Guideline for Cyclophosphamide treatment in patients with vasculitis and other organ/life threatening autoimmune disorders

This protocol does not override the individual responsibility of health professionals to make appropriate decision according to the circumstances of the individual patient in consultation with the patient and /or carer. If health care professionals do not follow this guidance they should be prepared to justify their reasons/actions.

Introduction

This guideline has been developed to support the management of patients aged 18 and over with vasculitis and other organ or life threatening autoimmune disorders requiring cyclophosphamide treatment. As this therapy requires specific and careful handling due to its hazardous nature, it can only be administered in designated areas by specifically trained and competent staff (see WAHT-NUR-064 for more details). This guideline outlines the procedures and pathways for the prescribing and administration of cyclophosphamide for this patient group.

This guideline is for use by the following staff groups:

Medical staff, nursing staff and pharmacy staff

Lead Clinician(s)

Dr Weng Oh	Consultant Nephrologist and Physician
Dr Caroline Cardy	Consultant Rheumatologist
Approved by Specialty Medicine Divisional Management Board on:	5th October 2022
Approved by Medicines Safety Committee on:	14th December 2022
Review Date: This is the most current document and should be used until a revised version is in place	14th December 2025

Key amendments to this guideline

Date	Amendment	Approved by:
December 2022	New document approved	Specialty Medicine DMB/ MSC

Introduction

Systemic vasculitis describes a group of multisystem disorders in which vascular inflammation may lead to rapid patient decline, with the potential for irreversible organ damage, including acute and chronic renal failure.

Cyclophosphamide, with corticosteroids, is recommended for use in patients with some types of systemic vasculitis (for example ANCA-associated vasculitis, AAV), and other organ/life threatening autoimmune disorders, in order to induce remission, and to prevent progressive organ damage. Current guidelines for the treatment of organ/life-threatening AAV with Cyclophosphamide are based on the CYCLOPS regime (see Appendix 1). Early administration of Cyclophosphamide is associated with improved outcome, and the aim is to initiate Cyclophosphamide therapy as soon as safely possible, and within 7 days (from time diagnosis suspected) as a maximum.

Background

Cyclophosphamide is principally used as systemic anticancer therapy (SACT). Use of SACT is described in more detail in WAHT-NUR-064v6: West Midlands Expert Advisory Group for SACT - Network Guidance.

There are no existing guidelines for cyclophosphamide use for non-malignant conditions, and this guideline includes systems to support timely and safe delivery of the first dose of intravenous (IV) Cyclophosphamide by staff expert in administering Cyclophosphamide as systemic anticancer therapy (SACT).

WAHT staff competent in the administration of SACT will administer therapy at the bedside for inpatients on non-oncology wards. Outpatient doses will be given on the Rheumatology Day-case Unit, unless otherwise agreed.

Inpatient Treatment Pathway

Lead/inpatient consultant:

It is essential that a consultant leads the treatment of the patient, in order to ensure that Cyclophosphamide is given **as soon as safely possible**, and within 7 days as a maximum. This will usually be an appropriate specialty consultant with experience in vasculitis. If not, decisions to treat with Cyclophosphamide must be guided by such a consultant. The lead's responsibility for patient care includes ensuring the pathway is followed, and the required MDT/specialty input is in place.

Diagnostic and treatment decisions need to be executed by those with experience in vasculitis and Cyclophosphamide therapy, augmented by MDT colleagues, in order to facilitate informed patient consent. Prescriptions require care, and familiarity with the protocols for Cyclophosphamide, which are not fixed, and may vary according to age, weight and renal function.

Treatment initiation:

Once the potential for urgent treatment with Cyclophosphamide is identified *(even if confirmatory tests are still outstanding)*, it is essential to make contact with Oncology Pharmacy, and the lead chemotherapy nurse at the earliest opportunity (see flow chart). This will ensure there are no delays in administration of the first dose as an inpatient.

The referring consultant must ensure all prescriptions in form WR5539 (Cyclophosphamide prescription, via CLIP) are completed clearly, and sent to pharmacy for screening and preparation. They must also ensure that the patient has received appropriate written information about Cyclophosphamide, and signed a consent form. Supportive medicines (outlined below) will need to be clearly prescribed on the in-patient medication chart.

