NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Hepatitis C (children) - pegylated interferons, peginterferon alfa, ribavirin and alfa interferon

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 Royal Hospital for Sick Children, YOrkhill, Glasgow: NHS Greater Glasgow and Clyde – invited on behalf of Healthcare Improvement Scotland

Are you (tick all that apply):

- ❹ a specialist in the treatment of people with the condition for which NICE is considering this technology?
- ❹ 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? Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

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)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

*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.*

Hepatitis C in children is asymptomatic in the vast majority of cases. Children are commonly tested and diagnosed having been identified as being at risk of mother to child perinatal transmission, although some may be tested in the differential diagnosis of raised transaminases, or as a result of blood born virus screening for s other reasons. Horizontal transmission of hepatitis C before adolescence is rare in the UK. Evidence already presented indicates that progression of chronic liver disease in childhood is rare, and until recently there were no randomised controlled trials of treatment in children, although observational studies suggested that outcome of treatment was similar to that in adults, with a similar spectrum of side effects, including autoimmune thyroid disease and reduced linear growth during treatment. Many clinicians caring for infected children therefore kept the children under review, monitoring for signs of liver disease, whereas as few specialist centres offered treatment with pegylated interferon and ribavirin to all infected children unless there were specific contraindications, if consent were obtained. Other centres offer this treatment to children with favourable genotypes (2 and 3), but have been more conservative in children with genotypes in which current licensed treatment offers only a 50:50 chance of success.

The alternative to this technology is periodic review, with monitoring to detect early signs of chronic liver disease. Those with signs of disease would be offered or referred for treatment. However, the vast majority of children will not develop these signs while within the paediatric age group, and so will enjoy a childhood free of

major medical intervention apart from annual or bi-annual review, and costs to the paediatric service are relatively small.

The disadvantages of this alternative are that the child will remain infected with hepatitis C, which can be associated with stigma, and with the fear (despite the small risk) of transmission). As many of these children come from home affected by intravenous drug use, some are accommodated, and foster parents and potential adopters may be deterred from taking on a child with hepatitis C because of concerns regarding transmission.

Furthermore the clinical tools for detection of chronic liver disease in childhood are blunt. ALT and AST are the most frequently used tests, but fibrosis can occur in the presence of normal transaminases. Fibro-scanning is not validated in children, and liver biopsy is invasive and requires a general anaesthetic. Thus chronic liver disease may be advanced before it is detected, thus adversely affecting the young person's prognosis, even with treatment at that stage.

In this model, treatment will still be necessary at some point. Adolescence, being a time of change, emotional turmoil and rebellion for many, is not the time to contemplate complex lengthy treatment which requires a good level of adherence, if it can be avoided so outcome of treatment in this age group is likely to be poorer. In addition, girls may become sexually active by their mid teens, with the risk of pregnancy, which contra-indicates treatment, and vertical transmission to the child, Adolescents may also engage in activities associated with a risk of transmission. By the time a young person is stable enough again to be offered treatment, they may be well into their twenties, by which time their risk of liver disease is high if infected perinatally..

Children infected with genotype 2 and 3 treated with the technology have a superior outcome to those with other genotypes (approx 70-80% vs 50%). In addition the length of treatment required is shorter in the former group (24 vs 48 weeks). In addition to the well documented contra-indications and side effects, needle phobia can become intense during treatment, and can increase in intensity throughout the course. This needs to be considered when weighing up the advantages and disadvantages of early treatment for children with less favourable genotypes.

The technology requires detailed pre-assessment, close monitoring for side effects, with dose adjustment if required, and for response, and support for children and families during treatment. For these reasons it should be delivered in settings where there is specialist expertise in terms of experience with antiviral medication, and appropriately trained multi-disciplinary staff. This includes paediatricians with expertise in hepatitis, and specialist nurses.

Within Scotland the technology is used within licensed indication, although such use predated licensing.

SIGN 92 Section 6, which addresses hepatitis C in children has recently been updated. The recommendations and evidence underpinning them are appended to this document.

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The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

The technology has the potential to achieve cure for the majority of patients infected with genotypes 2 and 3 before any significant liver disease has occurred, with the potential for long term normal life and no need for ongoing medical input. This is also true for half the patients with genotype 1 and 4 disease. This has obvious advantages in terms of quality of life, physical health, freedom from stigma, and from being a source of ongoing transmission.

Disadvantages are the requirement for intensive medical input for the duration of therapy. The side effects, while tolerated by most to the extent that they can be managed, and most children are able to complete the course of therapy, are considerable, particularly in terms of mood changes, behavioural issues, and blood cell abnormalities. As stated above, most children find the injections distressing, and linear growth is affected, although catch up is observed once treatment is completed. Contra-indications and criteria for termination of therapy are well documented in the adult literature, and the same principles apply. However, as many of these children come from vulnerable families, a detailed assessment is required prior to starting to determine whether the family, with appropriate support, is likely to be able to adhere to the treatment regimen, and treatment should only be contemplated if there is a reasonable expectation of adherence.

Clinical experience with this technology outwith a trial setting has shown results equivalent to those reported in the published studies.

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While there is a good case for implementation of the technology when compared to currently available technologies, consideration of its utility cannot exclude consideration of the technology which will be available in the future. There are clinical trials ongoing in adults with hepatitis C using newer agents, including protease inhibitors. Two agents are already licensed for adults and it is anticipated that more of these agents will in due course be licensed for adults, and the regimens developed will no longer include interferon. Trials in children will inevitably follow. Thus there is a strong argument that children with no signs of liver disease, for whom the current technology results in only a 50% chance of cure, despite the considerable side effects and distress resulting from treatment, should not be treated routinely until less toxic regimens with a better chance of success become available. Hence the recommendations contained in the revised SIGN 92 guideline

Equality and Diversity

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

Hepatitis C affects children who have multiple vulnerabilities, often from homes with problems of multiple deprivation. Generically this group does not access services efficiently, and many affected children are not brought regularly to clinic appointments, whether for monitoring or for treatment. The potential advantage of treatment, is that after in intense period of input from health, there will be no necessity to continue to follow the children long term, thus reducing the risk of their being lost to follow up and re-presenting with end stage liver disease to adult services. However, this will only be achieved with substantial input from nursing and social services.

Because of the specialist nature of the technology, children from remote and rural areas may have more difficulty accessing treatment. Robust networking arrangements will need to be developed to ensure equity of access.

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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.

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)?

From my perspective as Scottish representative, ensuring that all eligible children were offered treatment will require funding for the treatment itself, identification of a nursing resource, and building upon the already existing networking arrangements to

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support treatment of children in areas of the country which at present do not have an established service, and may see few children with this condition.