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Norwegian Institute of Public Health

REPORT

2018

# A SINGLE TECHNOLOGY ASSESSMENT:

## The MicraTM Transcatheter Pacing System, a leadless pacemaker, in patients indicated for single-chamber ventricular pacemaker implantations

**Title** The MicraTM Transcatheter Pacing System, a leadless pacemaker, in patients indicated for single-chamber ventricular pacemaker implantation: A single technology assessment

**Norwegian title** MicraTM Transcatheter Pacing system, en pacemaker uten ledning, til pasienter som behøver en enkel-ventrikkel pacemaker: En hurtigmetodevurdering

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Norwegian Institute of Public Health (NIPH)

Oslo, June 2018

# Bakgrunn, formål og konklusjon - Norsk

## Bakgrunn

Pacemakerimplantasjon er en effektive og nødvendig behandling for pasienter som har kronisk atrieflimmer og bradykardi.

I denne metodevurderingen har vi vurdert en ledningsløs pacemaker for pasienter med behov for 1-kammer pacemakere.

## Formål

Formålet har vært å undersøke den kliniske effekten, sikkerheten samt kostnadseffektiviteten for Micra™ Transcatheter Pacing System (Micra TPS) i pasienter som har behov for 1-kammer pacemakere.

Vi har definert to alternative pasientgrupper som kan ha fordel av en pacemaker som fører til lavere frekvens av komplikasjoner.

1) Alle pasienter med behov for 1-kammer pacemakere
2) Pasienter med behov for 1-kammer pacemakere, men som i tillegg har høyere risiko for komplikasjoner etter pacemakerimplantasjon

## Konklusjon

Micra TPS er en ledningsløs pacemaker som leverer elektriske impulser, og har en batterilevetid, i henhold til produsentens spesifikasjoner.

Forskningsresultatene kan ikke bevise at pasienter som får innsatt Micra TPS får færre komplikasjoner enn de pacemakerne som normalt brukes. Men Micra TPS er ledningsløs og i seg selv betyr dette at alle komplikasjoner som er relatert til ledning og lomme, som er rapportert til å være 2.5-5.5% av pasientgruppen (1;2). Videre er det bare rapportert fire dødsfall relatert til utstyret eller systemet i 1 575 implanterte pasienter.

Vi undersøkte budsjettkonsekvensen for å introdusere Micra til alle pasienter som trenger 1-kammerpacing, hvilket vil gi en økning av totale kostnadene til denne pasientgruppen på NOK 27,386,992 ved år fem. ICER for denne gruppen ble beregnet til å være langt over hva som er vurdert kostnadseffektivt i Norge.

Som beskrevet i formålet, definerte vi en undergruppe av pasienter som pasienter med høy risiko for komplikasjoner, og spesifikt dem med høy risiko for infeksjoner. Denne gruppen er i Norge vurdert til å være 10-30% av alle pasienter med indikasjonen. Budsjettkonsekvensanalysen viste at ved å tilby Micra TPS for denne undergruppen vil de totale kostnadene øke med NOK 4,652,759 ved år fem. Heller ikke for denne gruppen vurderes ICER å være kostnadseffektiv.

# Executive summary

## Background

Permanent cardiac pacing using pacemaker implantation is an effective and necessary treatment for patients suffering from atrial fibrillation and bradycardia.

In this single technology assessment, we assessed a leadless pacemaker for patients indicated for single-chamber ventricular pacemaker implantation. Through design and novel technology, Medtronic's ambition is to reduce the rate of complications following pacemaker implantations.

## Objective

The objective was to investigate the clinical efficacy, safety and cost effectiveness of Micra™ Transcatheter Pacing System (Micra TPS) in patients indicated for single-chamber ventricular pacemaker implantation.

We defined two alternative patient groups that may benefit from a pacemaker which can demonstrate a lower frequency of complications.

3) All patients recommended for single-chamber ventricular pacing
4) Patients recommended for single-chamber ventricular pacing, but who are at high risk for complications following pacemaker implantation.

## Methods

### Clinical efficacy and safety

We conducted a systematic review of the clinical efficacy and safety of the Micra TPS. The study population, intervention, comparator and outcomes (PICO) were identified in agreement with external experts and the submitter. We performed a systematic literature search to identify studies meeting our inclusion criteria. We critically appraised included studies using the Risk of Bias-tool, descriptively summarized the outcome data, and evaluated the certainty of the overall results using Grading of Recommendations Assessment, Development and Evaluation (GRADE).

We also critically assessed the documentation submitted by the manufacturer to evaluate information not retrieved by our literature search.

### Health economics

We assessed cost-effectiveness estimates provided by the submitter of Micra leadless pacing compared to a conventional pacing systems for patients recommended for single-chamber ventricular pacing who were at high risk for infections. A straight-forward Markov cohort model was used to estimate the cost-effectiveness of the new technology compared with current practice over a 10-year time horizon, for patients aged 77. The submitted model covered the most important health outcomes and costs associated with the pacing systems. The submitter considered variations in outcomes and costs depending on which pacing system a patient receives.

We performed a separate analysis where we adjusted some of the input variables based on revised assumptions. We also ran a scenario, which was not performed by the submitter where we considered the total indicated patient population.

## Results

### Clinical efficacy and safety

We identified three large multisite clinical trials with a total of 7 published articles, and three additional articles which presented single site case series with a small number of patients. All studies were prospective single-arm studies and were considered to have a high risk of bias.

The efficacy endpoints in the studies were electrical parameters and battery longevity. The results showed that after implantation, the Micra device had a pacing threshold according to the reference values (≤ 1V at 0.24 ms) in 93% and 97% of the patients, 12 and 24 months after implantation, respectively. Other electrical parameters such as pacing impedance and R-wave amplitude, as well as estimated battery longevity were shown to be consistent according to the reference values. We evaluated the technical measurements to be of low certainty due to the study design.

Safety endpoints were major clinical- and device-related complications. The two largest studies, the Micra TP Study and the Micra TPS CA Study Protocol, reported that 4% and 1.5% of patients receiving an implant had complications, respectively. These studies reported four device or system related deaths in the total population of 1 575 patients.

The complication rate was found to be lower than a historical control. However, we evaluated the evidence for this comparison to be of very low certainty, due to study design (single arm) and indirectness.

### Health economics

The calculated incremental cost-effectiveness ratio (ICER) based on the revised economic model for all patients recommended for single-chamber ventricular pacing, is more than 1 million NOK per QALY. The total added costs of implementing Micra to this group in Norway, would be NOK 27,386,992 in year five.

According to the objective, we also aimed to perform budget impact analyses on a sub-group of patients with high risk of complications. The submitter performed a budget impact analysis on this cohort, estimated to be 80 patients in a Norwegian setting. They estimated the total cost saving of implementing Micra to patients at high risk for complications to be NOK 724,656 in year five.

The external experts suggested that the sub-group of patients with high risk of complication would be about 10-30% of the patients with the indication in Norway. We recalculated the budget impact analysis and estimated that the total added costs of implementing Micra to patients at high risk for complications would be NOK 4,652,759 in year five. The calculated incremental cost-effectiveness ratio (ICER) based on the revised economic model for the sub-group of patients at high risk for infections was NOK 1,077,363. For this sub-population, the Micra system cannot be considered cost-effective if a threshold of NOK 500,000/QALY is applied. The performed one-way sensitivity analyses shows that relative risk of infection, the lead infection rate, the pocket infection rate and the lead infection costs have the greatest impact on the model.

## Discussion

### Clinical efficacy and safety

The efficacy of the Micra device was measured through electrical parameters and estimation of battery longevity. The results were within the reference values given in the manual of the device and although the study design was single-arm cohort studies, we have reason to believe that the device proved its efficacy.

It is more problematic to compare the safety profile, or complication rate, of different devices only using a historical control, as in one of the major studies included in this assessment. We therefore did not have confidence in the comparative analyses presented to us through the available literature. We do acknowledge the actual numbers of complications reported in the different studies, keeping in mind the possible reporting bias and bias due to the connection between the researchers and the producer of the device.

However, we need to take into consideration the reported rate of lead and pocket complications, the most frequent complications for standard pacemakers, which obviously are not an issue if a leadless pacemaker is used.

### Health economics

We did not find any published economic evaluations of leadless pacemakers. However, we did not perform a systematic search of studies comparing the two types of pacemaker devices in the specific sub-group analysed in this report. The effect estimates in the economic model are therefore highly uncertain which made it difficult to make any general judgements about the potential cost-effectiveness of the intervention. The exception is that the rates of lead and pocket infection and erosion for a conventional device are likely to have a significant impact on the results. Additional benefits for a leadless pacemaker have been suggested by CADTH in an evidence summary for leadless pacemakers from 2015 (3), including shorter procedure and recovery time, reduced fluoroscopy exposure for patients and staff, no visible lump or scar, better mobility in the shoulder and expected better quality of life. These benefits were however, not quantified and evidence has not been assessed.

Despite the shortcomings of the present report, this is the first economic evaluation being performed of a leadless pacemaker, and is for the Micra device only. Any inference to other leadless pacemakers, such as the Nanostim, should not be done. There is consequently a need for further research on implications of leadless pacemakers on the health economy.

## Conclusion

The Micra TPS is a leadless pacemaker which delivers consistent pacing as required and has a battery longevity according to the specifications for the device. The current evidence is not sufficient to prove that the Micra-TPS has fewer complications than standard pacemakers. However, the device is leadless and hence avoids all complications related to lead and pocket, which are previously reported to be in the range of 2.5-5.5% in the patient group (1;2). Published device or system related deaths were four in 1 575 implanted patients.

We looked at the budget impact of introducing Micra to all patients indicated for single chamber ventricular pacing and found that this would be a total added cost of NOK 27,386,992 in year five. The ICER for this group rises well above the level that has been considered cost-effective in Norway.

Offering the Micra device only to patients particularly susceptible to complications or who have a defined high risk of complications, may be an alternative model. Although there was no clinical evidence that the Micra may be beneficial to any specific sub-group of patients, we decided to analyse the cost-effectiveness for offering the Micra device to patients with a high risk of complications, and more specifically, with a high risk of infection. This group was estimated to be 10-30% of the total indicated patients. The analysis shows that the total added cost will be about NOK 4,652,759 in year five, by introducing Micra to this group in a Norwegian setting. After adjusting the model to account for important shortcomings in the submitted analysis, related to clinical effect input data, the ICER is considered to be not cost-effective for this sub-group.

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# Preface

A single-technology assessment is one of a series of health technology assessment (HTA) products that can be mandated in "The National System for Managed Introduction of New Health Technologies" within the Specialist Health Service in Norway (https://nyemetoder.no/).

Within this system, the Ordering Forum RHA ("Bestillerforum RHF"), where the four Regional Health Authorities are represented, evaluates submitted suggestions and decides on which technologies should be assessed and the type of assessment needed. In a single-technology assessment, the technology (a pharmaceutical or a device) is assessed based on documentation submitted by the company owning the technology, or their representatives ("the submitter").

The HTA unit of the Norwegian Institute of Public Health (NIPH) receives and evaluates the submitted documentation, but is not the decision-making authority. Single-technology assessments conducted at NIPH are published on our website (www.fhi.no) and on https://nyemetoder.no/

Following persons were involved in the process of making this single-technology assessment:

| Role | Name |
|---|---|
| Project coordinator | Beate C. Fagerlund |
| Health economist | Beate C. Fagerlund<br>Espen Movik |
| Efficacy and safety evaluator | Torunn Elisabeth Tjelle, PhD<br>Liv Giske, PhD<br>Ida Kristin Ørjasæter |
| Research librarian | Ingrid Harboe<br>Elisabeth Hafstad |
| Department director | Lene K. Juvet |
| External clinical expert | Ole Christian Mjølstad, MD, PhD, Senior consultant, Clinic of Cardiology, St Olavs Hospital<br>Reidar Bjørnerheim, MD, PhD, Head of Echocardiography unit, Oslo University Hospital |
| Submitter | Medtronic, contact person: Benny Borgman |

The aim of this report is to support well-informed decisions in health care that lead to improved quality of services. The evidence should be considered together with other relevant issues, such as clinical experience and patient preference.

| Kåre Birger Hagen | Lene K. Juvet | Beate C. Fagerlund |
|---|---|---|
| *Scientific director* | *Department director* | *Project coordinator* |

**Progress log**

| Date | Correspondence |
|---|---|
| May 5, 2016 | Publication of horizon scanning report on this device |
| June 13, 2016 | The commissioning forum commissioned a single technology assessment |
| Sept 2016 – April 2017 | Dialogue and meeting with technology manufacturer |
| January 2017 | Experts asked |
| June 2017 | Valid submission acknowledged |
| March 3, 2018 | Norwegian Institute of Public Health external review process |
| March – April 2018 | Norwegian Institute of Public Health internal review process |
| May 9, 2018 | Feedback from technology manufactory on the report |
| May 18, 2018 | Report Submitted |
| June 14, 2018 | Report available at FHI website |

# Objective

The objective was to investigate the clinical efficacy, safety and cost effectiveness of Micra™ Transcatheter Pacing System (Micra TPS) in patients indicated for single-chamber ventricular pacemaker implantation.

We have defined two alternative patient groups that may benefit from a pacemaker which can demonstrate a lower frequency of complications.

1) All patients recommended for a single-chamber ventricular pacing
2) Patients recommended for single-chamber ventricular pacing, but are at high risk of complications following a pacemaker implantation.

# Background

Permanent cardiac pacing by the implantation of a pacemaker is an effective and necessary treatment for patients suffering from atrial fibrillation and bradycardia. The purpose of cardiac pacing is to provide an appropriate heart rate and heart response to re-establish an effective circulation and normalize the haemodynamic that are compromised by a slow heart rate.

