Appendix D – Clinical specialist statement template

Colistimethate sodium powder and tobramycin powder for inhalation for the treatment of pseudomonas lung infection in cystic fibrosis

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: Dr Robert Ian Ketchell

Name of your organisation: Cardiff and Vale University Health Board

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **YES**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **YES**
- **Involved in the colistin dry powder study**
- 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.)? **YES**
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- **Director of the ALL Wales Adult Cystic Fibrosis Service, Cardiff**
- other? (please specify)

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.

Patients with Cystic Fibrosis (CF) and chronic Pseudomonas aeruginosa (PsA) infection in their lungs have a worse prognosis and Quality of Life than those with intermittent or no PsA. Chronic infection accelerates the progressive decline in lung function characteristic of CF and is central to the respiratory related morbidity and mortality. The advantages of inhaled antibiotic therapy for PsA infection in CF has been recognised for nearly40 years. The hypothesis is that an antibiotic delivered directly to the site of infection will be maximally effective, achieving sputum antibiotic levels far in excess of those achievable by intravenous administration without the risks of systemic toxicity.

Strategies aimed at preventing or delaying progression from initial acquisition of PsA to chronic infection are central to the management of patients with CF. Early eradication and subsequent reduction in the prevalence of chronic PsA is a major reason for increased patient survival. Early administration of aerosolised antibiotics once infection with PsA has been identified significantly reduces the risk of chronic infection.

Antibiotic management guidelines in CF are provided by the Cystic Fibrosis Trust through the UK CF Antibiotic Working Group (published in May 2009). I, like most CF consultants throughout the UK fully endorse these guidelines. At the time of publication however, there were only three inhaled anti-pseudomonal antibiotic preparations licensed for the treatment of PsA in CF, colistin (Colomycin® and Promixin®) and preservative free tobramycin for inhalation (TSI) or TOBI®. Historically nebulised colistin has been first line therapy for both eradication and prophylactic maintenance in chronic PsA infection in the UK. Following its licence nebulised TOBI® is often reserved for 2nd line therapy in chronic infection when colistin is not tolerated or if clinical progress is unsatisfactory. There is also evidence for the use of nebulised tobramycin in eradication of early PsA infection.

There now appears to be an increasing move throughout the UK to alternate therapy between nebulised colistin and nebulised tobramycin on an alternating monthly basis. Individual clinic protocols and the cost implications of this have unfortunately led to some "post-code prescribing" throughout the UK.

The British Thoracic Society Cystic Fibrosis Special Advisory Group have recently suggested a stepwise approach of nebulised colistin as first line when pulmonary function is normal but chronic pseudomonas infection is evident. "Nebulised tobramycin should be considered if despite continued therapy and good adherence to treatment, lung function continues to decline or there is a requirement for more than one course of intravenous (IV) antibiotics) in the preceding year. This may be prescribed with alternate months in conjunction with colistin. Nebulised Aztreonam Lysine (Cayston®) should also be considered if there is still progressive loss of lung function (defined as greater than 2% per year decline in FEV1 as % predicted) or there is continued need for IV therapy for exacerbations i.e more than 2 per year despite therapy with an alternating regimen of tobramycin and colistin".

Bramitob® has since been licensed as an alternative formulation of nebulised tobramycin. Clinically I have found neither TOBI nor Bramitob to be clinical superior to the other and prescribing is usually based on patient tolerance and preference.

More recently Cayston® has been licensed but the current high cost often precludes its use and experience within the clinical setting in the UK is limited. In Wales this can only be prescribed through application to individual patient Local Health Boards.

Colomycin®, TOBI®, and Bramitob® are licensed for administration through a Pari LC Plus re-usable nebuliser which takes 15-20 mins to nebulise on each occasion twice daily. However, many patients use more rapid mesh-based technology nebulisers such as the e-flow® nebuliser which takes 3-5 mins, again this has cost implications. There is some evidence for TOBI® that this is as effective as utilising the Pari LC Plus nebuliser. Promixin® is licensed through the I-neb® nebuliser and also takes approximately 3-5 minutes. Cayston® is licensed through the Altera® Nebuliser System and takes 3-5 minutes three times daily.

