Professional organisation statement template

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
Primary Care Cardiovascular Society

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.)? ✓
    - GPwSI representative of Primary Care Cardiovascular Society
- 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.

Current treatment is largely driven by symptoms as studies like AFFIRM, RACE etc have not demonstrated a difference between rate and rhythm control, However these studies had considerable flaws such as high crossover rateds and inadequate stroke prophylaxis particularly in the rhythm control arms. Also sinus rhythm was associated with reduced mortality in AFFIRM. Younger individuals with lone AF tend to be treated with rhythm control as sugg. by NICE AF guidance but longterm data is missing.
The most effective rhythm control agent is Amiodarone but this is dogged by serious potential side effects which makes it particularly unattractive in younger individuals and tends to be reserved for situations when other anti-arrhythmics are contraindicated like in structural heart disease and older people. Class Ic agents are preferable in younger individuals with structurally normal hearts and are safe in this setting. Soatalol is another agent which can be used in structurally normal hearts or in coronary heart disease. All drugs have limited effectiveness. All drugs are off patent. The second line treatment is catheter ablation. Rhythm control is recommended with the use of beta-blockers, non-dihydropyridine calcium channel blockers and digoxin or a combination thereof. Amiodarone is also used for rate control but only in very limited circumstances. Second line treatment is AV node ablation and pacemaker implantation.
No treatment has been shown to reduce cardio-vascular or all cause mortality. No treatment has been assessed in terms of reduction of hospital admissions.

Variation: considerable variation in practice between centres and clinicians mainly in the perseverance of rate control and the use of catheter ablation.

Subgroups: NYHA class IV heart failure patients with significantly reduced LVSDF should be excluded as ANDROMEDA was discontinued early due to increased cardiovascular mortality mainly due to worsening heart failure. NYHA class II and III with LVSDF <45% (but only 4% <35%) were successfully included in ATHENA. Permanent AF was not studied in ATHENA.

Setting: use of this drug is likely to be in secondary and tertiary care as well as specialist community clinics at least until it becomes a well established treatment with a proven safety record. No additional training required.

No previous use in NHS setting apart from research.

Current guidelines: NICE 2006
ACC/ AHA/ESC 2006

Rate vs rhythm control guidance based on various randomised controlled trials.Recommendation on AF in heart failure was speculative and further evidence has emerged which again did not show superiority of rhythm control in this setting either.
Recommendation on the use of anti-arrhythmic drugs was largely guided by the adverse effect profile of the various agents and limited efficacy.

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?

So far Dronedarone has been shown to modestly reduce time to recurrence of AF compared with placebo (EURIDIS and ADONIS). At 12 months 64% on Dronedarone and 75% on placebo had recurrences. It also reduces ventricular rate at rest and exercise with or without concomitant rate limiting agents (ERATO).
ATHENA showed a reduction in the combined primary endpoint of admission due to cardiovascular events or death in non-permanent AF by 24%. The latter was driven predominantly by reduction in hospital admissions due to atrial fibrillation but there was also a significant reduction in cardiovascular deaths mainly due to a reduction in arrhythmic deaths but the absolute number was small.
A post-hoc analysis of ATHENA also showed a reduction in non fatal strokes but although presented at various high profile meetings like the ESC in Munich data have not been published in peer reviewed journals. Therefore this should not be taken into account for the purpose of this review.

There was a high discontinuation rate in ATHENA of 30% with adverse effects of 12.7% vs 8.1% with placebo (rest due to patient request and use of disallowed anti-arrhythmic drugs). The adverse effects which were significantly more common were gastrointestinal side effect and skin rashes.
On a positive note there were no observed adverse events secondary to torsades in any trial as far as I am aware despite QT prolongation. Also the feared complications associated with Amiodarone in the form of thyroid dysfunction and pulmonary fibrosis were no more common with Dronedarone compared with placebo. However the longest study period of all Dronedarone trials was 21 months and this might not be long enough to observe particularly lung fibrosis.
ANDROMEDA investigated Dronedarone in non-permanent AF and heart failure due to systolic dysfunction. This trial of 600 patients was discontinued early after only a mean follow-up period of two months due to excess mortality in the heart failure group. This was mainly due to worsening heart failure in the group with the most severely reduced systolic function. However the absolute numbers were small 25 vs 12.

One trial has directly compared Dronedarone with Amiodarone (DIONYSOS) in a short 6 months trial of 500 patients in persistent AF. Although this trial has not been published in a peer review journal the results have been made widely public by the manufacturer. 36% of patients on Dronedarone and 24% of patients on Amiodarone had a relapse of AF. 83 patients on Dronedarone reached the main safety endpoint and 107 on Amiodarone. Gastrointestinal side effects were more common with Dronedarone and pulmonary, thyroid and neurological adverse effects were more common with Amiodarone.
Piccini et al (JACC 2009) have carried out a meta-analysis of randomised controlled trials and compared indirectly Amiodarone with Dronedarone. It was estimated that

for every 1000 treated patients with Dronedarone 228 more patients would suffer recurrence of AF in exchange of 9.6 fewer deaths and 62 fewer adverse events causing discontinuation compared with Amiodarone.
No comparative data exists on Dronedarone vs class Ic antiarrhythmics and Soalol. The efficacy in atrial fibrillation of these drugs is inferior to that of Amiodarone and I speculate that the efficacy will be comparable to Dronedarone.

The FDA has granted a licence for the maintenance of sinus rhythm in patients with atrial fibrillation but not for prevention of cardiovascular events or death.
The European Medicines Agency has recommended Dronedarone in September 2009 to be granted a licence for the prevention of AF in patients with non-permanent AF and for the control of ventricular rate.

In my opinion four factors need to be taken into account when suggesting a guideline recommendation for Dronedarone:

- Long-term safety is not proven yet although current evidence suggests few serious adverse events.
- Limited efficacy in the maintenance of sinus rhythm.
- Significant reduction in hospital admissions.
- Increased mortality in patients with heart failure and severely reduced systolic function.

Dronedarone should be considered for patients in non-permanent AF and who do not have heart failure with a wall motion index of less than 1.
On current evidence and despite the lack of longterm data I would suggest that Dronedarone should be made available to patients not suitable for class Ic drugs as a first line agent alongside Amiodarone in view of the superior adverse effect profile.

Dronedarone would appear to be a sensible 2nd line agent in patients suitable for class Ic anti-arrhythmics.

Dronedarone should be used as a third line agent or in addition to beta-blockers, non-dihydropyridine calcium channel blockers and digoxin.

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)?

If Dronedarone is prescribed in secondary care and specialist clinics it is unlikely that further training is required. It might have an impact on the number of patients choosing a rhythm control strategy. The number of cardioversions has been steadily falling in many localities and an increase might be seen as a result of Dronedarone.

As Dronedarone has been shown to reduce hospital admissions mainly secondary to atrial fibrillation a coast analysis of its use will be useful but unfortunately I do not have any expertise in this field. Also any data must be viewed with caution as other agents have not been explicitly investigated in this regard.