The lead chemotherapy nurse/outreach chemotherapy nurse will liaise with the consultant and ward staff to ensure the prescription, delivery and administration of pre-meds as detailed in WR5539, prior to the administration of Cyclophosphamide.

Infusion:

When administering Cyclophosphamide on a ward not on the designated areas list, the outreach chemotherapy nurse must take with them a spillage kit, and appropriate equipment to ensure the safe administration of the medication, subsequent flushing through with sodium chloride 0.9%, as well as safe disconnection of administration set and/or removal of cannula. They should stay with the patient throughout the infusion where possible. For checking purposes, the administrating nurse must take another SACT-trained nurse with them to carry out initial checks as per WAHT-NUR-064.

Verification:

Active patient identification is essential at all stages of the checking procedure. Prior to administration of Cyclophosphamide, the patient must be asked to identify themselves, and to provide their date of birth. Hospital number or address must be checked against their Cyclophosphamide prescription chart, and their identity bracelet. This must be an active not a passive response, unless the patient does not have the capacity to identify themselves (see local trust guidance for identification of patients without capacity).

To verify a patient's Cyclophosphamide treatment:

• The name of the medication and dose must match exactly with that recorded on the medication chart or prescription
• The name of the medication must correspond exactly with the regimen recorded within the patient's health care records
• The dose corresponds with the dose calculation
• Correct diluent and diluent volumes have been used
• The medication is to be administered via the route intended
• The medication is to be administered in the correct sequence as prescribed
• The medication will not expire before administration is completed. *Note: Pharmacy must be consulted in individual cases where there is a possibility that the medication may expire before administration is complete*
• The details on the prescription chart match with the patient's identification bracelet
• Any dose or schedule modification must be documented clearly, with reasons for changes, in the patient's health care records
• Supportive medications have been given as per prescription
• Critical test results have been checked
• Minimum monitoring requirements as per protocol have been met
• Response assessment has been performed as per regimen and treatment intention
• Patient's most recent weight must be checked against the prescription and height verified
(NHS England, 2014)

Note: If there are any discrepancies do not proceed and seek advice from a senior colleague or pharmacist The medication should be administered intravenously in accordance with WAHT-NUR-064.

Post infusion:

The outreach chemotherapy nurse must discuss potential side effects and safety implications post infusion with the ward staff to ensure any risk of exposure to hazardous waste is reduced, and to ensure staff are aware of the potential risks and side effects. The outreach chemotherapy nurse must ensure documentation is completed to include form WR5539 and also document within the patient's notes.

The referring consultant will need to ensure post infusion medications are prescribed on the inpatient medication chart, and will then need to arrange follow up and subsequent treatment venue as appropriate (i.e. Rheumatology Day case/Chemotherapy Day unit) ensuring all prescriptions and documentation are completed and sent to appropriate areas.

Supportive Medications:

Mesna is given as bladder protection:

- 400 mg orally 2 hours before Cyclophosphamide infusion
- 400 mg orally 2 hours after Cyclophosphamide infusion
- 400 mg 6 hours after Cyclophosphamide infusion