Colomycin®, Promixin® are therefore the current alternatives to the new technology Colistimethate sodium powder and TOBI® and Bramitob® current alternatives to the new technology tobramycin powder for inhalation (TIP). Cayston® does not have a dry powder alternative.

Disadvantages of the current technologies are:

1) Time to nebulise can be in excess of 30-40 minutes daily when using licensed nebulisers and does not include the time to clean the nebuliser after use. An additional burden for patients who often also have to nebulise a number of other medications including bronchodilators and mucolytics such as Pulmozyme and Hypertonic saline. This is in addition to taking multiple oral therapies and performing regular chest physiotherapy. Concordance with nebuliser therapy is inherently poor.

2) Nebulisers require cleaning after each use to reduce the risk of infection, illness or injury from contamination and should be disinfected after every other treatment. Aerosol heads require changing every 6 months and compressors should be regularly cleaned and maintained. More than 50% of patients do not clean their nebulisers according to guidelines and more than 50% of nebulisers are contaminated with bacteria.

3) TOBI®, Bramitob® and Cayston® ampoules require storage in a refrigerator (2-8°C or 36-46°F).

3) Lack of portability

4) Nebulisation can release antibiotics into the atmosphere sensitising family members and staff and should therefore be performed in a well ventilated room.

Advantages of the current technologies are:

1) May be preferred or better tolerated by some patients

Although there are milder genotypes it is difficult to categorise patients as there is poor correlation between genotype and phenotypical expression i.e between genetic background and disease expression. All patients with chronic pseudomonas infection have the potential to benefit from this technology. The technology should be specialist initiated but is appropriate for continued primary care prescribing. Other than initial demonstration of use of the technology by CF physiotherapists, CF specialist nurses, or CF pharmacists there is no requirement for any additional input and indeed requires less than current nebulised technologies.

Tobramycin powder for inhalation (TIP) for the treatment of pseudomonas lung infection in cystic fibrosis is currently available within the UK. Colistimethate sodium powder is not. Personally I have applied to the Bro Taf Localities Drugs and Therapeutic Committee using a fast-track new drug request form to have Tobramycin powder for inhalation added to the formulary.

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?

Advantages of the new technologies are:

1) Faster and easier administration over current technologies.

2) Comparable safety and efficacy data to current technologies, with no additional requirements for testing or monitoring. Treatment regimes consistent with current UK practice.

3) The new hand-held dry powder inhalers require minimal set-up, and can be wiped clean with a dry cloth. Low risk of bacterial contamination of inhaler compared to nebulisers.

4) Increased portability, ease of administration, room temperature storage and thereby acceptability, potentially increasing patient concordance with therapy. Carer support may be reduced.

5) Incidence of adverse reactions mild to moderate with incidence of severe reactions comparable to current technologies. I am unaware of any adverse effects not apparent in the clinical trials of the new technology.

6) A step towards "normalisation" of CF management for patients making some aspects of treatment comparable to those in other more common disease areas such as use of dry powder inhalers in asthma

Other than patient preference and potential cost differences, I can think of no disadvantages to offering this technology as an alternative to current technologies.

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.

I am unaware of any additional information not already in the general public domain.

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)?

Although current technologies in Cystic Fibrosis are effective with significant increases in patient survival over recent years, this comes at a cost to the patient of being increasingly isolated and over burdened with unpleasant, time consuming technologies which in themselves have become prone to post-code prescribing due to lack of central guidance. Implementation of NICE guidance in support of this new technology would provide unquestionable benefit to CF patients in promoting patient-centered treatments that are safe, easier and faster to administer than current technologies and require less education and training, with no requirement for additional equipment, facilities or monitoring.

Dr R I Ketchell