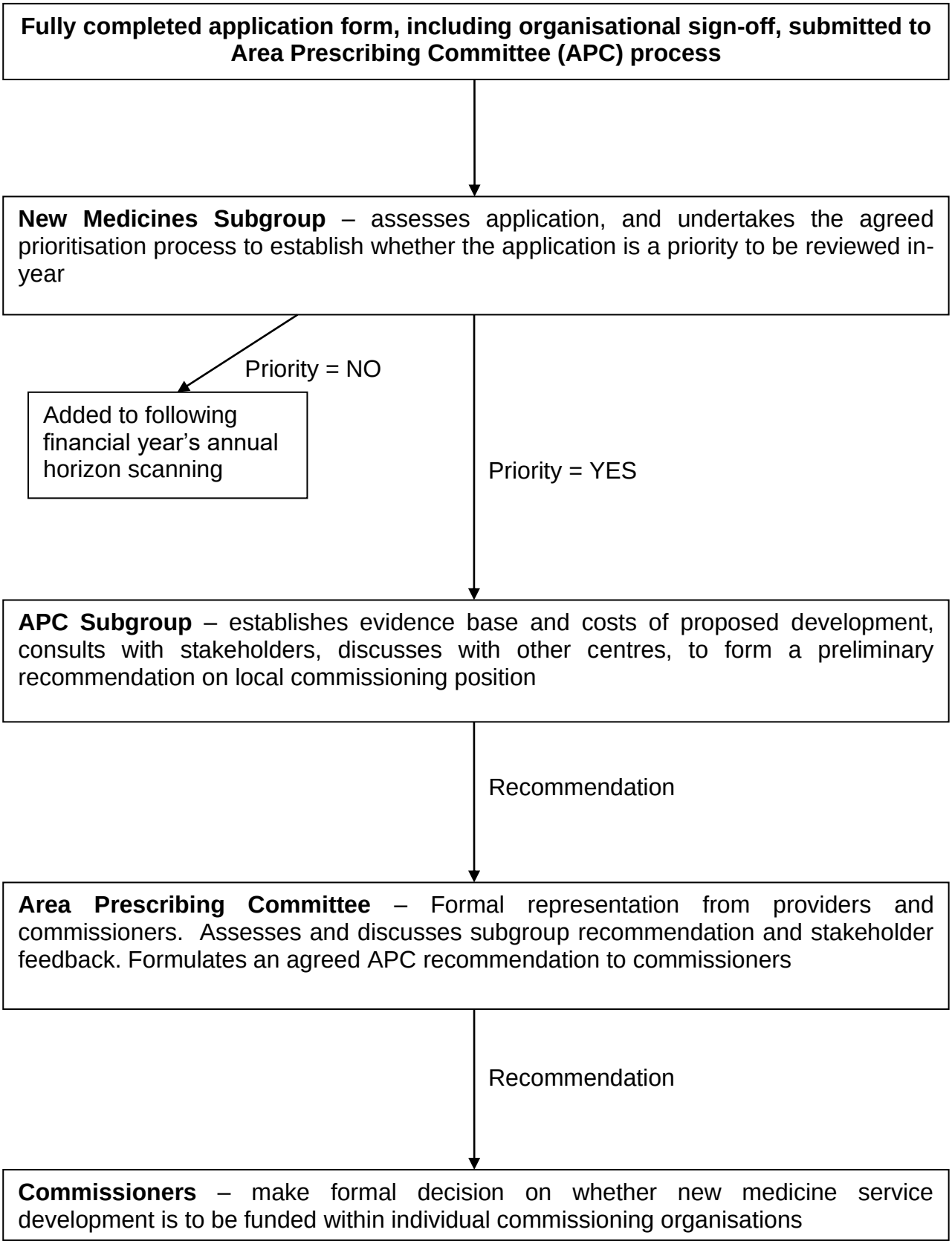
Application for: **Biologics in patients with flare of active inflammatory arthritis during pregnancy**

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 to the commissioner. 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 drug costs are passed on to commissioners. The annual horizon scanning process should be used as the preferred route to identify the majority of new developments, and any in-year funding applications will be subject to a prioritisation process to establish whether it is a local priority to review within the current financial year. Applicants are advised that prioritisation for review does not guarantee a positive commissioning recommendation outcome.

For minor formulary changes please use the Request for amendment to existing formulary choice or a medicine switch form.

This form is not to be used for Individual Funding Requests (IFR). These are considered where the individual or treatment is exceptional; i.e. where the treatment can be described as exceptional by virtue of the rarity of the condition or the difference of the individual from the generality of similar patients. Separate IFR documentation is available. Sometimes new, innovative treatment options are presented as exceptional: in this case every effort is made to direct the clinical team to the commissioning decision route, via this service development application, although the first few requests via the exceptional treatment route may be considered so as to offer benefit to patients where this is likely.