Conventional pacing systems consist of a pacemaker device containing the electronics and battery typically implanted in a subcutaneous pocket in the chest region, and one or two leads from the device pocket through the veins and into the heart. Since their introduction in the 1960s, pacemakers have steadily shrunk in size and grown in sophistication, yet their components remained the same.

Two recent studies report a high frequency, 12.4%(1) and 9.5% (2), of patients experiencing short term complications after a pacemaker implant. One of the most reported of this type of complications is related to the pacemaker leads (1).

Reducing complication rates for pacemaker patients will be beneficial in particular for patients who for different reasons will not tolerate complications. Making a leadless pacemakers is therefore a relevant approach to reduce the rate of complications experienced by the patients.

There are two available leadless pacemakers newly available; the Micra™ Transcatheter Pacing system from Medtronic Inc, and the Nanostim™ from St. Jude Medical. In the present report we will only assess the Medtronic device.

## The technology

**Name of device system:** Micra™ Transcatheter Pacing System (Micra TPS)

**Name of the technology:** Medtronic Micra MR Conditional single chamber implantable transcatheter pacing system

**Manufacturer which submitted the application and provided the documentation package**: Medtronic Norge AS, Martin Linges Vei 25.

*(Information from submitter's document package)*

The Medtronic Micra Model MC1VR01 MR Conditional single chamber implantable transcatheter pacing system is a programmable cardiac device that monitors and regulates the patient's heart rate by providing rate-responsive bradycardia pacing to the right ventricle.

The device senses the electrical activity of the patient's heart, using the sensing and pacing electrodes enclosed in the titanium capsule of the device. It monitors the heart rhythm for bradycardia and responds to bradycardia by providing pacing therapy based on the pacing parameters programmed. The device provides rate response, controlled through an activity based sensor. It also provides diagnostic and monitoring information for guidance in the pacing system evaluation and in patient care.

## Regulatory status (CE-marking) and market access of the technology

*(Information from submitter's document package)*

Micra TPS received CE Mark approval on April 14, 2015 based upon early performance results of the first 60 patients at 3 months. Micra TPS was approved by the Food and Drug Administration (FDA) on April 6, 2016. The indications for use of Micra TPS are the same indications as for single-chamber ventricular pacemakers.

It is registered as a Medical device class III to treat symptomatic bradycardia.

In Norway, Haukeland University Hospital, Department of Heart Disease, Bergen and St. Olav, Trondheim University Hospital, Clinic of Cardiology, participate in one of the Micra TPS studies (4).

## Description and use of the technology

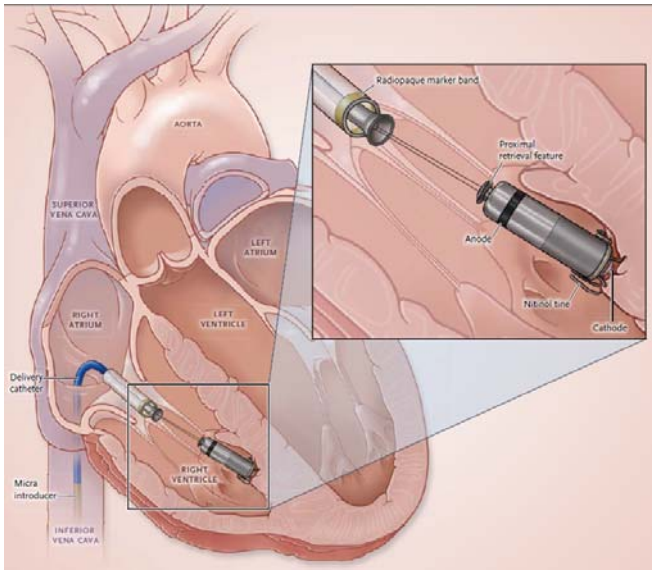
### Micra™ Transcatheter Pacing System (Micra TPS)

*(Information from submitter's document package)*

The Micra is a miniaturized (0.8 cc), leadless, full featured single chamber ventricular pacemaker that is implanted directly in the right ventricle (*Figure 1*). The Micra TPS is comprised of a delivery system, an introducer, and the pacemaker device (Micra). The Micra is delivered to the heart via the femoral vein using an introducer and delivery tool. The Micra is deployed from the delivery system, allowing its fixation tines to engage into the cardiac tissue. Micra provide rate responsive pacing as well as automated pacing capture threshold management to maximize battery longevity. Patients with an implanted Micra have access to a MRI scan, allowing for full body scans at 1.5T and 3T (Surescan). Importantly, the Micra provides the option to be

programmed to Device Off mode, permanently disabling pacing and sensing, allowing it to remain in the body beyond its useful life without inappropriate interaction with concomitant device therapy. For cases when percutaneous retrieval is needed, Micra TPS has a retrieval feature.

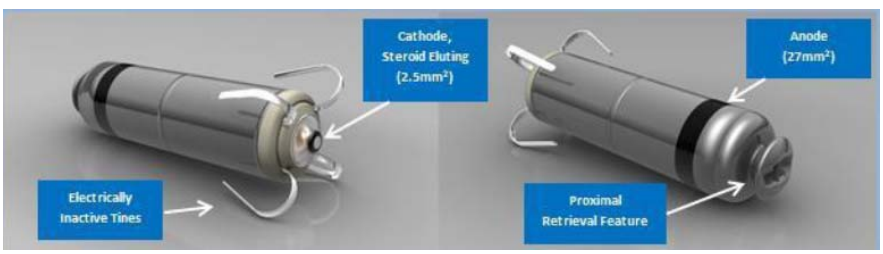
***Figure 1.*** *Micra TPS positioned in the right ventricle. Figure is taken from Reynolds et al (5).*




### *Pacemaker device*

The Micra Model MC1VR01 is a miniaturized, single chamber transcatheter pacemaker that provides bipolar sensing and pacing in the right ventricle. The device has an active fixation mechanism consisting of 4 electrically inactive tines designed to anchor it in the cardiac tissue at the implant location in the right ventricle. In order to develop a device 93% smaller than conventional pacemakers, extensive miniaturization efforts were required, specifically for the battery which is the largest single component of the Micra device. Medtronic created new electronics and, using proprietary chemistry, a downsized hybrid high-energy density battery. The result is a device 2.8 mm in diameter and 25.9 mm long that is self-contained in a hermetically enclosed capsule (*Figure 2*).

***Figure 2.*** *The Micra Implantable Device*



### *Micra Introducer*

The Micra Introducer is a single-use, disposable, hydrophilic coated sheath that provides a flexible and hemostatic conduit for the insertion of the Micra device (*Figure 3*). The introducer system is comprised of 2 components: a dilator which accommodates a 0.035 in (0.89 mm) guide wire, and an introducer sheath. The introducer is comprised of a hydrophilic, coil-reinforced sheath that is attached to a rigid seal housing containing the hemostatic valve assembly. A side port extension with a 3-way valve is permanently attached to the seal housing. A radiopaque marker band is located at the distal tip of the sheath. The Micra introducer also has a suture loop for attaching it to the patient.

***Figure 3.*** *The Micra Introducer*

### *Delivery Catheter*

The single use Micra transfemoral catheter delivery system consists of the delivery catheter required to deliver, deploy, and test the Micra device placement (*Figure 4*). It is constructed of two braided shaft assemblies, one placed inside another and attached to a handle at the proximal end. The distal end of the system can be articulated by activating a button on the handle. The Micra device sits inside a cup at the distal end of the catheter and is deployed by activating a button on the handle. The Micra device is locked to the delivery system by means of a tether that goes through the proximal end of the device, through the braided shafts to the handle, and can be released (or locked) by means of a button on the handle. The delivery system is used in conjunction with the introducer sheath.

***Figure 4.*** *Transfemoral Delivery Catheter*

### *Retrieval Tool*

The Micra proximal retrieval feature allows for retrieval of the device pre-encapsulation with commercially available off the shelf tools. The following sterile system

components and accessories are required to retrieve and reposition the implanted device:

- Micra Introducer
- Micra Model MC1VR01 transcatheter pacing system
- Device retrieval snare that is 175 cm long or longer with a 4 French or smaller outer diameter

If the device needs to be repositioned after removing the tether during the initial implant procedure, the original introducer and delivery system can be used.

Generally Micra does not need to be explanted as it can be turned off and an additional Micra can be added or another device (e.g. an upgrade) can be implanted. The device is expected to be fully encapsulated at the end of the battery longevity and the device would be permanently programmed to Device OFF, which allows for an additional Micra or transvenous therapy to be added for the patient. Micra takes up <1% of the volume of a normal right ventricle. The right ventricle and trabeculation will likely accommodate at least 3 devices.

***Novelty of the technology***

*(Modified information from submitter's document package)*

The Micra TPS differs from conventional pacemakers (from Medtronic) in the following points:

- Electrodes are placed directly on the pacemaker capsule, allowing the device to directly stimulate the ventricle
- It is small and can be implanted directly into the ventricle, therefore no leads are needed
- Longer battery life (estimated to be until 14.9 years)
- New technology concerning electronics, capacitor, battery, and mechanical design and configurations
- Implanted through the femoral vein
- Novel fixation mechanism (FlexFixTM Tines)
- Conducting hourly safety margin confirmation to ensure pacing outputs remain at safe levels
- End-of-Service operation: Micra can be permanently programmed OFF (to OOO mode) to shut off the pace and sense features. In addition, when battery voltage reaches a certain level, the device permanently deactivates pacing and sensing and switches to the device OFF to OOO mode
- Lower risk of infection and any complications due to lead and pocket is totally eliminated due to the nature of the technology.

## Description of the context of use

### Indication

*(Information from submitter's document package)*

A normal heartbeat begins as an electrical impulse, typically generated at the sinus node, which travels along a conduction pathway. The atrioventricular node regulates the timing between the upper (atrial) and lower (ventricular) chambers of the heart. Parts of this conduction pathway can stop working as they should, resulting in an abnormally slow heart beat—or bradycardia.

The two most common forms of bradycardia are related to abnormal function of the sinus node or the atrioventricular node. Sinus Node Dysfunction (SND), occurs when a disease of the heart causes a prevention of the initial impulse generation or a delay of propagation through the atrium. Acquired atrioventricular Block occurs when there is an impairment of the conduction of a cardiac impulse from the atrium to the ventricles.

Symptoms associated with bradycardia include fatigue dizziness, confusion, syncope, angina, and palpitations. Patients with untreated bradycardia exhibit reduced quality of life compared with the general population with comparable age distribution. Quality of life scores are similar to patients entering cardiac rehabilitation programs after suffering a myocardial Infarction, heart failure, angioplasty or cardiac surgery (6).

For symptomatic and non-reversible bradycardia, the only effective treatment is pacemaker therapy that reduces symptoms by maintaining a normal heart rhythm when the intrinsic heart rhythm gets too slow. By delivering electrical stimulus to the heart muscle or myocardium the pacemaker starts a local depolarization process that becomes a self-propagating wavefront of contraction. In order for an electrical pulse from the pacemaker to stimulate (capture) the myocardium, it must be applied with sufficient amplitude and duration. Therapy efficacy is therefore mainly assessed by the pacemaker's ability to deliver such pulses on demand. The minimum required pacing output needed to capture the myocardium is called the pacing threshold. A pacemaker system's threshold values can be measured with a simple test via a device known as a pacemaker programmer. In clinical practice, efficacy or device performance is monitored by health care professionals at regular follow-up visits or by the patients themselves reporting the reoccurrence or onset of bradycardia symptoms.

Pacemaker therapy has been shown to significantly improve quality of life, both in the short and long term and in some instances prolong life (1;6-8). Pacemaker treatment for bradycardia is frequently used, with more than 1 million people worldwide receiving a cardiac pacemaker each year (9).

### Patient group

Single-chamber ventricular pacing is a Class I recommendation for patients with persistent bradycardia, permanent atrial fibrillation, and atrioventricular block. The design of Micra TPS eliminates the need for lead and pocket and may therefore reduce the frequency of complications following a pacemaker implantation. Hence, patients who are particularly susceptible to complications or are at a defined high risk of complications may be benefited by a device with a lower complication rate, and can be identified by different clinical conditions (4). In a Norwegian setting, the rate of patients with such conditions were estimated to be 10-30 % of the total indicated patient population, suggested by the clinical experts.

# Methods – Clinical evaluation

We have assessed available documentation of a novel pacemaker, the Micra Transcatheter Pacing System (Micra TPS) from Medtronic.

According to the submitter, the benefits of Micra TPS are: "Elimination of complications related to leads and pocket; expanded access to the therapy to patients precluded from a conventional device; potential quality of life benefit and patient satisfaction from removal of visible pocket and chest scar".

We have systematically evaluated available evidence to address this issue.

## Literature search and selection

### Inclusion and exclusion criteria

We used the population, intervention, comparison, outcome, and design (PICO-D) framework to evaluate the suitability for inclusion of studies (*Table 1*). Two external experts and the submitter were involved in the process together with the project team, and all agreed to the below PICO-D.

***Table 1**. PICO –D framework*

| | |
|---|---|
| Population | Patients that are indicated for single-chamber ventricular pacing |
| Intervention | MICRA™ Transcatheter Pacing System, Medtronic Inc |
| Comparator | Conventional transvenous pacemaker or no comparator |
| Outcomes | Efficacy<br>- Pacing performance<br>- Battery longevity<br>Safety<br>- Major clinical complications (including death) (defined in text)<br>- Device related complications (procedure complications, perforations)<br>- Pacemaker induced arrhythmia<br>Patient satisfaction |
| Study design | All study designs except single case studies, Health Technology Assessments (HTA). English language |

We excluded animal studies, in vitro studies in cadavers, and abstracts.

