Appendix G -Professional organisation statement template

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Rituximab in combination with corticosteroids for treating anti-neutrophil cytoplasmic antibody-associated vasculitis

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation: British Association for Paediatric Nephrology
Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? ✓

- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)?√

- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc)?

- other? (please specify)

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What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS?

Current standard treatment for children with newly presenting severe disease has been high dose steroids and a course of 6 or 7 intravenous cyclophosphamide infusions; some centres use plasmapheresis as adjunctive therapy in the children judged to have life or organ threatening disease.

Mild to moderate disease is usually treated with high dose steroids and azathioprine of mycophenolate mofetil. Conversion to intravenous cyclophosphamide has been contemplated if there is poor disease control or deterioration on treatment.

Is there significant geographical variation in current practice?

Treatment of severe disease is relatively consistent across the UK. The use of rituximab has varied between centres with some using it during the maintenance phase of therapy or when disease control is deemed successful but before completion of the course of cyclophosphamide. Rituximab has often also been used as add on in the children with most active disease.

Are there differences of opinion between professionals as to what current practice should be?

There is presently uncertainty if the use of cyclophospohamide can be reduced by adjunctive therapy such as rituximab as it's role in has not yet been fully established.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Cyclophosphamide is associated with leukopenia, infection, cancer and gonadal failure. ANCA-associated Vasculitis (AAV) is much commoner in adults and one year mortality is 11% as a result if complications of Vasculitis and infection.

Rituximab seems to be associated with fewer severe side-effects and is not associated with pancytopenia or gonadal dysfunction and most likely also with less serious bacterial infection.

Reported side effects include:
Infusion reactions – a cytokine release syndrome characterised by bronchospasm and hypoxia, chills, fever, rigors, urticaria and angioedema may develop after one to two hours of the first infusion. These symptoms are readily managed by slow initial infusion, the use of antihistamines and hydrocortisone. The symptoms tend not to occur in subsequent infusions. A true anaphylactic reaction can rarely occur and is seen within a few minutes of the start of the infusion.

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Progressive multifocal leukoencephalopathy as a result of JC infection is rarely reported, often in patients with autoimmune disease and additional immunosuppressive therapy.

Severe lung injury has been reported in a few cases after treatment with rituximab. The aetiology of this lung injury is not known and a high mortality has been reported.

Hepatitis B reactivation has been reported and can result in fulminant hepatitis and liver failure.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

The use of rituximab should at present be restricted to tertiary care. Patients having rituximab infusions are admitted as a day case to a clinical facility with cardio-respiratory resuscitation equipment and medical and nursing staff competent in its use. No additional support will be required as the therapy requires 2-4 infusions (depending on local protocol) and is consequently a shorter course than usually required for cyclophosphamide.

If the technology is already available, is there variation in how it is being used in the NHS?

There is variation in use as described above. Furthermore, availability of the treatment is determined by local arrangements with the CCG to provide funding in response to Individual Funding Requests made on behalf of patients.

Is it always used within its licensed indications? If not, under what circumstances does this occur?

This is not a licensed use for rituximab.

Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Recently published consensus expert recommendations were published (Guerry M et al Rheumatology 2011) and state:

1. In newly diagnosed ANCA-associated vasculitis Rituximab is as effective as cyclophosphamide for remission induction of previously untreated patients. Rituximab may be preferred, especially when cyclophosphamide avoidance is desirable. (Level of evidence 1b).

2. In refractory and/or relapsing disease Rituximab is an effective treatment of refractory and/or relapsing forms of ANCA-associated vasculitis and can be recommended when conventional therapy has failed. (Level of evidence 1b).

The advantages and disadvantages of the technology

The use of rituximab is likely to be easier than the current therapies and is also likely to reduce healthcare costs as the number of hospital admissions are fewer than for cyclophosphamide.

The effectiveness of the therapy is readily assessed by routine clinical assessment including clinical history and examination to assess disease activity, routine laboratory testing of blood and urine and by serial measurement of ANCA titres. There is considerable experience in the use of rituximab and clinicians are familiar with dosing and treatment intervals.

The Rituxivas trail1 and Rave trials have reported and show that rituximab is not superior to cyclophosphamide however there are cost benefits as a result of fewer complications and reduced health care costs. The clinical settings for these trials are appropriate for routine clinical care but did not include children. However, as the immunological basis of the disease is identical in adults and children it is assumed therapeutic strategies that are successful in adults can be applied to children.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

The number of children with AAV is small and it is thus not likely that there ever will be a randomised controlled trial in children. Case series like 'Eleftheriou D et al Biologic therapy in primary systemic vasculitis of the young' will thus together with studies in adult patients be the best evidence that we will get.

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Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

No significant additional staff resource, education or training will be required for the implementation of this guidance.

Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

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There is no clinical trial evidence to inform the use of rituximab in children with AAV. AAV is rare in children and it is unlikely trial data as obtained for adults will ever become available; consequently, it is appropriate to extrapolate use in children from adult evidence. However, there is case report and anecdotal evidence of successful use of this therapy in children. The British Association for Paediatric Nephrology strongly supports the inclusion of children in guidance relating to the use of this technology and does argue that their exclusion will be discriminatory.