Process:


Fully completed application form, including organisational sign-off, submitted to Area Prescribing Committee (APC) process
New Medicines Subgroup – assesses application, and undertakes the agreed prioritisation process to establish whether the application is a priority to be reviewed in-year
Priority = NO
Added to following financial year's annual horizon scanning
Priority = YES
APC Subgroup – establishes evidence base and costs of proposed development, consults with stakeholders, discusses with other centres, to form a preliminary recommendation on local commissioning position
Recommendation
Area Prescribing Committee – Formal representation from providers and commissioners. Assesses and discusses subgroup recommendation and stakeholder feedback. Formulates an agreed APC recommendation to commissioners
Recommendation
Commissioners – make formal decision on whether new medicine service development is to be funded within individual commissioning organisations

Please complete this form as fully as possible. Please complete all relevant sections legibly and include full references. Any missing or illegible information will delay the application. You must discuss this application with the relevant Pharmacy Dept. / Medicines Management team within your organisation and obtain organisational support and sign-off for the application before it is submitted. 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 and 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 (after initial dose titration)
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.

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Proposed Indication (if different from or in addition to the above):	Female patients with rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis or active spondyloarthritis, who are pregnant and suffer disease flare that is not adequately controlled by their current therapy, where alternative disease modifying anti rheumatic drugs (DMARDs) are contraindicated but symptoms are not sufficiently severe to fulfil NICE criteria for biologic agents. DMARDs that are contra-indicated include methotrexate and leflunomide.
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 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	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

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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

Recommendations for anti-TNF medications in pregnancy and breastfeeding (Taken from BSR and BHPR guidelines on prescribing drugs in pregnancy and breast feeding.

Rheumatology.2016, 55, (9):1693–1697

Abbreviations:

level of evidence (LOE) 1-5

grade of recommendation (GOR) A-D

strength of agreement (SOA) (%)

i. Infliximab (IFX) may be continued until 16 weeks and etanercept (ETA) and adalimumab (ADA) may be continued until the end of the second trimester (LOE 2−, GOR D, SOA 98.9%).
ii. To ensure low/no levels of drug in cord blood at delivery, ETA and ADA should be avoided in the third trimester and IFX stopped at 16 weeks. If these drugs are continued later in pregnancy to treat active disease, then live vaccines should be avoided in the infant until 7 months of age

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	(LOE 3, GOR D, SOA 98.9%). iii. Certolizumab pegol is compatible with all three trimesters of pregnancy and has reduced placental transfer compared with other TNF inhibitors (TNFis) (LOE 2−, GOR D, SOA 97.9%). iv. Golimumab is unlikely to be harmful in the first trimester (LOE 4, GOR D, SOA 97.9%)
Proposed place in therapy relative to other therapies (include protocol for use if available)	If the patients clinical condition is not adequately managed with sulphasalazine or hydroxy-chloroquine or low dose oral prednisolone or intermittent intramuscular depomedrone during pregnancy, the treating clinical team would suggest use of anti-TNF therapy for a period of up to 9 months throughout remainder of 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 treatment with anti-TNF therapies after conception. After delivery alternative DMARD therapy will be commenced at next specialist review and anti-TNF will not be continued. **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.

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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.
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 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, including criteria for treatment success. Include any relevant morbidity, mortality, health economic and quality of life benefits.	See evidence above (included in section on proposed change) covering evidence for intervention efficacy, safety and tolerability of anti-TNF therapy. Reasons for DMARD contraindication is concern about teratogenicity of these therapies (1,2). 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 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.(3) Accumulating evidence from observational studies looking at pregnancy outcomes in patients treated with anti-TNF therapies has not demonstrated any

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	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 (4). 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 (4,5,6,7).
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. Katz PP (2006) Childbearing decisions and family size among women with rheumatoid arthritis. Arthritis Rheum 2006 Apr 15; 55(2):217-23. 4. 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]. 5. 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].

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	6. 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]. 7. 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]. 8. 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: Number of patients per year to be treated for the whole organisation: *Where possible / applicable, include assessment of patient numbers across Pan Mersey area.* Additional costs e.g. day case tariff, tests per patient per year: Any impact on PBR activity? Please give details: Overall financial impact:	Anticipated average 6 months anti-TNF treatment per patient is £4750 (use of biosimilar versions will be less costly). 10 patients/ year estimated across the Pan Mersey area. • Additional TB screening tests prior to starting treatment • Chest X-ray (with lead shield over the abdomen in order to protect the fetus from radiation exposure). £60 • Interferon-gamma release assay testing for latent TB £64.00 per patient. These therapies are PBR excluded . No additional appointment activity anticipated. Over a year treating 10 patients for an average of 6 months would cost £45,000 (use of biosimilar versions will be less costly).

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Current treatment(s) usually used (if any):	In situations where DMARDs cannot be used 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 Additional costs for IM injection tariff
Number of patients per year currently treated:	
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, other personal or non-personal or family interest etc. in relation to this request:	No conflicts of interest

Name of Applicant

Role

Organisation name

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

Name of Clinical Director / CCG Prescribing Lead

Signature Clinical Director / Prescribing Lead

Name of Chief Pharmacist / Head of Medicines Management

Signature of Chief Pharmacist / Head of Medicines Management

Note: Medicines Governance Group approved (July 2019)

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