### Literature search and identification relevant literature

We performed systematic search for literature to identify studies on Micra TPS on 30. August 2017. The search terms and strategy was tested by two experienced research librarians. Sources of the search, search terms and hits are found in Appendix 2. We also received a literature list from the submitter which was compared to our result. We did not compare the submitters search terms with ours.

Two reviewers (BCF, TET) independently assessed title and abstracts to determine relevant full-text articles to be examined. Subsequently, the same reviewers independently assessed the full-text articles to decide which articles to include in our report.

## Data extraction and analyses

We compared the patient information and study design as well as clinical study numbers from the retrieved articles to avoid duplicate patient cohorts.

We extracted the following variables from the included articles:

- Information about the study (authors, year of publication, setting, study design, clinical trial identification number and funding source)
- Participant characteristics (number of participants in the trial, age)
- Intervention and control characteristics
- Outcome

### Appraisal of methodological quality of studies

Two reviewers (TET, LG) independently appraised the methodological quality of the studies. For studies with a control group, we used the Risk of Bias tool in RevMan. For studies with no control group, we used a checklist for case series from New York Department of Health Evidence-based Review Process for Coverage Determinations (https://www.health.ny.gov/health_care/medicaid/redesign/docs/dossier_submission_form.pdf). We did not critically appraise the single centre case series including less than 50 patients since the quality of such studies will be considered low based solely on the study design and since data from large ( < 500 patients) multi centre studies were available.

### Certainty of the evidence

We (TET, LG) evaluated certainty of the evidence for each outcome by using the GRADE-tool developed by the GRADE working group (10). According to this system,

we categorized the certainty of the documentation for each outcome into four levels: high, moderate, low and very low certainty.

### Presentation of results

We made a narrative summary of the results as the only published data were patient series. Unpublished results presented by the submitter through in the document package were discussed.

## Stakeholder involvement

Initially, the project leader contacted external clinical experts, designated by the Regional Health Authorities, and provided information about the project. We incorporated their experience and knowledge when defining the inclusion and exclusion criteria. The experts agreed to the confidentiality terms and conditions and signed corresponding forms before initiation of the work.

We also read the document package from the submitter (Medtronic) and contacted them when we needed additional information. We used parts of the document package for background information.

Internal experts and external clinical experts read the first draft of the assessment for relevance and other comments and subsequently peer-reviewed the final draft.

# Results – Clinical evaluation

## Literature search and selection

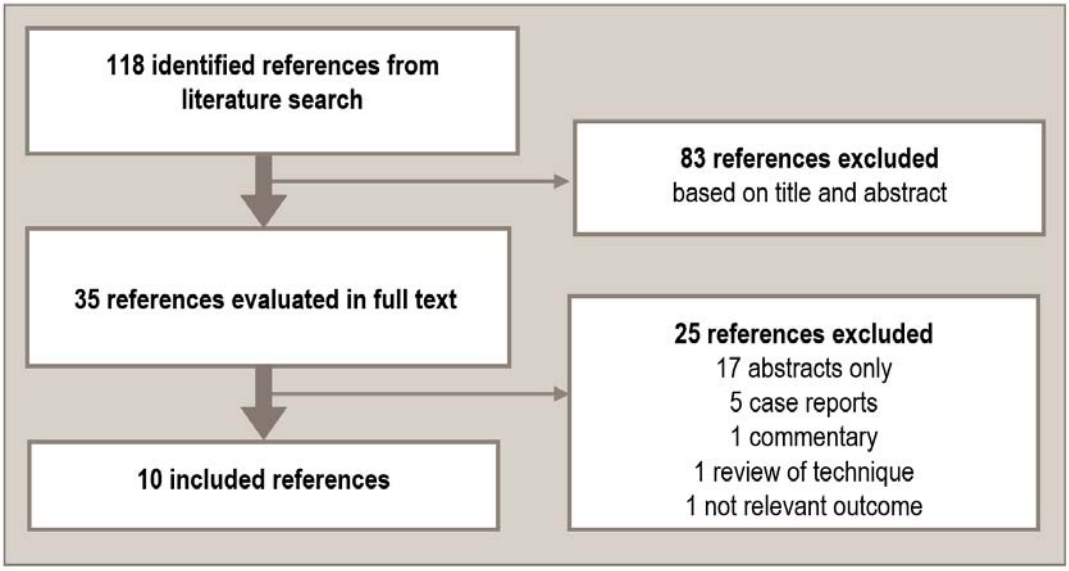
### Literature search and selection

We performed systematic literature search to identify publications evaluating the Micra TPS according to our inclusion criteria.

The search results from the databases are presented in *Figure 5* and Appendix 2. We included 30 references for in full text screening. However, 17 of these were abstracts only and were excluded without any further evaluation. We reviewed the remaining 13 references and found that 10 of them met our inclusion criteria. The excluded references are presented in Appendix 3. (NOTE: We only present excluded full text references. The excluded abstracts are not listed as they were excluded based on the format only.)

The search results from other sources (Appendix 2) identified 4 unique clinical trials, of which three of them presented published results (*Table 2*). The latter clinical trial was not yet recruiting.

***Figure 5.*** *Flow chart of the literature search*



### Literature search and selection from submitter's document package

The submitter performed a systematic literature search described in the document pack. They identified 34 references of which 7 were included. They included both full-text articles and meeting abstracts. We only had 3 overlapping references, probably explained by timing, they performed the literature search 9.November, 2016, while ours were performed 30. August, 2017, and that they included meeting abstracts which we did not. The list of included references of both NIPH and the submitter are presented in Appendix 4.

### Study characteristics

The 10 included references, sorted under the corresponding clinical trials, are listed in *Table 2*. Details about the clinical trials are elaborated below.

***Table 2.*** *Included references, sorted under the corresponding clinical trial*

| References | Participant characteristics (indication, no / age) | Outcome | Comparator |
|---|---|---|---|
| *"Micra Transcatheter Pacing Study (Micra TP Study)"*<br>*A prospective single-arm, multicentre study. NCT02004873.* | | | |
| Ritter 2015 (11) | Class I or II indication for VVI pacing.<br>N=140* / 76.8±9.9 years. | Efficacy (electrical parameters) and safety and after 1.9±1.8 months follow-up. | No control. |
| Reynolds 2016 (5) | Class I or II indication for VVI pacing.<br>N=725* / 75.9±10.9 years. | Efficacy (electrical parameters) and safety at 6 months. | Historical control.<br>N=2667 |
| Duray 2017 (12) | Class I or II indication for VVI pacing.<br>N=726* / 75.9±10.9 years. | Efficacy (electrical parameters) and safety at 12 months. | Historical control.<br>N=2667 |
| Lloyd 2017 (13) | Subset of the study for exercise.<br>N=42* / 75.5±5.3 years. | Adaptive pacing. | No control. |
| Piccini 2017 (14) | Patients with Micra implant having high pacing treshold.<br>N=83* / 75.8 ± 11.0 years. | Describe acute elevated Micra vs conventional transvenous lead thresholds. | Capture study.<br>N=538 |
| *"Micra TP Study" (as above) and*<br>*"Micra Transcatheter Pacing System Continued Access Study Protocol (Micra TPS CA Study Protocol)"*<br>*A prospective single-arm, multicentre study. NCT02488681.* | | | |
| Grubman 2017 (15) | Class I or II indication for VVI pacing<br>NCT02004873: N=720*<br>NCT02488681: N=269 / information not given | Revision experience. | Historical control.<br>N=2667 |
| *" Micra Transcatheter Pacing System Post-Approval Registry (Micra TPS Post approval Registry)"*<br>*A prospective single-arm, multicentre study. NCT02536118.* | | | |
| Roberts 2017 (16) | Patients intended to be implanted with a Micra device.<br>N=795 / 75.2±14.2 years | System- or procedure-related major complications, and electrical performance.<br>30 days post implant. | No control. |
| *Single site studies* | | | |

| References | Participant characteristics (indication, no / age) | Outcome | Comparator |
|---|---|---|---|
| Pachon 2016 (17) | Patients with standard indication for a permanent pacemaker and with a clinical profile and indication appropriate for VVI pacing.<br>N=10 / 77.1±5.1 years | Initial efficacy (electrical parameters) and safety, and at follow up (55 ±33 days). | No control. |
| Da Costa 2017 (18) | Patients contraindicated for or unable to receive conventional pacemaker implantation.<br>N=14 / 75±10 years | Feasibility, efficacy and safety. 3 month follow-up. | No control. |
| Martinez-Sande 2017 (19) | Indication for single-chamber pacemaker implantation.<br>N=30 / 79.4±6.4 years | Efficacy (electrical parameters) and safety after 5.3±3.3 months follow up. | No control. |

** Same patient population. VVI, Ventricle paced, ventricle sensed, pacing is inhibited if beat is sensed*

### *Micra Transcatheter Pacing Study (Micra TP Study)*

The Micra Transcatheter Pacing Study (NCT02004873) is a prospective, nonrandomized, single-study-group, multicentre, international clinical study to evaluate the efficacy and safety of the Micra TPS. The study is ongoing, but not recruiting participants.

Six of the included references present data from this study.

- Ritter et al (20), Reynolds et al (21) and Duray et al (12) presents efficacy and safety results up to 3 months (n=140), 6 months (n=725) and 12 months (n=726) follow up, respectively.
- Lloyd et al (13) presents adaptive pacing in a subset of the patients (n=42),
- Piccini et al (14) presents long-term outcomes in Micra implants with elevated pacing thresholds (n=83) at implantation and compare them to a cohort from a contemporary study design to assess pacing thresholds in EnPulse, a dual chamber device from Medtronic (the Capture study) (22).
- Grubman et al (15) presents implant retrieval data in a subset of the patients from this trial and the Micra TPS CA Study Protocol (see below).

The Micra TP Study enrolled patients who met class I or II guideline-based indication for pacing (i.e., for bradycardia due to atrial tachyarrhythmia, sinus-node dysfunction, atrioventricular node dysfunction, or other causes), were considered to be suitable candidates for single-chamber ventricular demand (VVI) pacing, were not prevented from participating as a result of coexisting conditions, and provided written informed consent. Patients with an existing pacemaker or implantable cardioverter-defibrillator were not included in the study. The study planned to implant 720 patients at up to 70 centres worldwide. The main endpoints were efficacy, as

measured by electrical parameters (pacing threshold, pacing impedance, R-wave), and safety, as measured by complication rate, and adaptive pacing. Adverse event evaluation was planned to be at 1, 3, 6 and 12 months, and then biannually at least until all implanted patients had the opportunity to complete their 12-month visit, at which time the study was closed. The study and its rational is thoroughly described in a separate paper (23). Reynolds et al (5) and Duray et al (12) performed post hoc analyses using a historical control, which was detailed in an appendix of Reynold et al (5).

### *Micra Transcatheter Pacing System Post-Approval Registry (Micra TPS post-approval registry)*

The Micra Transcatheter Pacing System Post-Approval Registry (NCT02536118) is a prospective, nonrandomized, multicentre post-approval release registry, designed to further evaluate the safety and effectiveness of the Micra TPS when used as intended, in "real-world" practice (24). The study is currently recruiting participants.

One of the included references presents data from this study (24).

Patients intended to be implanted with a Micra, were eligible for enrolment in the study. Patients previously implanted with cardiac electronic implantable devices were not excluded, as opposed to the Micra TP Study. The study plans to implant 1830 patients in the study and the enrolment is ongoing (per search in August 2017). Implanted patients are followed in accordance with the standard care. In addition, patient and device status are reported 30 days post implant and at least annually thereafter for a minimum of 9 years.

The main endpoints were efficacy, as measured by electrical parameters (pacing threshold, pacing impedance, R-wave), and safety, as measured by complication rate.

### *Micra Transcatheter Pacing System Continued Access Study Protocol (Micra TPS CA Study Protocol)*

The Micra Transcatheter Pacing System Continued Access Study Protocol (NCT02488681) is a study to allow continued access for the Micra TPS in the United States of America while the device was pending Food and Drug Administration approval. Patients were enrolled under the same conditions and centres as the Micra TP Study. The study is now completed.

One of the included references presents data on patients from this study and the Micra TP Study (15).

***Pachon study (17)***

This study was presented as a letter, reporting experiences with the Micra TPS, performed at Hospital Virgen de la Salud, Toledo, Spain. The study is a case series where the Micra was implanted in patients (n=10) with a standard indication for a permanent pacemaker and with a clinical profile and indication appropriate for VVI pacing. The endpoints were success rate of implantation, details of implantation procedure and electrical parameters.

***Da Costa study (18)***

The study reported experiences with the Micra TPS, performed at the University of Saint Etienne, France.

The study is a consecutive cohort (n=14) where the Micra TPS was implanted in patients contradicted for or unable to receive conventional endovenous pacemaker implantation. The primary endpoints were implant success rate and pacemaker performance characteristics (pacing threshold, battery voltage and R-wave amplitude). The secondary endpoint was absence of serious adverse events at least 3 months.

***Martinez-Sande study (19)***

The study is a prospective, observational study (n=30) enrolling patients indicated for single-chamber pacemaker replacement. The aim of the study was to evaluate the electrical parameters at implantation and over follow-up, and to report on major complications, according to the Micra TP Study.

Targeted parameters at implantations were: pacing threshold ≤ 1.0 V to 0.24 ms, pacing impedance 400 to 1500 Ohm, and R-wave amplitude ≥ 5 mV.