Ondansetron is given to prevent nausea and vomiting

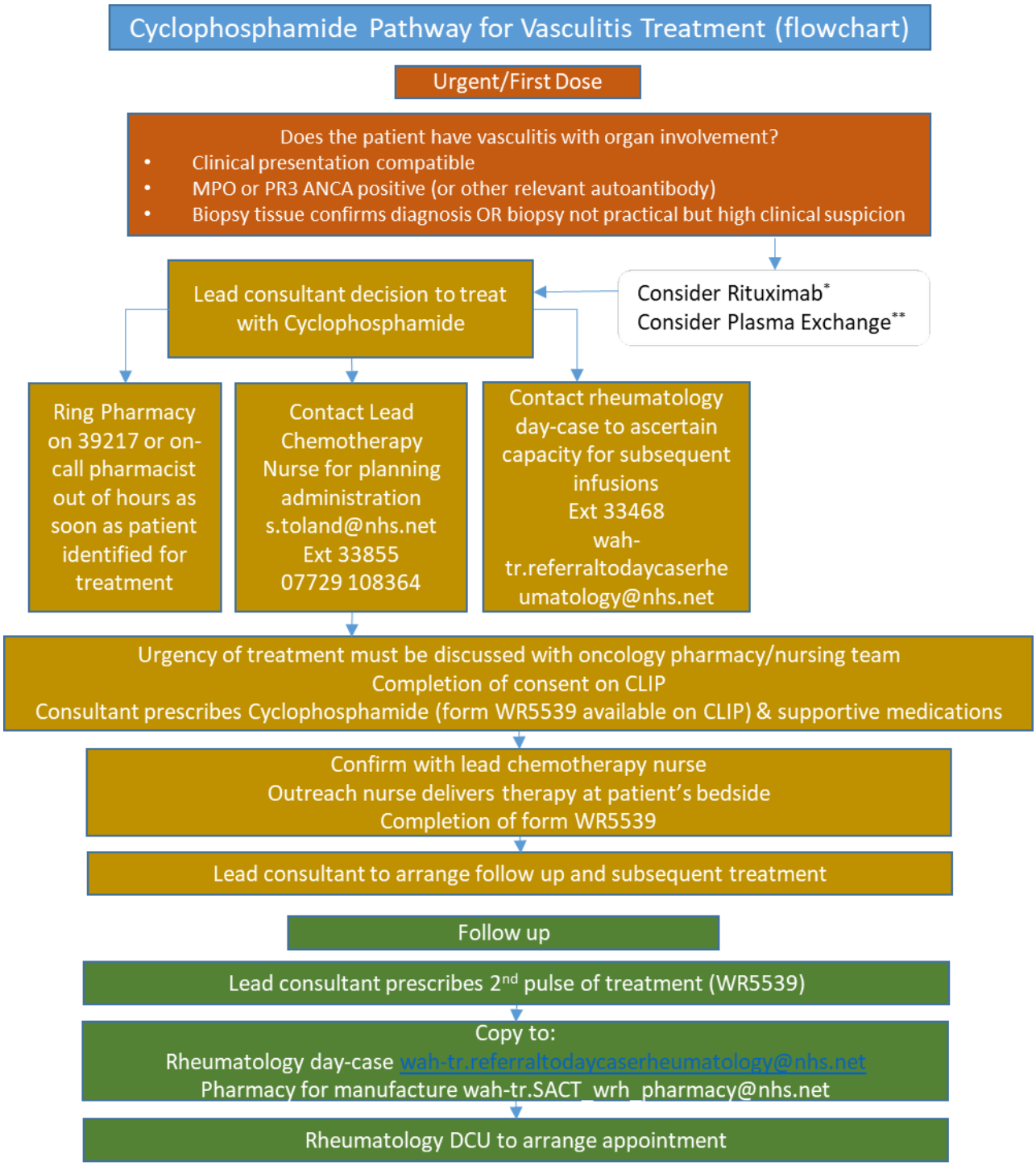
- 8 mg orally 1 hour prior to Cyclophosphamide infusion
- 8 mg continued twice daily for 24 hours
  consider additional Cyclizine or Metoclopramide as required

Gastroprotection (e.g. Omeprazole 20 mg daily, or patient's usual gastroprotection) is given whilst patient receiving high dose steroids

Co-trimoxazole is usually prescribed as PJP pneumonia prophylaxis for the duration of Cyclophosphamide therapy *(up to 6 months)*

- 960 mg orally, taken once daily on 3 days a week
- Use half normal dose if eGFR 15–30 mL/minute/1.73 m^2.
  N.B. check allergies (e.g. sulphonamides) + drug interactions

Antifungal: consider Nystatin 1 ml oral QDS or Fluconazole 50 mg OD



* Rituximab may be considered as an alternative to Cyclophosphamide if clinically appropriate or if any delay in cyclophosphamide treatment that may cause harm. Requires discussion with specialist centre.

** Plasma exchange maybe indicated for patients with ANCA associated vasculitis and severe renal disease (see Appendix 2).

