Appendix G - professional organisation submission template

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Tolvaptan for treating autosomnal dominant polycystic kidney disease

Thank you for agreeing to make a submission 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 submission, 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.

Your name:

[redacted]

Mobile number [redacted]

Name of your organisation:

[redacted] NHS Trust

I am a consultant nephrologist employed by the [redacted] NHS Trust based in the [redacted] in [redacted]. I have a special interest in genetic renal disease and a particular interest in autosomal dominant polycystic kidney disease (ADPKD). I completed a PhD in the Department of Medicine in [redacted] on the molecular biology of ADPKD and now run a specialist clinical service for patients with this condition. I have been local principle investigator for the TEMPO ¾ trial of tolvaptan in ADPKD in my hospital.

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

Autosomal dominant polycystic kidney disease (ADPKD) is a common single gene disorder affecting between 1:1000 and 1:2000 of the population. The disease is associated with the development of renal cysts which enlarge and proliferate throughout life culminating in end stage renal failure. Renal failure can occur at any age but typically occurs in middle age. ADPKD accounts for about 10% of cases or renal failure requiring renal replacement therapy in the UK.

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?

Currently there is no specific disease-modifying treatment available for ADPKD. Treatment for ADPKD is therefore based in standard and generic approaches for the management of chronic kidney disease (CKD). NICE guidelines on CKD management are typical of this approach. Management strategies will include blood pressure control, cardiovascular risk factor modification, renal anaemia management, renal bone disease management and ultimately preparation for renal replacement therapy in the form of dialysis or renal transplantation.

Most renal units do not have a disease specific approach for the management of ADPKD and no specific ADPKD guidelines are widely used. Most renal units do not have specific care pathways for ADPKD and do not separate ADPKD patients into specialist clinics. Very few units routinely offer formal genetic counselling in conjunction with clinical genetic services.

The unstructured way in which ADPKD is managed in UK renal units is a consequence of the lack of any disease specific therapies. The introduction of an effective disease specific therapy such as tolvaptan would require renal units to develop specialist pathways for ADPKD management.

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?

Patients with ADPKD have a diverse phenotype. Some have very mild disease with well preserved or normal renal function and may never develop end stage renal failure. These patients will benefit least from tolvaptan. Some have more aggressive disease with rapid renal enlargement and renal failure at a young age. These patients would benefit most from tolvaptan. A minority of patients have severe cystic liver enlargement requiring input from hepatology and liver transplantation services. Whether these patients would benefit from tolvaptan is uncertain.

Based on the available evidence, patients most likely to benefit from tolvaptan are those with significant renal enlargement who are demonstrating early biochemical signs of declining renal function. The risk of tolvaptan therapy is modest in all patients and can be mitigated by careful monitoring foe evidence or liver toxicity. The inconvenience of tolvaptan therapy for patients is not to be underestimated however. Patients taking tolvaptan develop significant polyuria and require a high water intake to compensate. Taking tolvaptan therefore has significant quality of life implications for patients.

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)?
In my opinion this therapy should only be used in secondary care. The safe and effective use of tolvaptan in ADPKD would require units to develop ADPKD specific care pathways and resourced clinical services. In practice this would probably mean the establishment of ADPKD clinics with support from a clinical nurse specialist.
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?
This treatment is not currently available for the treatment of ADPKD.
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.
There are no useful ADPKD clinical guidelines that I am aware of.

<u>The advantages and disadvantages of the technology</u>

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?
There is currently no ADPKD disease specific treatment available.
The practical challenges of treating ADPKD with tolvaptan will be;

Patient selection
Drug tolerability due to polyuria and thirst
Monitoring for hepatotoxicity
Monitoring response to therapy
Determining when to discontinue treatment

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.
In my opinion treatment with tolvaptan should be considered in adult patients with significantly enlarged kidneys on clinical examination or imaging and whose renal function is starting to decline. I would not recommend specifying a numerical value for a renal volume threshold for starting treatment. Accurate renal volume measurements are difficult to obtain and are only loosely associated with prognosis. I would recommend that patients are selected for treatment by accurately assessing solute clearance at baseline and during follow-up. Patients should be demonstrating evidence of early decline in solute clearance but must still have enough renal function to make disease modifying therapy worthwhile. There would be little benefit in treating a patient with stable normal renal function or patients with advanced renal failure. Patients most likely to benefit are those whose renal function is just starting to decline.

Monitoring and assessing response is a major challenge. I would recommend that each patient has renal solute clearance monitored annually, perhaps using an accurate test such as isotopic GFR or iohexol clearance. Assessment of response cold then be based on rate of decline of renal function. Monitoring of renal volume is much less likely to be clinically useful.

I**f 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?**

There is only one published report of benefit of tolvpatan which is based on the TEMPO3/4 study. Patients enrolled in this study did reflect typical UK ADPKD patients.

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 main side effect of tolvaptan is predictable given its mode of action to increase urinary free water clearance. All patients taking tolvaptan develop increased urine output and have an impaired ability to concentrate the urine. Patients report polyuria and nocturia with urine outputs usually between 5 and 10 litres per day. In some patients this limits the tolerability of the drug. Normal homeostatic mechanisms cause patients to become thirsty and increase their fluid intake to compensate for the increased urine output. The benefit of tolvaptan on retarding the decline in renal function needs to be balanced against the inconvenience to patients of mainlining this high urine output and fluid intake. There is a theoretical risk of dehydration with tolvaptan if adequate water intake is not maintained although this has not proven to be a problem in clinical practice. Discontinuation of tolvaptan results in the restoration of normal renal water handling within 24 hours.

The main unpredicted side effect of tolvaptan in TEMPO3/4 was derangement of liver function tests which occurred in 6% of patients. This was reversible in all cases on discontinuation of the drug. This side effect will require a specific monitoring strategy to be in place during clinical use.

No other clinically significant side effects have been noted in use.

<u>Any additional sources of evidence</u>

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.
There is no data available for the utility of tolvaptan for the treatment of ADPKD in humans other than that derived from the TEMPO3/4 study and held by Otsuka. There is reasonable data defining the natural history of ADPKD in affected populations which demonstrate the wide intra-individual variability of the phenotype of the condition.

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)?

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.

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