**Critically appraisal of the methodological quality of the included studies**

All studies were designed as single arm with no control group. Primarily we therefore critically appraised the methodological quality of the studies. Several of the studies performed post hoc comparisons with historical data sets, and for these, we assessed the quality of the studies using the risk of bias tool. All studies were found to have low methodological quality or high risk of bias. The main contributor to this result was the study design. The results are presented in Appendix 5.

## Efficacy of Micra TPS

Therapy efficacy is mainly assessed by the pacemaker's ability to deliver the necessary pulses on demand. In clinical practice, efficacy or device performance is monitored by health care professionals at regular follow-up visits or by the patients themselves reporting the reoccurrence or onset of bradycardia symptoms.

### Electrical parameters

The minimum required power (voltage) to execute the heartbeat is called the pacing threshold. A pacemaker system's threshold values can be measured with a simple test via a device known as a pacemaker programmer. The amplitude of the electrical signal provided by the heart itself is also measured, the R-wave. A technical assessment of pacemaker function often also includes a test of the pacing impedance, which provides insights into the status of the tissue-pacemaker physical interface or fixation.

Reference values given by Medtronic for the Micra device are as follows (25):

- Pacing threshold: ≤ 1.00 V measured at pulse width of 0.24 ms
- R-wave: ≥ 5 mV
- Impedance: 400 – 1500 Ω

Most of the studies routinely checked the efficacy of the pacemaker on the scheduled controls. The results show that the mean of the electrical parameters in all patients were within the reference range and kept stable over time (*Table 3*).

Both the Micra TPS Post-Approval Registry (16) and the Micra TP Study (12) reported the rate of patients within the safe threshold levels (≤ 1 V at 0.24 ms) which was 87.2% (6 months after implantation) and 93% (12 months after implantation), respectively. Duray et al (12) showed that 97% of the patients (n=58) had a pacing level below 1 V after 24 months (97%).

***Table 3.*** *Electrical parameters and battery longevity*

| Reference | | Pacing threshold at 0.24 ms | Pacing impedance | R-wave |
|---|---|---|---|---|
| *Micra TP Study* | | | | |
| Ritter2015 (n=60) | | | | |
| | *Implantation* | 0.57±0.31 V | 717±226 Ω | 11.7±4.5 mV |
| | *1 month* | 0.48±0.21 V | 622±133 Ω | 15.6±4.8 mV |
| | *3 months* | 0.51±0.22 V (95% CI, 0.45-0.56; P<0.0001) | 651±130 Ω | 16.1±5.2 mV |
| | *Within range* | All patients | | |
| Reynolds2016 (n=297) | | | | |
| | *Implantation* | 0.60 V | 724 Ω | 11.2 mV |
| | *6 months* | 0.64 V | 627 Ω | 15.3 mV |
| | *Within range* | 98.3% < 2.0 V (95% CI, 96.1 to 99.5) | | |
| Duray2017 (n=630) | | | | |
| | *12 months* | 0.60±0.38 V 93% ≤ 1 V | 596 Ω | 15.1 mV |
| | *24 months* | 0.53±0.23V | NR | 15.5 mV |
| | *Within range (n=58)* | 97% ≤ 1 V | | |
| Piccini2017 (n=711) | | | | |
| | *Implantation* | 88.3 % ≤ 1 V | | |
| *Micra TPS Post-Approval Registry* | | | | |
| Roberts2017 | | | | |
| | *Implantation (n=701)* | 0.6±0.5 V | 721±181 Ω | 11.4±5.3 mV |
| | *3 months (n=39)* | 0.5 ± 0.3 V | 632±143 Ω | |

| | | | |
|---|---|---|---|
| *6 months (n=25)* | 0.6 ± 0.3 V | 572±115 Ω | |
| *Within range at implantation* | 87.2% ≤ 1.0 V<br>97.0% ≤ 2.0 V | | |
| *Single site studies* | | | |
| Da Costa2017 (n=14) | | | |
| *Implantation* | 0.57 ± 0.2 V | 780 ± 210 Ω | 12 ± 6 mV |
| *3 months* | 0.5 ± 0.1 V | 663 ± 100 Ω | 14 ± 7 mV |
| Martinez-Sande2017 (n=30) | | | |
| *Implantation* | 0.59 V | 711 Ω | 12.3 mV |
| *Before discharge* | 0.49 V | 661.3 Ω | 14.1 mV |
| *1 month* | 0.45 V | 302.6 Ω | 14.4 mV |
| *3 months* | 0.51 V | 575.8 Ω | 13.8 mV |
| *6 months* | 0.49 V | 590.6 Ω | 14.9 mV |
| *12 months* | 0.54 V | 560.0 Ω | 14.4 mV |
| Pachon2016 (n=10) | | | |
| *Implantation* | 0.56±0.39 V | 739±161 Ω | 12.7±4.8 mV |
| *Follow-up** | 0.60±0.27 V | 633±139 Ω | 13.4±5.1 mV |

*Values are given ±standard deviation, when reported; Rate of patients with pacing threshold below the given voltage is given in percentage; NR = not reported;*Follow up ranged from 27 to 112 days.*

### *Long-term outcome by elevated pacing threshold*

Piccini et al (14) analysed a sub group of patients from the Micra TP Study where the device showed elevated pacing threshold at implantation and compared the results with a contemporary study designed to assess pacing thresholds in a standard dual chamber device, the EnPulse, (the Capture study). They showed that 11.7% (n=711) of the patients had an implant pacing threshold of > 1.0 V, similarly to the Capture study (9.3%, N=538). The pacing threshold were the same or lower in 94.4% of the patients after 6 months. The result were comparable to the Capture study.

### *Certainty of evidence of the electrical parameters*

The results are produced through single-arm studies with high risk of bias and will therefore have very low certainty according to the GRADE-tool. However, as these results are technical measurement and the results are not compared to other groups, we consider the reported measurements as is, to be of low certainty. We only included the multicentre studies, the Micra TP study and the Micra TPS Post-Approval Registry, in the summary of findings table (*Table 4*). The other studies were singe site case series with low number (N < 50) of patients. However, there were no contradictions between the results.

***Table 4.*** *Summary of findings for electrical parameters*

Patient or population: Patients indicated for single-chamber ventricular pacemaker implantation
Intervention: Micra TPS transplantation
Comparison: No comparator

| Outcomes | Impact | № of participants (studies) | Certainty of the evidence (GRADE) |
|---|---|---|---|
| Pacing threshold of Micra TPS | The Micra device show a pacing threshold level ≤ 1 V in 97% of the patients 12 months after implantation. | 630 (1 observational study) | ⨁⨁◯◯ LOW |
| Pacing impedance at implantation | The pacing impedance was within the reference values at implantation. | 1004 (2 observational studies) | ⨁⨁◯◯ LOW |
| Pacing impedance at 6 months | The pacing impedance was within the reference values at least 6 months after implantation. | 655 (2 observational studies) | ⨁⨁◯◯ LOW |
| R-wave | The R-wave was within reference values at least 6 months after implantation | 655 (2 observational studies) | ⨁⨁◯◯ LOW |
| Elevated pacing threshold at implantation | Elevated pacing threshold at implantation is the same or lower in 94.4% of the Micra implanted patients. | 83 (1 observational studies) | ⨁⨁◯◯ LOW |

### Battery longevity

Four articles estimated battery longevity based on current measurement during the first months after implantation. Results show (*Table 5*) that the estimated battery longevity complies with the specifications given for the Micra device, which is 12-15 years. The estimations are done at different time-points after implantation.

***Table 5.*** *Estimated battery longevity*

| Reference | Battery longevity |
|---|---|
| Duray2017 (n=630) | Estimated at 12 months: 12.1 years, with 89% patients estimated >10 years |
| Roberts2017 (n=54) | Estimated at 180 days: 14.9 years |
| Pachon2016 (n=10) | 8 > years |

### *Certainty of evidence of estimated battery longevity*

The results are produced through single-arm studies and high risk of bias and will therefore have very low certainty according to GRADE. However, as these results are based on technical measurement and are not compared to other groups, we consider the reported measurements as is, to be of low certainty (*Table 6*).

***Table 6.*** *Summary of findings for estimated battery longevity*

Patient or population: Patients indicated for single-chamber ventricular pacemaker implantation
Intervention: Micra TPS transplantation
Comparison: No comparator

| Outcomes | Impact | № of participants (studies) | Certainty of the evidence (GRADE) |
|---|---|---|---|
| Battery longevity | The estimated battery longevity was > 10 years. | 684 (2 observational study) | ⨁⨁◯◯ LOW |

### Adaptive pacing

An implanted pacemaker should rapidly and proportionally adapt the pacing rate to match the workload generated during walking or running. Most pacemakers therefore has a build-in sensor which ensures this flexibility of the device. The Micra uses an accelerometer sensor.

A subset of the patients in the Micra TP study (n=42), performed a treadmill test, 3 and 6 months post implant (13), using a Kay–Wilkoff (K-W) model. The output of the model is a fitted line in a graph where the x-axis is the normalized work load and y-axis is the normalized sensor rate. An excellent rate of adaptive pacing performance is defined to be a like with K-W slope=1.0 and y-intercept=0. Generally, reaching the upper rate too soon will result in a slope > 1.0; alternatively, if the pacemaker does not achieve the upper sensor rate during the maximum test, the slope will be < 1.0. The results reported by Lloyd et al (13) showed an average slope of 0.86 (90% CI 0.77-0.96), based on 30 tests performed by 20 patients who completed more than 4 stages of the test (the remaining patients did not manage to complete the 4 stages). The results confirmed that the Micra device achieved a linear relationship of pacing rate to workload in the majority of patients with the implant.

#### *Certainty of evidence of adaptive pacing*

The evidence for Micra's ability to deliver adaptive pacing are produced through case series with no control group and low (N < 50) number of patients. The evidence therefore have very low certainty according to GRADE. Summary of findings table is not presented.

## Safety of Micra TPS

All studies presented the safety outcome as major clinical complications, including deaths, and device related complications. The results from the Micra TP Study were compared to a historical control, the Micra TPS Post Approval Registry results were compared to the Micra TP Study and the remaining references had no control group.

### Deaths

Duray et al (12) summarizes all deaths in the Micra TP Study (745 enrolled patients, 726 implanted patients). Of 78 deaths, only one was considered related to the device, more specifically, to the implant procedure. Of the remaining, 10 were due to sudden cardiac death, 22 to non-sudden cardiac death, 43 were due to non-cardiac death and 2 for unknown reasons. Also, Roberts et al (16) reported one death related to the implant procedure in the Micra TPS Post-Approval Registry (n=795) (see *Table 7* for details about deaths). None of the other studies reported any procedure or device related deaths.

We contacted the manufacturer to receive an updated number of device related death. By 31. July, 2017, they had reported 4 deaths to FDA, that is, two deaths in addition to the two published deaths. These were patients in the Micra TPS Post-Approval Registry. We were also informed that by this date, more patients had been included in the Micra TPS Post-Approval Registry. Hence, in a population of 2.131 implanted patients, there were 4 device related deaths, three of them occurred within the first day after implantation, the fourth 22 days after implantation.

***Table 7.*** *Reported deaths with Micra*

| Study | Case description |
|---|---|
| Micra TP study (5) | "A 77 year old female patient had a concomitant procedure (AV nodal ablation) performed during the transcatheter pacemaker implantation, which resulted in prolonged procedure time. Of note, the patient had end stage renal disease and was scheduled for dialysis that day (it had been 3 days since the last dialysis session). No arterial blood gases were monitored during the procedure and no autopsy was conducted; however, the Investigator felt the most likely cause of death was metabolic acidosis due to prolonged procedure time with underlying end stage renal disease. There was no perforation but the patient became hypotensive post procedure." |
| Micra TPS Post-Approval Registry (16) | "The patient was a 96-year-old male with aortic valvular disease who was undergoing an implantation attempt for complete atrioventricular block and who had no suitable access for transvenous pacing. The day after implantation, the patient developed pulmonary edema and could not be resuscitated. There was no evidence of tamponade or device migration, and the device was functioning normally at the time of his arrest. The pulmonary edema was thought to be related to the patient's valvular heart disease." |
| Micra TPS Post-Approval Registry (personal communication with Medtronic) | 92 year, female. Reported to FDA according to Medtronic quality assurance system, but not yet published. Details are therefore not official. |
| | 76 year, female. Reported to FDA according to Medtronic quality assurance system, but not yet published. Details are therefore not official. |

### Major complications

According to the Micra TP Study protocol (5), a major complication was defined as one event leading to death or serious deterioration of the patient's clinical condition, an event producing a vital risk and requiring some type of intervention for resolution, and any complication that prolonged hospital admission more than 48 hours.

Roberts et al (16) and Martinez-Sande et al (19) used the same definition in their analyses.

*Table 8* presents the major complications reported by the researches. The percentage is patients affected by complications. One patient may have more than one complication.

Complication rate of the Micra TPS Post-Approval Registry (16) (n=795, 1.51%) was compared to the complication rate in the Micra TP Study (n=726, 2.89%) one month after implantation. The odds ratio was 0.515 (95% CI 0.251-1.053, p=0.0691) favouring the Micra TPS Post-Approval Registry.