Appendix 1 – CYCLOPs regime for ANCA associated vasculitis

Systemic Vasculitis – CYCLOPS regime[1]

Cyclophosphamide intravenous pulses given as below *(aim for remission within 3 months and further 3 months of treatment = 6 months in total)*

Frequency of pulses	Number of pulses	Week number
Every 14 days	3 pulses	0, 2, 4
Every 21 days	7 pulses	7, 10, 13, 16, 19, 22, 25

Cyclophosphamide dose reductions for renal function and age

Pulsed cyclophosphamide dose reductions for renal function and age			**Maximum dose 1.2 gram per pulse**
Age (years)	**Creatinine (umol / L)**		
	150 – 300	**300 – 500**	
< 60	15 mg/kg/pulse	12.5 mg/kg/pulse	
> 60 and < 70	12.5 mg/kg/pulse	10 mg/kg/pulse	
> 70	10 mg/kg/pulse	7.5 mg/kg/pulse	

Oral cyclophosphamide can be used for week 7 onwards at a dose of 5 mg/kg per day for 3 days (depending on renal function)

Prednisolone regime used in CYCLOPS study
Consider Methylprednisolone depending on clinical condition

Time from entry (weeks)	Prednisolone dosage (mg/kg/day)	Prednisolone dosage (mg/day for 60 kg)
0	1	60
1	0.75	45
2	0.5	30
3	0.4	25
6	0.33	20
8	0.25	15
Reduce at end of month 3	12.5	12.5
Reduce at end of month 5	10	10
During months 12 -15	7.5	7.5
During months 15 -18	5	5

Subsequent prescriptions & blood test monitoring

Every Cyclophosphamide prescription throughout a course of 3-6 months should be an individualized new prescription. The dose and timing of Cyclophosphamide will depend on risk factors such as age, renal function, new or active infection, and white cell counts (WCC) taken before and after subsequent doses as follows:

- after the 1st infusion check FBC, U&Es, LFTs and CRP at day 7, 10 and 14
- after the 2nd and 3rd infusions check FBC, U&Es, LFTs and CRP at 7-10 days and 14 days
- for subsequent infusions check FBC, U&Es, LFTs and CRP at 10-14 days, and the day of, or day prior to, infusion

Dose reductions

WCC at infusion < 4.0: postpone until >4.0 and/or reduce dose by 25% / seek advice
WCC nadir 1.0–2.0 or neutrophil nadir 0.5–1.0: reduce cyclophosphamide infusion by 40% of previous dose
WCC nadir 2.0–3.0 or neutrophil nadir 1.0–1.5: reduce cyclophosphamide infusion by 20% of previous dose
If reduction in neutrophil or WCC, repeat FBC at 7, 10 and 14 days after next infusion
If WCC satisfactory, thereafter check FBC, U&Es, LFTs, and CRP at day 10-14 and on day prior to infusion