***Table 8.*** *Reported complications*

| Reference | Major clinical complications | Comment |
|---|---|---|
| *Micra TP Study* | | |
| Ritter2015 (11)<br>Reynolds2016 (5)<br>Duray2017 (12)<br>(n=726) | 0-1 months: 2.89 %<br>1-6 months: 0.83%<br>Above 6 months: 0.28%<br>12 months: 4.0%<br><br>Infections: 3.6%, but none were related to the Micra device or procedure.<br><br>Cardiac effusion/perforation: 1.52% (6 months data)<br><br>Deaths: 10%. One death was considered related to the implant procedure. | Compare with historical data and safety performance goal. |
| *Micra TPS Post-Approval Registry* | | |
| Roberts2017 (16)<br>(n=795) | 30 days: 1.51%<br><br>Cardiac effusions: 5 incidences. Only 1 met the major complication criteria.<br><br>Deaths: 2.8%. One death was considered related to the implant procedure. | Compare with the Micra TP Study |
| *Other studies* | | |
| Da Costa2016 (18)<br>(n=14) | 1 patient was described with complication. | A subset of patients with contraindications or limited venous access were enrolled. |
| Martinez-Sande2017 (19)<br>(n=30) | 1 patient was described with complications. | |
| Pachon2016<br>(n=10) | No complications in any patients | |

***Major complications compared with historical control.***

In the Micra TP Study, the safety data were compared with a historical control (n=2667) which was data compiled from six studies of dual-chamber pacing systems (23). The authors approximated the data set for single-chamber devices by excluding

events related only to the right atrial lead. Twelve months after pacemaker implantation the historical control reported 7.6% (95% CI 6.6-8.7%) major complications as compared with results from the Micra TP Study (4.0%; 95% CI 2.8-5.8; p≤0.001) (26). The most frequent types of complications for the two populations are listed in *Table 9* (183 days post-implant. Numbers are taken from the supplement of Reynolds et al (5)).

Compared to the historical control, device dislocation was lower in the Micra group, showing a frequency of 1.5% (1.1-2.1%) and 0% (0.0-1.2%, p=0.011), respectively (183 days post-implant). Other than that, none of the individual complications showed a statistical significant difference between the device types.

***Table 9.*** *Selected types of complications 183 days post-implant (5).*

| Type of complication | Micra TP Study (n=725) % patients (95% CI) | Historical control (n=2667) % patients (95% CI) |
|---|---|---|
| Total* | 4.0% (2.7-6.1%) | 7.4% (6.4-8.4) |
| Atrial fibrillation | 0% (0.0-1.2%) | 0.6% (0.4-1.0%) |
| Arteriovenous fistula | 0.6% (0.2-1.5%) | 0% (0.0-0.2%) |
| Implant site infection | 0% (0.0-1.2%) | 0.2% (0.1-0.4%) |
| Other infection | 0% (0.0-1.2%) | 0.1% (0.0-0.3%) |
| Viral infection | 0% (0.0-1.2%) | 0.1% (0.0-0.3%) |
| Pneumothorax | 0% (0.0-1.2%) | 1.2% (0.9-1.7%) |
| Cardiac perforation | 0.4% (0.1-1.3%) | 0.4% (0.2-0.7%) |
| Pericardial effusion | 1.1% (0.6-2.3%) | 0.5% (0.3-0.9%) |
| Device capturing issue | 0% (0.0-1.2%) | 0.4% (0.2-0.8%) |
| Device pacing issue | 0% (0.0-1.2%) | 0.5% (0.3-0.8%) |
| Device dislocation* | 0% (0.0-1.2%) | 1.5% (1.1-2.1%) |
| Device connection issue and device lead damage | 0% (0.0-0.0%) | 0.1% (0.0-0.4%) |
| Cardiac failure | 0.9% (0.3-2.9%) | 0% (0.0-0.2%) |
| Coronary artery disease | 0% (0.0-1.2%) | 0.2% (0.1-0.5%) |

** p < 0.05, reported by the authors*
*Numbers in red indicates a higher complication rate compared to the other group.*

### *Certainty of evidence of major complications*

We consider the evidence for the given numbers of complications to have low certainty according to GRADE. The main contributors to this result were the study design (single-arm) and that the studies are supported by the manufacturer of the device (*Table 10*).

We consider the evidence for reduced complication rate by Micra over existing devices as represented by the historical control, to have very low certainty. The main contributors to this result were the study design (single-arm), and the use of a historical control group with risk of indirectness (difference in patient population) (*Table 10*). The main contribution to the increased risk of indirectness was the difference

in patient population between the study arm and the control group, which was patients indicated for single ventricle pacing or a mixture of single- and dual- ventricle pacing, respectively.

***Table 10.*** *Summary of findings for major complications.*

Patient or population: Patients indicated for single-chamber ventricular pacemaker implantation
Intervention: Micra TPS transplantation
Comparison: Historical control

| Outcomes | Impact | № of participants (studies) | Certainty of the evidence (GRADE) |
|---|---|---|---|
| Major complications | 30 days after Micra implantation: The percentage of major complications is 1.51-2.89%. | 1520 (2 observational study) | ⊕⊕◯◯ LOW |
| Major complications, no control | 12 months after Micra implantation: The percentage of major complications is 4%. | 726 (1 observational study) | ⊕⊕◯◯ LOW |
| Major complications, compared | The complication rate 6 months after implantation is lower using the Micra implant (N=725) than conventional implants (N=2667): 4.0% (95%CI 2.7-6.1%) vs 7.4% (95%CI 6.4-8.4%) | 3393 (1 observational study) | ⊕◯◯◯ VERY LOW [a,b] |

*Explanations*
a. Indirectness due to the historical control.
b. Study is supported by the manufacturer.

## Device related complications

### *Revision of device*

Grubman et al (15) summarized the system revision experience in both the Micra TP Study (n=720) and the Micra TPS CA Study Protocol (n=269). They reported a total of 11 system revisions in 10 patients (1.4% of the study population). In 7 of the revisions, the device was disabled and left in situ. The results were compared with the previously described historical control which reported 5.3% revisions, which gave a hazard ratio of 0.25 (95% CI 0.13-0.47; p<0.001) of the Micra TPS over historical control, 24 months post implant.

### *Implantation procedure success*

None of the data on the implantation procedure were compared to control groups. From the Micra TP Study, Ritter et al (11) reported 100% successful implant procedures after the 140 first patients had been enrolled. When 726 patients had been implanted, the success rate was 99.2% (12). The Micra TPS Post-Approval Registry reported a success rate of 99.6%. The three single site studies, with patient numbers of 10, 14 and 30, respectively, all reported 100% success rate (17-19).

The researches also reported how many attempts the operator needed to properly position the device. Data from 140 patients in the Micra TP Study (11), and 795 patients in Micra TPS Post-Approval registry (16), showed that 71.1% and 77% of the implantations required 2 or fewer attempts, respectively. Further, Pachon et al reported 3 repositions in his 10 patient cohort (17) and Da Costa calculated the mean number of attempts to be 1.7±0.7 (18).

### *Certainty of evidence of device related complications*

We consider the evidence for reduced rate of revisions by Micra over existing devices as represented by the historical control, to have very low certainty based on the study design (single-arm) and high risk of bias, according to the GRADE-tool. The numbers of successful implantations are not compared to any control group and the numbers as is, is of moderate certainty. Summary of findings table is not presented.

### Pacemaker induced arrhythmia

None of the included studies report specifically on pacemaker induced arrhythmias.

### Patient satisfaction

We found no studies reporting patient satisfaction.

### Results presented in the document pack but not published in peer-reviewed journals

The submitter presented a systematic review of pacemaker complications in the document pack. Fifty studies were included to identify rates of specific complications. The results are presented in *Table 11*. The review identified individual complications which may be important for sub-grouping patients eligible for the Micra TPS in a clinical setting.

***Table 11.*** *Types of complications after conventional pacemaker implantation.*

| | No. of studies | No. of patients | Random pooled risk (95% CI) | Heterogeneity $I^2$ |
|---|---|---|---|---|
| Bleeding | 19 | 659 558 | 1.0% (0.6-1.6) | 99% (p < 0.001) |
| Pneumothorax | 20 | 658 364 | 0.9% (0.7-1.1) | 97% (p < 0.001) |
| Symptomatic upper extremity deep venous thrombosis | 3 | 6 539 | 0.7% per year (0.1-4.3) | 92% (p < 0.001) |
| Infections | NA | NA | NA | NA |
| Cardiac injuries related to right ventricular lead | 9 | 6 424 | 0.7% (0.4-1.1) | 49% (p=0.06) |
| Lead dislodgements/displacements related to right ventricular lead | 19 | 12 139 | 1.5% (1.0-2.1) | 79% (p < 0.001) |
| Lead fractures/insulation breach related to right ventricular lead | 4 | 2 976 | 0.6% per year (0.5-0.8) | 0% (p=0.77) |

*Results are taken from the systematic review, attached to the document package.*

# Method - Cost-effectiveness analysis

## Methods for evaluating submitted cost-effectiveness models

### Cost-effectiveness analysis

The primary objectives of health economic modelling are to provide a mechanism to determine the relative cost-effectiveness of the specified health intervention(s) compared to standard treatment, using the best available evidence, and to assess the most important sources of uncertainty surrounding the results. In order to make comparisons across different types of treatments and multiple potential health outcomes, economic models typically measure health outcomes in terms of quality-adjusted life years (QALYs), a variable designed to capture both life extension and health improvement. QALYs, by definition, take on a value of 1 for perfect health and 0 at death. The output of a cost-effectiveness model is expressed as an incremental cost-effectiveness ratio (ICER), which can be thought of as the extra cost of obtaining an extra life-year in perfect health. The ICER is defined as

$$Cost_{Intervention} - Cost_{Comparator} \Big/ QALY_{Intervention} - QALY_{Comparator}$$

### Evaluating cost-effectiveness models

There is no single correct way to build an economic model to estimate the cost-effectiveness of a specific health initiative. Modelling requires consulting with clinical experts to gain an understanding of normal disease progression, and to determine, based on the research question, the relevant treatment population, relevant comparator; and important health outcomes and adverse events connected to treatment. This information informs the basic model structure, and also determines which clinical effect data is most important to retrieve in the systematic literature search. Once the model structure is in place, systematic searches and evidence grading are used to provide the most reliable risk information for the model, but must also to collect all of the relevant cost and quality of life data that is needed for cost-effectiveness calculations.

A model is rarely meant to capture every potential detail of the treatment landscape; rather the goal is to include enough detail to provide a realistic view of the most significant pathways in disease progression, given the research question(s) one is trying to answer. Evaluating, any given model is primarily about determining whether the choices made by the submitter regarding model structure and treatment comparator are reasonable given the research question; whether baseline epidemiological data reflect the population in which the analysis is being performed; whether the clinical effect data used in the model are of adequate quality; whether resource use and costs reflect the conditions of the healthcare system in question; whether there has been sufficient sensitivity and scenario analysis to determine the degree and source of uncertainty in the model results; and whether the model displays external and internal validity. Checklists are available to help researchers systematically examine these issues.

We proceed by first describing the health economic model used in the submission and the results generated by the model. We then provide our evaluation of the model, focusing on the following issues: model structure, choice of model parameters, use of appropriate sensitivity and/or scenario analysis to examine the extent of uncertainty in model results, and relevance of the model for the Norwegian context (27).

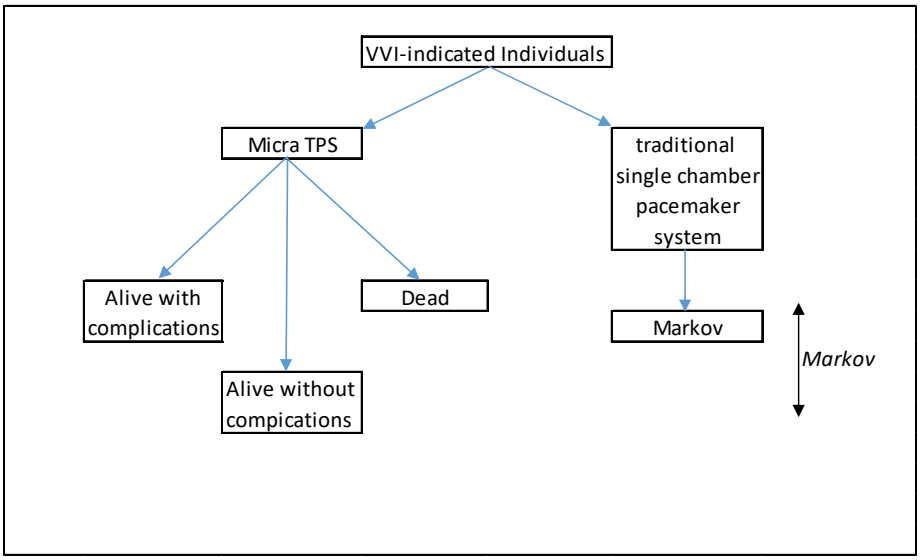
## Type of analysis and decision model

The submitter's cost-effectiveness analysis is based on a Markov model with monthly cycles built in Microsoft Excel. The submitted model assesses lifetime health outcomes and economic consequences of leadless pacing compared to single-chamber ventricular pacing. The base case analysis is focused on so-called "high risk" patients, i.e. the patient group for which a conventional pacemaker is considered to be associated with a high-risk of complications. The patients start age is 77 years. A 10 year time horizon is used, because it is seen to represent a clinically realistic lifetime for most individuals considered. The analysis is carried out from the perspective of the Norwegian health care system. The discount rate in the analysis is set to 4% for both costs and QALYs. The model includes two arms: the Micra™ Transcatheter Pacing System arm and the single-chamber ventricular pacing system arm. The analysis implies that individuals in need for a pacemaker either use the Micra system or a conventional pacing system throughout lifetime. As mentioned the

model is Markov based with monthly cycles, meaning that an individual`s health state with cost and effect implications is evaluated in monthly intervals.

In the first step the submitted model assigns VVI-indicated individuals to either Micra or conventional pacemaker therapy. In the second step the individuals enter the Markov part of the model (*Figure 6*). The model determines changes in health status of the individuals in every cycle by assigning probabilities to: experiencing complications, maintaining the current health status, or experiencing death. Individuals that remain alive are then put back to the beginning of the cycle and enter the model again. The submitter uses a threshold of NOK 500,000/QALY, previously published by NIPH to determine cost-effectiveness (28).