Appendix 2 – ANCA-associated vasculitis with renal involvement

Day 0	*New referral with suspected ANCA-associated vasculitis and renal involvement:* • Check urine dipstick for blood and protein; send urine for MC&S and casts in green tube to microbiology **AND** for albumin:creatinine ratio in yellow (not green) tube to biochemistry • Request daily U&E, creatinine, FBC, fluid balance • Arrange urgent ANCA test (for MPO/PR3): *please also request all other tests on ICE panel under specialties-renal patients-acute glomerulonephritis immunology:* **please ask biochemist on duty in Worcester laboratory to prioritise ANCA sample for sending to immunology laboratory at Wye Valley NHS Trust, and chase result** • Arrange urgent Anti GBM titres (included in the renal immunology panel). • Request Hepatitis B/C and HIV serology *(also on ICE renal patient panel under BBV).* Consider *Varicella* serology unless definite history of past chicken pox infection, and Quantiferon (interferon gamma release assay/IGRA) • Request clotting and group & save tests • Request urgent CXR (?nodules, ?pulmonary haemorrhage), unless chest imaging already available • Avoid prescribing nephrotoxins e.g. NSAIDs • Book urgent renal ultrasound (unless renal imaging already available) • Pause anticoagulants including thromboprophylaxis, and Aspirin/Clopidogrel *(if possible)* in expectation of renal biopsy • Refer for urgent renal (wah-tr.referral-renal@nhs.net) and other specialty assessment (e.g. rheumatology wah-tr.rheumatologyinpatientreferrals@nhs.net) dependent on clinical picture and organ involvement • Transfer patient to Aconbury 3 renal ward (unless other urgent needs e.g. needing ITU)
Day 1-2	*New referral with suspected ANCA-associated vasculitis and renal involvement:* • Consider steroid treatment after consulting with renal/rheumatology/specialty team; *consider intravenous Methylprednisolone or oral prednisolone 60mg od depending on the clinical condition of the patient* • Start blood glucose monitoring chart • Optimise blood pressure control (BP needs to be < 160/< 90 prior to renal biopsy) • Alert oncology and pharmacy department to ensure appropriate staff available to give cyclophosphamide in the ward as early as possible. The team should be alerted even if the final decision on treatment is awaited (see flow chart)
Day 3-5	*Renal biopsy (as early as feasible)* • If on warfarin or anti-platelet: preferable to wait until day 6 to do renal biopsy • If on NOAC preferable to wait until day 5 to do biopsy • *Renal biopsy usually not advised if imaging shows renal obstruction, or bilateral renal atrophy*
Day 3-7	*Lead consultant recommendation/decision to treat with Cyclophosphamide* • Evaluation for any contraindications to treatment • Ensure patient given Cyclophosphamide patient information leaflet available from Rheumatology OPD, or Versus Arthritis web download.

	• Complete written or electronic consent form ***mandatory*** • Ensure IV cyclophosphamide has been prescribed by an appropriate prescriber i.e. lead consultant, or clinician experienced in vasculitis/Cyclophosphamide prescribing per appropriate protocol • Prescribe Mesna, anti-emetics, prophylaxis against *Pneumocystis* pneumonia/PJP (e.g. Co-trimoxazole), and consider anti-fungal for prophylaxis against oral candidiasis (*see "Supportive medications")*
Day 5	• Ensure high fluid intake (*IV fluids if necessary*) prior to Cyclophosphamide treatment
Day 6-7	• Aim to give 1st dose of Cyclophosphamide by day 6-7*

***in patients with severe disease (e.g. pulmonary haemorrhage, rapidly declining kidney function), the 1st dose may be given earlier at the discretion of the lead consultant**

1st dose may be given before renal biopsy if:

1. There is significant delay in doing renal biopsy (due to coagulopathy/deranged haematological parameters/hypertension), *and/or*
2. Renal biopsy not possible but clinical evidence highly suggestive of vasculitis causing renal decline, *and/or*
3. Already evidence of other significant organ involvement by vasculitis e.g. lungs/nervous system.

There is now new evidence that plasma exchange improves renal survival in patients with ANCA associated vasculitis and severe renal disease[2]. Patients with dual antibody positive vasculitis (ANCA and anti GBM) will also benefit from plasma exchange. Currently the Trust does not provide plasma exchange treatment. If plasma exchange is required, the patient will need to be referred to a tertiary renal unit (UHB).

The following scenarios may require an urgent referral to UHB renal team for consideration of plasma exchange:

1. **If the patient's creatinine is > 300 umol/l either on presentation or during the inpatient admission,**
2. **If the patient has dual antibody positive vasculitis (ANCA and anti GBM positive).**

For both these scenarios the referring clinician will need to assess the risk of infection based on age, co-morbidity and frailty and whether the risk of infection outweighs the benefits of providing plasma exchange.

Please discuss these clinical scenarios with the renal team in Worcester Royal Hospital during weekdays Monday - Friday 9am to 5pm and weekends from 8.30am to 2pm via e-mail (wah-tr.referral-renal@nhs.net) or telephone (via switchboard). For out-of-hours referrals, please refer directly to the renal team in UHB via NORSE. First dose treatment with Cyclophosphamide should not delay transfer to UHB renal unit for plasma exchange and acute haemodialysis. If this can potentially lead to a delay in transfer, the priority would be for the patient to be transferred to UHB for plasma exchange and haemodialysis first before receiving Cyclophosphamide.

Monitoring Tool

This should include realistic goals, timeframes and measurable outcomes.

How will monitoring be carried out?
Monitoring will be carried out by auditing the compliance of the clinicians to the treatment pathway

Who will monitor compliance with the guideline?
The specialist teams involved in using the pathway (renal/rheumatology/neurology)

Page/ Section of Key Document	Key control:	Checks to be carried out to confirm compliance with the policy:	How often the check will be carried out:	Responsible for carrying out the check:	Results of check reported to: *(Responsible for also ensuring actions are developed to address any areas of non-compliance)*	Frequency of reporting:
	WHAT?	**HOW?**	**WHEN?**	**WHO?**	**WHERE?**	**WHEN?**
	These are the 'key' parts of the process that we are relying on to manage risk. We may not be able to monitor every part of the process, but we MUST monitor the key elements, otherwise we won't know whether we are keeping patients, visitors and/or staff safe.	What are we going to do to make sure the key parts of the process we have identified are being followed? (Some techniques to consider are; audits, spot-checks, analysis of incident trends, monitoring of attendance at training.)	Be realistic. Set achievable frequencies. Use terms such as '10 times a year' instead of 'monthly'.	Who is responsible for the check? Is it listed in the 'duties' section of the policy? Is it in the job description?	Who will receive the monitoring results? Where this is a committee the committee's specific responsibility for monitoring the process must be described within its terms of reference.	Use terms such as '10 times a year' instead of 'monthly'.
	Key elements- 1. time to 1st cyclophosphamide administration 2. Referral to specialist tertiary unit where indicated	Audit	Annually	Specialist teams involved in using the pathway (renal/rheumatology/neurology)	Specialist medicine governance team and rheumatology governance	Annually

REFERENCES

(1) Pulse versus daily oral cyclophosphamide for induction of remission in antineutrophil cytoplasmic antibody-associated vasculitis (CYCLOPS study). Kötter I. Z. Rheumatol. 2009 Sep; 68(7): 575-7
(2) The effects of plasma exchange in patients with ANCA associated vasculitis: an updated systematic review and meta-analysis. Walsh et al. BMJ 2022: 376: 1-10

Contribution List

This key document has been circulated to the following individuals for consultation;

Designation
Countywide lead pharmacist cancer and aseptic services – SC
Clinical Governance Lead Rheumatology – AF – retired April 2022
Clinical Lead – Neurology – TH
Clinical Lead – Renal Medicine – WO
Clinical Lead – Rheumatology - CC
Lead Chemotherapy Nurse – ST
Consultant Renal and General Medicine – MF
Clinical Governance Lead Rheumatology – BD Apr 2022 onwards
Lead Pharmacist rheumatology – MG

This key document has been circulated to the chair(s) of the following committees / groups for comments;

Committee
Divisional Governance/Management Board – all divisions
Medicines Safety Committee

Supporting Document 1 - Equality Impact Assessment Tool

To be completed by the key document author and attached to key document when submitted to the appropriate committee for consideration and approval.

Herefordshire & Worcestershire STP - Equality Impact Assessment (EIA) Form
Please read EIA guidelines when completing this form

Section 1 - Name of Organisation (please tick)

Herefordshire & Worcestershire STP		Herefordshire Council		Herefordshire CCG	
Worcestershire Acute Hospitals NHS Trust	v	Worcestershire County Council		Worcestershire CCGs	
Worcestershire Health and Care NHS Trust		Wye Valley NHS Trust		Other (please state)	

Name of Lead for Activity	**Dr Weng Chin Oh and Dr Caroline Cardy**

Details of individuals completing this assessment	**Name**	**Job title**	**e-mail contact**
	Dr Weng Chin Oh	**Consultant nephrologist**	**wengchin.oh1@nhs.net**
Date assessment completed	**5.10.22**		