***Figure 6.*** *Markov model*




*The figure is taken from the submission*

## Cost-effectiveness model provided by the submitter

From a technical point of view the model utilised by the submitter is transparent and simple in terms of structure of the factors that determine a cohort's progress during the model, assumptions made, and parameters effecting outcomes. According to our clinical experts, the model captures all relevant health states.

The NIPH had access to the model build in Microsoft Excel as well as to the underlying assumptions and parameters. However, the submitted model lacked alignment with Norwegian health care parameters. The model was widely set in an international context. Rates of complications, for instance, were not separately analysed with Norwegian-based input data. Further, mortality rates in the model are based on Japanese data (the written report wrongly states they are based on UK data), not Norwegian mortality rates.

## Population, intervention and comparator in the cost-effectiveness model

According to the objective we analyzed two population groups in the cost-effectiveness model. Below we describe the populations with the related effect estimates.

1) All patients recommended for a single-chamber ventricular pacing

In a Norwegian setting the number of patients in this category is estimated to be 650 per year. For cost-effectiveness analyses we used the rate of short term complications (up to year 1) from the Micra TP Study (5).

2) Patients recommended for single-chamber ventricular pacing, but are at high risk of complications following a pacemaker implantation

There are different clinical conditions for patients at high risk of complications (4) which can be used to define a sub-group of patients, as patients with renal disease, prior infections or malignancies. A common feature for these patients is that they have high risk of pacemaker infections. In a Norwegian setting this patient group were estimated to be at least 10-30 % of the total indicated patient population, suggested by the external experts.

The estimated complication rate for this group was not assessed in the safety analyses of the present report. Rather, we, the external experts, and the submitter, made the following assumptions for the cost-effectiveness analyses for year 1:

a. Pacemaker complications in the model were stratified into three categories: lead infections (endocarditis); pocket infections; and pocket erosions (29). Pocket infections were defined as infections without a positive lead culture while lead infections were infections with a positive lead culture (29).

b. The total number of pocket and lead infections were 0.4 % and 0.3 % respectively, while pocket erosions were estimated to be 0.75 % (29).

c. The reported risk rate for patients with high risk of complications, as defined above, vary between 2.23 – 8.73% (30). The submitter therefore introduced an increased relative risk with a factor of three for this group, which we also used in our analyzes.

The rate and types of complications used in the analyses related to the conventional pacemaker are mainly taken from a meta-analysis on complication rates after pacemaker implants provided by the submitter. The rate and types of complications used

in the analyses related to Micra is taken from Reynolds et al (5). For both population groups, the long-term adverse events (endocarditis, pocket infection, erosions, upper extremely deep venous thrombosis and lead fractures) were suggested to only occur in the conventional pacemaker arm (29;30). The assumption that there will be no long term complications after a Micra implant, is highly uncertain as no data on long term complications by the Micra device are available, but this prerequisite will be used in our economic analyses.

## Efficacy input in the economic model

The model assumes that Micra is equivalent with conventional pacemakers in terms of performance. Major complications are defined as adverse events resulting in death, permanent loss of device function, hospitalization, or system revision. However, in patients at high risk of complications, reduction of infections after pacemaker implantation is particularly relevant.

For the sub-group of patients with high risk of complications, pooled estimates for infections were taken from the PEOPLE study (29), because of inconsistent definitions of infections and differing patient populations. Moreover a threefold risk multiplier has been taken from a meta-analysis (30), which includes the PEOPLE study (29). The submitter therefore multiplied the infection rates by the factor of three to account for a higher risk of complications in this patient group. The complication and infection rates used in the model are therefore based on an assumption rather than an actual study which makes the results highly uncertain.

Acute complication rates using the Micra system are obtained over a 12-month period from the Micra trial (5). However long-term complications are seen as eliminated due to the Micra system design (no pocket and lead infections or erosions). Thus, for the Micra system, only acute complication probabilities are included in the efficacy data. For conventional pacemakers, acute complication probabilities as well as long-term probabilities are included in the model. Acute complication rates include complications that occur during the first year after the pacemaker implant procedure. Long-term complications include complications that can occur multiple times over the lifespan of the device, including lead infections (endocarditis), pocket infections, and erosions (29).

A summary of mortality risk are listed in *Table 12*. Patients that survive infections are assumed to not be at additional future risk of infections. However, patients remain at risk of lead fractures and deep venous thrombosis. The submitter provides confidence intervals for most complications, but were no confidence intervals could

be identified from the submitter, they uses a +/- 30% range from the reported probabilities. A sensitivity analysis is used to test the variability on the cost-effectiveness results.

***Table 12.*** *Summary of mortality risk in patients with high risk of complications for conventional pacemakers*

| Mortality Risk | Probability | 95% CI | Source (Reference) |
|---|---|---|---|
| Age-adjusted mortality rate | Norwegian life tables | - | Statistisk sentralbyrå (31) |
| Lead infection mortality risk | 29% | +/-30% | Sandoe et al (32) |
| Pocket infection mortality risk | 5% | +/-30% | Sandoe et al (32) |

## Cost input in the economic model

The submitter identifies resource use and cost data by deriving the cost of complications from the Norwegian DRG tariffs published in the 2017 (33). Costs of the Micra device as well as the costs of conventional pacemaker are taken from Medtronic data. All costs are stated in Norwegian kroner (NOK).

The submitter derives DRG tariffs by matching the observed complications to the closest matching DRG. Where more than one DRG tariff matches a complication the submitter uses, in a first step, the NiceF software for accurate deriving DRG tariffs by using a combination of ICD10 code and specific procedure code. In a second step the submitter weights the costs by the proportion that would be managed inpatient or as hospital day case using data on health resource utilization provided in the Delphi panel group (to establish consensus for recommendations). The panel includes recommendation from 11 electrophysicians from several Western European countries, Norway not included.

### Cost of the intervention

The device cost of a Micra system is NOK 63 000 per implantation compared with the device cost of a traditional pacing system of NOK 4 266 per implantation. Both values are taken from Medtronic data. The submitter gave us information halfway through the project time period about an additional cost related to the implantation of leads in a conventional pacemaker procedure. This cost is about NOK 1 750 and should be added to the implantation cost of NOK 4 266. They did not include this cost in their analyses.

### Cost of complications

For the Micra system the submitter uses costs related to groin injuries, embolism, deep venous thrombosis, cardiac injury, and pacing issues with system revision.

Costs of the first three complications are directly derived from Norwegian DRGs (33). The unit cost related to cardiac injury is calculated by using more than one DRG and by weighting these DRGs according to rates obtained from the Delphi panel. Unit costs related to the devices are based on information from the submitter.

For pacing issues with system revision the costs are assumed to equal the costs of a new device implantation.

For conventional pacemaker the submitters report costs related to pneumothorax, bleeding, cardiac injury, lead dislodgments, upper extremity deep venous thrombosis, lead fractures, lead infections (endocarditis), pocket infections, and erosions. Costs for the first four complications were directly derived from Norwegian DRGs. The latter are calculated by using more than one DRG and by weighting these DRGs according to rates obtained from the Delphi panel. *Table 13* illustrates the obtained costs per unit in NOK.

***Table 13.*** *Calculated cost of complications*

| Complication | Probability (reference) | Cost per unit |
|---|---|---|
| Micra Device | 100% | 63,000 |
| Groin injuries | 0.7% (5) | 32,749 |
| Embolism | 0.1% (5) | 51,004 |
| Deep venous thrombosis | 0.1% (5) | 51,004 |
| Cardiac injury | 1.6% (5) | 42,454 |
| Pacing issues with system revision | 0.3% (5) | 63,000 |
| Conventional Pacemaker | 100% | 4,266<br>1,750 (leads)** |
| Pneumothorax | 0.9% (*) | 42,582 |
| Bleeding | 1.0% (*) | 32,749 |
| Upper extremity deep venous thrombosis | 0.7% per year (*) | 10,291 |
| Cardiac injury | 1.2% for age ≥ 75 (*) | 42,454 |
| Lead dislodgements | 1.5% (*) | 17,529 |
| Lead fractures | 0.6% per year (*) | 85,391 |
| Lead infections | 0.3% (29) | 304,904 |
| Pocket infections | 0.4% (29) | 209,586 |
| Erosions | 0.75% (29) | 114,268 |

*Costs in Norwegian Kroner (NOK)*

** Meta-analysis provided by the submitter*

*** The submitter gave us this information halfway through the project time*

## Utility input in the economic model

Health-related quality of life (HRQL) utility values, based on EQ-5D visual analogue scale (VAS), are available for all health states. The utility values are taken from the Micra clinical trial and, due to a lack in evidence regarding general device-related effects on quality of life impact, are assumed to be the same for both Micra and conventional pacemaker treatments. Thus the submitter assumes parity in HRQL between Micra and conventional pacemakers in cases where no complications occur. In cases of complications a utility decrement is applied.

Due to the lack of evidence utility decrement values are taken from a Health Technology Assessment study authorized by UKs National Institute for Health and Care Excellence (NICE) (34). Contrary to the submitted report which examines clinical and cost effectives of leadless pacing the study by Fox et al (34) examines biventricular pacing.

In estimating the utilities for the considered complications the submitted model distinguishes between utilities related to infections and utilities related to other complications. For infections the utility loss that assumed to depend on the type of infection are listed up in *Table 14*. Based on Fox et al. 2007 (34), the utility loss of a lead infection is estimated to be 0.25 (0.15 infection + 0.1 surgical complication) and lasts, according to the Delphi panel, 21 days in line with IV antibiotic therapy duration. Additional 14 days are added if a device extraction and replacement is necessary. A similar scheme is applied for pocket infection utility loss. A utility loss of 0.25 (0.15 infection + 0.1 surgical complication) is taken from Fox et al. The duration of complication is assumed to be 9.6 days plus potential 14 days for a device extraction and replacement. Erosions utility loss is assumed to last 14 days after extraction and removal of the device. The utility loss is estimated with 0.1 due to complications requiring a surgical re-intervention. All other complications are assumed to have identical utility loss durations as erosions. The sensitivity of the model in regard to utility decrements is tested in a one-way sensitivity analysis.

***Table 14.*** *Summary of Utility Decrements*

| Complication | HRQL weighting | Range | Source (Reference) |
|---|---|---|---|
| Baseline for both Micra and conventional devices | 0.652 | +/-30% | EQ-5D visual analogue scale – Micra clinical trial |
| Lead infection | -0.25 for 35.3 days | +/-30% | (34) |
| Pocket infection | -0.25 for 23.6 days | +/-30% | (34) |

| | | | |
|---|---|---|---|
| Erosions | -0.1 for 14 days | +/-30% | (34) |
| All other complications | -0.1 for 14 days | +/-30% | (34) |

*HRQL: Health related quality of life; EQ-5D: EuroQol-5D*

## Input data provided by the submitter

There is significant uncertainty connected to the efficacy data. Input data for the model is taken from several different studies, from different countries with various study populations.

A deviation between submitted report and submitted model concerns mortality rates. While the report states that mortality rates are obtained from UK life tables, the applied mortality rates in the model were obtained from Japan. Japanese mortality rates however might differ even more from the Norwegian mortality rates. In addition, the risk factor of infections in high risk groups as well as the risk factor of mortality are based on conservative estimates, which might not represent the Norwegian population.

Contrary to traditional pacemakers, according to the submitter, no long-term complications are occurring for patients receiving treatment with Micra device. Thus no long-term complication costs for Micra devices are considered in the model. Certainly this influences the cost-effectiveness analysis as well as the budget impact model in favour of Micra device.

# Results - Cost-effectiveness

## Base-case cost-effectiveness results

### Base-case cost-effectiveness results by submitter

The submitter provides cost-effectiveness results comparing Micra leadless pacemaker to traditional single-chamber pacemaker in regards to high risk patients in need for a pacemaker. The submitter applies, a risk factor of 3 (35) in order to include the risk of mortality and the risk for lead or pocket infections in the conventional pacemaker arm in the cost-effectiveness analysis. These were applied to risk probabilities of 0.29 % and 0.39 % for lead and pocket infections, and mortality risk probabilities of 29% and 5% (32), for lead and pocket infection accordingly. This renders infection-related mortality figures in the model of 87% and 15%, respectively. These figures seem to be exceptionally high, even for a high risk patient group. We find it problematic to apply a risk multiplier rather than using mortality figures from actual studies. Further, the submitter also uses Japanese mortality rates in their cost-effectiveness model.

The results are submitted in a scenario, where a NOK 500,000/QALY threshold determines cost-effectiveness.

The submitter concludes that total costs, including device costs and costs for complications, are NOK 64,200 and total costs for traditional pacemaker are NOK 47,216. Consequently, the incremental costs are NOK 16,983. Total number of QALYs are 4.250 for Micra and 4.086 for traditional pacemaker. The incremental QALYs was 0.164. Considering these numbers the incremental cost-effectiveness ratio (ICER) is NOK 103,760 (*Table 15*). The submitted results show that, regarding the patient is at high risk of infections, the Micra system can be considered cost-effective if a threshold of NOK 500,000/QALY is applied.