Section 2

Activity being assessed (e.g. policy/procedure, document, service redesign, policy, strategy etc.)	**Title:** Guideline for Cyclophosphamide treatment in patients with vasculitis and other organ/life threatening autoimmune disorders				
What is the aim, purpose and/or intended outcomes of this Activity?	Aim: Improve access to inpatient treatment with cyclophosphamide for patients with vasculitis and life-threatening auto-immune disorders Outcomes: To improve patient safety and overall survival by ensuring timely treatment for these patients during their impatient stay				
Who will be affected by the development & implementation of this activity?	❑ v□ ❑ ❑	Service User Patient Carers Visitors	☑ ❑ ❑ ❑	Staff Communities Other _____	
Is this:	□ Review of an existing activity ❑v New activity ❑ Planning to withdraw or reduce a service, activity or presence?				
What information and evidence have you reviewed to help inform	This guideline was undertaken following a				

this assessment? (Please name sources, eg demographic information for patients / services / staff groups affected, complaints etc.	review of a Serious Incident involving delay of cyclophosphamide treatment for a patient with vasculitis
Summary of engagement or consultation undertaken (e.g. who and how have you engaged with, or why do you believe this is not required)	I have engaged with the rheumatology department and the chemotherapy nurse
Summary of relevant findings	Future delays can now be avoided with the creation of an inpatient pathway for cyclophosphamide administration

Section 3

Please consider the potential impact of this activity (during development & implementation) on each of the equality groups outlined below. **Please tick one or more impact box below for each Equality Group and explain your rationale**. Please note it is possible for the potential impact to be both positive and negative within the same equality group and this should be recorded. Remember to consider the impact on e.g. staff, public, patients, carers etc. in these equality groups.

Equality Group	Potential positive impact	Potential neutral impact	Potential negative impact	Please explain your reasons for any potential positive, neutral or negative impact identified
Age	v			The treatment dose for cyclophsohamide is adjusted for age
Disability				
Gender Reassignment				
Marriage & Civil Partnerships				
Pregnancy & Maternity				
Race including Traveling Communities				
Religion & Belief				
Sex				
Sexual Orientation				
Other Vulnerable and Disadvantaged Groups (e.g. carers; care leavers; homeless; Social/Economic deprivation, travelling communities etc.)				
Health Inequalities (any preventable, unfair & unjust differences in health status between groups, populations or individuals that arise from the unequal distribution of social, environmental & economic conditions within societies)				

Section 4

What actions will you take to mitigate any potential negative impacts?	Risk identified	Actions required to reduce / eliminate negative impact	Who will lead on the action?	Timeframe
		.		
How will you monitor these actions?				
When will you review this EIA? (e.g in a service redesign, this EIA should be revisited regularly throughout the design & implementation)				

Section 5 - Please read and agree to the following Equality Statement

1. Equality Statement

1.1. All public bodies have a statutory duty under the Equality Act 2010 to set out arrangements to assess and consult on how their policies and functions impact on the 9 protected characteristics: Age; Disability; Gender Reassignment; Marriage & Civil Partnership; Pregnancy & Maternity; Race; Religion & Belief; Sex; Sexual Orientation

1.2. Our Organisations will challenge discrimination, promote equality, respect human rights, and aims to design and implement services, policies and measures that meet the diverse needs of our service, and population, ensuring that none are placed at a disadvantage over others.

1.3. All staff are expected to deliver services and provide services and care in a manner which respects the individuality of service users, patients, carer's etc, and as such treat them and members of the workforce respectfully, paying due regard to the 9 protected characteristics.

Signature of person completing EIA	Dr Weng Chin Oh
Date signed	5.10.22
Comments:	None
Signature of person the Leader Person for this activity	Dr Weng Chin Oh
Date signed	5.10.22
Comments:	

Supporting Document 2 – Financial Impact Assessment

To be completed by the key document author and attached to key document when submitted to the appropriate committee for consideration and approval.

	Title of document:	Yes/No
1.	Does the implementation of this document require any additional Capital resources	No
2.	Does the implementation of this document require additional revenue	No
3.	Does the implementation of this document require additional manpower	No
4.	Does the implementation of this document release any manpower costs through a change in practice	No
5.	Are there additional staff training costs associated with implementing this document which cannot be delivered through current training programmes or allocated training times for staff	No
	Other comments:	

If the response to any of the above is yes, please complete a business case and which is signed by your Finance Manager and Directorate Manager for consideration by the Accountable Director before progressing to the relevant committee for approval