***Table 15.*** *The submitted cost effectiveness results for Micra vs. conventional pacemaker for one patient at high risk of infections (based on the submitted input data).*

| Measure: | Total costs (NOK) | Total number of QALYs | ICER |
|---|---|---|---|
| Micra device | 63,000 | 4.250 | 103,760 |

| | | | |
|---|---|---|---|
| Complication related cost | 1,200 | | |
| Conventional pacemaker<br>Complication related costs | 4,266<br>42,950 | 4.086 | - |

*NOK: Norwegian Kroner; QALYs: quality adjusted life year; ICER: incremental cost effectiveness ratio*

### Base-case cost-effectiveness results by NIPH

We made some changes to the base case analysis to investigate the effect of certain parameters: Norwegian mortality rates from Statistics Norway (2016) replaced the Japanese rates in the model and increased the implantation cost of conventional pacemaker from NOK 4,266 to NOK 6,016, which resulted in a reduction of the ICER. However, removing the threefold multiplier for the infection-related mortality and keeping the threefold multiplier for lead and pocket infections for only the first year in the model brought the ICER up to NOK 1,077,363 (*Table 16*). Even though this result would be in the range of what is considered as not cost-effective, the lack of confidence intervals and a probabilistic analysis makes it difficult to assess the uncertainty surrounding these results.

***Table 16.*** *Recalculated cost effectiveness results for Micra vs. conventional pacemaker for patients at high risk of infections (Norwegian Institute of Public Health).*

| Measure: | Total costs (NOK) | Total number of QALYs | ICER |
|---|---|---|---|
| Micra<br>Complication related costs | 63,000<br>1,200 | 4.418 | 1,077,363 |
| Conventional pacemaker<br>Complication related costs | 6,016<br>26,187 | 4.389 | - |

*NOK: Norwegian Kroner; QALYs: quality adjusted life year; ICER: incremental cost effectiveness ratio*

Nevertheless, as pointed out in the introduction to this chapter, it is not only the patients at high risk of complications but the total indicated patient population that should be included in a model. The structure of the submitted model would allow for this, but there yet no appropriate data that could be used to run such an analysis. We attempted entering complication rates from a historical control group (5). This produced an ICER of well over 1 million NOK per QALY (*Table 17.* ***Recalculated cost effectiveness results for Micra vs. conventional pacemaker for the total population***). The study by Haug et al. (36) might be used in a model, but was not readily adaptable to the submitter's structure. It is therefore not possible to draw any conclusions regarding the cost-effectiveness of Micra compared with conventional pacemakers in the indicated patient population in Norway.

**Table 17.** *Recalculated cost effectiveness results for Micra vs. conventional pacemaker for the total population (Norwegian Institute of Public Health).*

| Measure: | Total costs (NOK) | Total number of QALYs | ICER |
|---|---|---|---|
| Micra<br>Complication related costs | 63,000<br>1,200 | 4.418 | 1,686,825 |
| Conventional pacemaker<br>Complication related costs | 6,016<br>22,903 | 4.397 | - |

*NOK: Norwegian Kroner; QALYs: quality adjusted life year; ICER: incremental cost effectiveness ratio*

**Feedback on the cost-effectiveness analysis by the submitter**

The submitter supported NIPHs modifications related to replacing the Japanize life tables with data from Norwegian statistics and removing the threefold multiplier for the infection related mortality probabilities. However, they think that removing the threefold multiplier for lead and pocket infection probabilities after the first year post surgery for a high-risk population seems clinically counter-intuitive. They revised the long-term infection and found a study supporting that infection risk drops in the general pacemaker population after the first year (ref: Johansen et al. 2011). The submitter pointed out that the infection rate is likely to be elevated in the first year because of procedure related risks and then settles to a lower level in subsequent years. Johansen et al. 2011 reported a hazard ratio of 0.35 for the infection risk post 1 year. To reflect decreasing infection risk in a general pacemaker patient population after the first year they have applied the hazard ratio of 0.35. Further, they have defined the incremental risk as the difference between the general pacemaker infection risk and the infection rate for the high-risk patients. The infection rate for the high-risk patients is still estimated through a threefold multiplier as before based on the infection rate of the general pacemaker population in year 1. They assume the risk due to the chronic conditions to be constant over time based on clinical mechanisms (patients that have chronic conditions such as renal disease with future or current need of dialysis, history of chronic infections or malignancies, which require chemotherapy).

Table 18. ***Scenario analysis – pacemaker infection rates in high-risk patient population*** illustrates three scenarios with different infection rates in a

high-risk patient population. The infection rates are only related to a patient using conventional pacemaker.

**Table 18.** *Scenario analysis – pacemaker infection rates in high-risk patient population*

| | 1st Year Rates | | 2 + Year Rates | | | |
|---|---|---|---|---|---|---|
| | **Lead** | **Pocket** | **Lead** | **Pocket** | **ICER** | **Infection risk assumed** |
| Scenario 1: Submitted analysis* | 0.88% | 1.17% | 0.88% | 1.17% | 231,000 NOK | Constant infection risk for general pacemaker population and high risk |
| Scenario 2: New analysis | 0.88% | 1.17% | 0.69% | 0.92% | 367,000 NOK | Infection rate for general pacemaker population falls after year 1. Constant incremental risk for high-risk patients. |
| Scenario 3: Analysis by NIPH | 0,88% | 1.17% | 0.29% | 0.39% | 1,077,363 NOK | Constant infection risk for general population. Infection rate for high risk patients falls to the level of the general pacemaker population after year 1. |

*Norwegian life tables included, relative risk factor for mortality removed.

We have noted that the submitter assumes that the risk of infections in the high-risk population is constant over time. We still believe that the provided documentation does not support this assumption to a degree that it will affect the model.

## Sensitivity analysis by submitter

The submitted model includes a one-way sensitivity analyses using a 95% confidence interval for variables where a confidence interval could be obtained. For the other variables an arbitrary range of +/- 30% is used. However, an arbitrary range is not the most optimal method to perform a sensitivity analysis. It demonstrates the models sensitivity, but does not reflect uncertainty. The performed one-way sensitivity

analyses shows that relative risk of infection, the lead infection rate, the pocket infection rate and the lead infection costs have the greatest impact on the model. All of them were tested with a +/- 30% arbitrary range.

## Severity considerations – Absolute shortfall

The calculation of absolute shortfall (AS) is based on the submission guideline of the Norwegian Medicined Agency (37) which is based on the white paper on priority setting (38), a Norwegian life table (39) and health related quality of life information from a Swedish population (40). Absolute shortfall is defined as the difference in quality adjusted life expectancies at age (A) without the disease ($QALY_{sA}$) and prognosis with the disease ($P_A$):

$$AS = QALY_{sA} - P_A$$

In accordance with the economic model, we first assume that patients are 77 years of age when entering the model. At this age, the expected quality adjusted life expectancy is 8.5. The prognosis with disease expected to be 4.389 QALYs for the conventional pace maker is based on simulations from the health economic model provided by the submitter, after adjustments made by NIPH (Table 16). The absolute shortfall with these assumptions is:

$$AS = 8.5 - 4.4 = \underline{4.1 \text{ QALYs}}$$

According to the white paper (ref), the cost-effectiveness threshold should be weighted according to severity classes suggested by the Norheim and Magnussen commissions. It was suggested that AS falling below 4 QALYs belong to the least severe group, and AS being above 20 QALYs are to be considered among the highest severity diseases. With AS of 4.1, the argument for giving special priority to Micra leadless pacemaker based on severity appear weak.

## Budget impact analysis

### Budget impact analyses by submitter

The submitter calculated the budget impact, from a Norwegian health care perspective, of applying Micra™ Transcatheter Pacing treatment to individuals with symptomatic bradycardia which are at high risk of infections. The budget impact is estimated as the net cost difference between a scenario in which the Micra system is adopted for a full cohort of eligible individuals relative to a scenario in which the device is not adopted. The budget impact was estimated over a 10-year time horizon. A discount rate of 4% annual is applied. The model is based on the annual Norwegian VVIR implant rate of circa 800 patients. 10% of these patients, equalling 80 individuals, are assumed to be eligible to receive Micra devices. In addition, the rate of implants is assumed to be constant. New patients entering the analysis are thus not modelled.

The submitter created a budget impact scenario analyses in which the Micra device impact gets compared to conventional pacemaker treatment as described in the cost-effectiveness analysis.

In the budget calculation the price of a Micra device, including implantation, is assumed to be NOK 63,000 per patient resulting in NOK 5,040,000 for the cohort of 80 individuals. The conventional pacemaker price, including implantation, was assumed to be NOK 4,266 per patient, resulting in NOK 341,280 for 80 individuals.

The budget impact analysis illustrates that both acute complication costs as well as long-term complication costs are higher for the conventional pacemaker treatment. Acute complication costs, only occurring in year 1, are NOK 126,509 for conventional pacemaker treatment and NOK 95,961 for Micra pacemaker treatment. Long-term complication costs are NOK 507,274 for conventional pacemaker treatment and NOK 0 for Micra pacemaker treatment due to the fact that no long-term complication rates are reported for Micra devices.

Based on the outlined scenario costs accumulated over a 10-year time horizon show that the budget impact of conventional pacemaker treatment compared to Micra pacemaker treatment is NOK 1,358,660 lower. Total costs are NOK 3,777,301 and NOK 5,135,961 for conventional pacemaker treatment and Micra pacemaker treatment respectively (*Table 19*).

***Table 19.*** *The submitted total budget impact over a 10-year time horizon for 80 individuals (based on the submitted input data).*

| Year | Conventional pacemaker treatment | Micra pacemaker treatment | Difference |
|---|---|---|---|
| Year 1 | 975,063 | 5,135,961 | 4,160,898 |
| Year 2 | 463,661 | 0 | -463,661 |
| Year 3 | 421,899 | 0 | -421,899 |
| Years 4-5 | 724,656 | 0 | -724,656 |
| Years 6-10 | 1,192,023 | 0 | -1,192,023 |
| Total | 3,777,301 | 5,135,961 | 1,358,660 |

*Costs in Norwegian Kroner (NOK)*

### Budget impact analyses by NIPH

By using the health economic model with adjusted input data, we recalculated the budget impact over a five year time horizon. Long-term complication costs only occur for patients with conventional pacemaker implants, certainly this influences the budget impact in favour of Micra devices. In addition to take long-term adverse event into account, we calculated 80 new implanted pacemakers per year in both cases based on the submitted input data. *Table 20.* ***Total budget impact over a 5-year time horizon, for 80 high risk patients (based on the submitted input data)*** shows a total added cost of NOK 2,209,402 in year five, by introducing Micra to the Norwegian health care system for 80 high risk patients. Total costs during five years for this patient group are NOK 9,443,281 and NOK 25,679,806 for conventional pacemaker treatment and Micra pacemaker treatment respectively.

***Table 20.*** *Total budget impact over a 5-year time horizon, for 80 high risk patients (based on the submitted input data)*

| Year | Conventional pacemaker treatment | Micra pacemaker treatment | Total added cost |
|---|---|---|---|
| Year 1 | 957,063 | 5,135,961 | 4,160,898 |
| Year 2 | 1,438,724 | 5,135,961 | 3,697,237 |
| Year 3 | 1,860,623 | 5,135,961 | 3,275,338 |
| Year 4 | 2,242,312 | 5,135,961 | 2,893,649 |
| Year 5 | 2,926,558 | 5,135,961 | 2,209,402 |
| Total | 9,443,281 | 25,679,806 | 16,236,525 |

*Costs in Norwegian Kroner (NOK)*

The submission shows a budget impact of a cohort of 80 patients, which was supposed to represent the annual Norwegian pacemaker implantations. However, this

estimated cohort might differ from the actual number of patients eligible to the implantation of a Micra device in Norway, which may be about 650 individuals based on expert opinions.

We calculated 120 new implanted pacemakers per year in both cases – with respect to a high risk population in Norway (based on expert opinions). We also removed the discounting rate of 4 %.

*Table 21* shows a total added cost of NOK 4,652,759 in year five, by introducing Micra to the Norwegian health care system for 120 high risk patients. Total costs during five years for this patient group are NOK 11,928,841 and NOK 38,519,709 for conventional pacemaker treatment and Micra pacemaker treatment respectively.

***Table 21.*** *Total budget impact over a 5-year time horizon, for 120 high risk patients (Norwegian Institute of Public Health)*

| Year | Conventional pacemaker treatment | Micra pacemaker treatment | Total added cost |
|---|---|---|---|
| Year 1 | 1,691,773 | 7,703,942 | 6,012,168 |
| Year 2 | 2,052,564 | 7,703,942 | 5,651,378 |
| Year 3 | 2,400,035 | 7,703,942 | 5,303,906 |
| Year 4 | 2,733,285 | 7,703,942 | 4,970,657 |
| Year 5 | 3,051,183 | 7,703,942 | 4,652,759 |
| Total | 11,928,841 | 38,519,709 | 26,590,868 |

*Costs in Norwegian Kroner (NOK)*

Further, we recalculated the budget impact with a five year time horizon based on the number of patients who are eligible to the implantation of a Micra device in Norway. This may be about 650 individuals. *Table 22* shows a total added cost of NOK 27,386,992 in year five, by introducing Micra to the Norwegian health care system for these patients. . Total costs during five years for the total patient group are NOK 53,653,667 and NOK 208,648,424 for conventional pacemaker treatment and Micra pacemaker treatment respectively.

***Table 22.*** *Total budget impact over a 5-year time horizon, 650 patients (Norwegian Institute of Public Health)*

| Year | Conventional pacemaker treatment | Micra pacemaker treatment | Total added cost |
|---|---|---|---|
| Year 1 | 6,963,535 | 41,729,685 | 34,766,150 |
| Year 2 | 8,922,111 | 41,729,685 | 32,807,574 |
| Year 3 | 10,808,212 | 41,729,685 | 30,921,473 |
| Year 4 | 12,617,117 | 41,729,685 | 29,112,568 |
| Year 5 | 14,342,693 | 41,729,685 | 27,386,992 |
| Total | 53,653,667 | 208,648,424 | 154,994,757 |

*Costs in Norwegian Kroner (NOK)*

# Discussion

## Summary of results

The Micra™ Transcatheter Pacing System (Micra TPS) is a miniature single chamber pacemaker can be used in patients indicated for single-chamber ventricular pacemaker implantation.

In this single technology assessment, we have systematically reviewed and summarized studies on

- Efficacy; measured through electrical parameters, battery longevity and adaptive pacing
- Safety; reported as deaths, major complications and device related complications
- Economic impact of introducing the device in two alternative populations:
  - All patients recommended for a single-chamber ventricular pacing
  - Patients recommended for single-chamber ventricular pacing, but are at high risk of complications following a pacemaker implantation

### Main clinical outcomes

- The electrical parameters are within the reference values.
- There are four device or procedure related deaths in a cohort of 1521 patients
- The major complication rate for the Micra device is 4% (95%CI 2.7-6.1%) six months after implantation.
- The major complication rate for conventional pacemakers, as represented in a historical control, is 7.4% (95%CI 6.4-8.4%) six months after implantation.

### Economical outcomes

- For the indicated patient population:
  - An estimated total added cost of NOK 26,653,195 in year five based on a patient population of 650 patients.
  - ICER was over NOK 1,770,495 per QALY gained.
- For patients with high risk of complications:
  - An estimated total added cost of NOK 3,394,763 in year five based on a patient population of 10-30% of the total indicated patient population.
  - ICER was estimated to be NOK 1,136,288 per QALY gained.

## Discussion of clinical outcomes

Micra™ Transcatheter Pacing System (Micra TPS) is a miniature single chamber pacemaker designed without lead and implanted directly into the heart (no pocket). We have performed a single technology assessment of the use of this device for patients indicated for single-chamber ventricular pacemaker implantation.

We conducted an independent review of the clinical evidence using a PICO framework (Population, Intervention, Comparator and Outcome). The PICO components were selected in collaboration with clinical experts and in understanding with the device developer, Medtronic. In addition, results presented in the submission file but not retrieved by our literature search is discussed.

Our main outcomes were efficacy, as measured by pacing performance, safety, as presented by clinical and device related complications, and a health economic evaluation.

### Efficacy

The electrical parameters measured in the studies were consistent with the reference values given by Medtronic for the Micra device (25). The results were presented as mean values of all implanted devices. In addition, the Micra TP Study reported rate of patients within the pacing threshold reference values. The efficacy data were consistent and according to the reference values for most patients, from 87.2% to all patients, depending on when the measurement was performed.

### Safety

The results from the Micra device were compared to a historical control group, or to no control group. The clinical studies which evaluated safety all report number of major complications from prospective cohort studies. We chose to have confidence the investigators reporting of major complications based on their definition in the clinical protocol and that independent health personnel reported the complications. The challenge in the retrieved literature is whether there are evidence supporting a lower risk of complications with the Micra device compared to conventional devices. Randomized controlled trials are the golden standard to generate evidence with high certainty. However, we experience that medical device producers do not have the tradition of running such trials. For the Micra TPS there is no obvious reason why the producers did not add a control group using existing devices. Not at least since they already compare their results with results from experiences with exactly this, existing devices. One can argue that any pacemaker being ten times bigger, holding a

different technology and having leads, will not be suitable for comparison to the novel leadless Micra device. On the other hand, biased situations as different patient groups, operators training, follow-up of patients and recording of events would more likely be unbiased if a control group implanted with a conventional single-chamber device by the same operators, were included. When introducing a new device to the market, it is expected that the operators are more trained and more closely followed up, than when the device is established. For conventional devices, it has been shown that operators with less than 50 operations, has a higher chance of experiencing major complications in their patients than higher volume operators (2).

Instead of a control group, the major complications following a Micra device implantation (n=726) were compared with safety data from a historical control using a dual-chamber pacemaker implant (n=2667). The results show a hazard ratio for the Micra device of 0.49 (95% CI, 0.33-0.75; p=0.001) over the historical control (5). The certainty of evidence of this result is very low due to the study design and the choice of control.

In the whole cohort of implanted patients in the Micra TP Study and Micra TPS Post-Approval registry (n=1521), four deaths related to the device was reported. In the smaller single-site studies (n=54) no deaths were reported.

### *Type of pacemaker complications*

When the Micra group was compared to the historical control group, the only single complication showing statistical significant differences between the groups, was device dislocation (0.0%, 95% CI 0.0-1.2% vs. 1.5%, 95%CI 1.1-2.1%, p=0.011) (5). However, the results from a systematic review attached to the document package, as well as Dutch (1) and Danish (2) studies reports that lead and pocket complications accounts for the single most frequent complication after conventional pacemaker implantation (2.8%, 5.54% and 2.4%, respectively). The primary benefit of the Micra over the other devices is therefore that it is leadless.

### *Device related complications*

Results on the implantation procedure show that only 9 out of 1575 patients had an unsuccessful implantation. This result was not compared to experiences with conventional devices and must be considered as is. However, number of Micra revisions in the Micra TP Study and the Micra TPS CA Study Protocol was compared with a historical control group of conventional pacemakers and found less frequent (1.7% vs 5.3% respectively) (15). Of note is that in most of the revisions, the device was disabled and left in situ, indicating that although the device system has a method of retrieving non-functional devices, it is expected that it will be fully encapsulated after a

certain time and is preferably left in the heart. The submitter claims that the heart chamber can hold up to three devices.

### Certainty of the evidence

None of the studies included in this assessment are randomized controlled trials, meaning that the certainty of the evidence is low, using the GRADE-tool. Further, the main studies with most patients were funded by Medtronic, the device manufacturer.

The evidence for stable electrical parameters over time (1-2 years) (efficacy) are technical parameters, and we evaluated this evidence to be of low certainty.

However, the evidence showing that the complication rate Micra implants is lower than the conventional pacemakers, we determent to be of very low certainty, both because of the study design (single-arm) and that the choice of comparator (historical control).

### Other international assessments

We found a HTA on leadless pacemakers for right ventricle pacing, by the Ludwig Botlzmann Institut, Vienna, Austria (41). This group evaluated two leadless pacemakers, the Micra™ TPS and the Nanostim™ LCP, developed and manufactured by Medtronic and St Jude Medical, respectively. The report was an update from 2016. They concluded that evidence was not strong enough to prove that leadless peacemakers are as effective as, but safer than, conventional VVI pacemakers. Note that their assessment was based on results from both the leadless pacemakers available.

Another HTA, conducted by the Haute Autoritè de Santè in 2016 (42), assessed the added clinical value of Micra relative to conventional pacemakers and published a relative rating. Their clinical rating of Micra TPS, relative to conventional single chamber pacemaker, was (1) Substantial improvements for patients with venous access issues and prior infections, estimated to be 370 patients per year, (2) Moderate improvements for patients with risk of lead complication or the need to preserve the veins for other therapy, estimated to be 310 patients per year, and (3) No difference for the general indication for a VVI, estimated to be 15 700- 18 900 patients per year. We were not able to find the literature search and critically assessment of the studies in this report.

## Discussion of cost-effectiveness

In the cost-effectiveness analyses, we estimate added costs for introducing the Micra device to the whole population of patients recommended for single-chamber ventricular pacing. Since the safety data suggests that the rate of major complications after Micra implantation is lower than after conventional pacemaker implantation, we also wanted to analyse the cost-effectiveness for a sub-group consisting of patients who are particularly susceptible to complications or with high risk of complications following a pacemaker implantation. There are different clinical conditions for patients at high risk of complications (4) which can be used to define a sub-group of patients. In a Norwegian setting patients with such conditions were estimated to be 10-30 % of the total indicated patient population, suggested by the external experts and the submitter, and this number was used in the economic analyses.

Another important, but highly uncertain, estimation in the cost-effectiveness analyses was that patients with the Micra device will not experience any long term complications, that is, complications after year 1. Although the most frequent long term complications are related to lead and pocket infections and erosions, only associated with conventional pacemakers, there are no available studies on other long term complications with the Micra device to reveal leadless-pacemaker specific complications.

We have not found any published economic evaluations of leadless pacemakers. Also, we did not find any studies comparing the two types of pacemaker devices in the specific sub-group analysed. The effect estimates in the economic model is therefore highly uncertain and made it difficult to make any general judgements to the potential cost-effectiveness of the intervention. The exception is that the rates of lead and pocket infection and erosion for a standard device is likely to have a significant impact on the results. Additional benefits for a leadless pacemaker has been suggested by CADTH in an evidence summary for leadless pacemakers from 2015 (3), including shorter procedure and recovery time, reduced fluoroscopy exposure for patients and staff, no visible lump or scar, better mobility in shoulder and expected better quality of life. Further, Sideris et al (43), lists advantages as eliminating potential complications related to venous access, vascular manipulation of the lead and chronic lead related complications as venous thrombosis and obstruction and tricuspid valve incompetence. None of these benefits were however, quantified and evidence has not been assessed.

Despite the shortcomings of the present report, this is the first economic evaluation being performed at a leadless pacemaker, and is for the Micra device only. Any infer-

ence to other leadless pacemakers as the Nanostim, should not be done. It is therefore a need for further research on implications of leadless pacemaker on the health economy.

## Implications for clinical practice

The clinical data indicates that there are less complications following Micra implantation than conventional devices, mainly due to lead and pocket related complications. Despite a high ICER this could suggest to offer the Micra device to a sub-population of patients who are particularly susceptible to, or at high risk of, complications. As discussed above, there are recognized clinical conditions for such patients and the surgeon will need to identify whether a patient is in a high risk group before the implantation.

## Need for further research

In this report we have identified two main issues where evidence is poor or completely lacking:

- There is no strong evidence that the Micra device has a lower short term complication rate than conventional pacemakers. Although the Micra TPS Post Approval Registry is ongoing and will generate new data until 2026, we do not know if this will generate sufficient results increasing the certainty of the evidence. For this, we would need to see results from a randomized controlled trial where the complication rate could be compared between existing and novel devices.
- We do not have any evidence showing that the Micra device has a complete absence of long-term complications or would be a benefit for specific subgroup of patients. For this, we would need to see results from larger cohorts estimating the risk factors and rates for complications after a Micra device implantation compared to conventional pacemakers for single-chamber ventricular pacing, both short term and long term complications.

# Conclusions

The Micra TPS is a leadless pacemaker which delivers consistent pacing as required and has a battery longevity according to the specifications for the device. The current evidence is not sufficient to prove that the Micra-TPS gives less complications than standard pacemakers. However, the device is leadless and hence avoids all complications related to lead and pocket, which is previously reported to be in the range of 2.5-5.5% in the indicated patient group (1;2). Published device or system related deaths were four in 1.575 implanted patients.

We looked at the budget impact of introducing Micra to all patients indicated for single chamber ventricular pacing and found that this would a total added cost of NOK 27,386,992 in year five. The ICER for this group rises well above the level that have been considered cost-effective in Norway.

Offering the Micra device to only patients particularly susceptible to complications or have a defined high risk of complications, may be an alternative model. Although there were no clinical evidence that the Micra may be beneficial to any specific sub-group of patients, we decided to analyse the cost-effectiveness for offering the Micra device to patients with high risk of complications, and more specific, with high risk of infections. This group was estimated to be 10-30% of the total indicated patients. The analysis show that the total added cost will be about NOK 4,652,759 in year five, by introducing Micra to this group in a Norwegian setting. After adjusting the model to account for important shortcomings in the submitted analysis, related to clinical effect input data, the ICER is considered not to be cost-effective for this sub-group.

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# Appendix

## Appendix 1. Abbreviations and glossary of terms

| | |
|---|---|
| Class I recommendation | American College of Cardiology and the American Heart Association recommendations for indications for device therapy (44): "Conditions for which there is evidence and/or general agreement that a given procedure or treatment is beneficial, useful, and effective". |
| DRG | Diagnosis-related group |
| FDA | Food and Drug Administration |
| GRADE | Grading of Recommendations Assessment, Development and Evaluation |
| HRQL | Health related quality of life.<br>An individual's or a group's perceived physical and mental health over time. |
| HTA | Health technology assessment |
| ICER | Incremental cost effectiveness ratio.<br>The difference in the mean costs of two interventions in the population of interest divided by the difference in the mean outcomes in the population of interest. |
| Micra device | The pacing part of the Micra TPS |
| Micra TPS | Micra Transcatheter pacing system (the device to be assessed) |
| NIPH | Norwegian Institute of Public Health |
| NOK | Norwegian Kroner |
| QALY | Quality adjusted life year |
| RCT | Randomised controlled trial |
| VAS | Visual analogue scale |
| VVI pacing | Ventricle paced, ventricle sensed, pacing is inhibited if beat is sensed |

## Appendix 2. Search strategies

Search for: Micra leadless pacemaker / Micra transcatheter pacemaker

Date Run: 30. Aug, 2017 (23. Oct, 2017, see below)

Databases: Cochrane Library: Cochrane Database of Systematic Reviews, Other Reviews, Trials, Technology Assessments and Economic Evaluations; Centre for Reviews and Dissemination; Embase (OVID); OVID MEDLINE; Epistemonikos; PubMed; Trip.

Other sources: NICE; PROSPERO; POP database; SBU; ClinicalTrials.gov; WHO ICTRP; AETS; CADTH.

Total unique hits:

From databases: 118

From other sources: 6

Searched by: Ingrid Harboe, peer reviewed by Elisabeth Hafstad (research librarians/senior advisors)

### Summary of search

| Search source | Hits |
|---|---|
| *Databases* | |
| Cochrane library | 3 |
| Centre for Reviews and Dissemination: DARE/ HTA | 1 |
| MEDLINE/ Embase | 126 |
| MEDLINE/ Embase, additional seach | 18 |
| Epistemonikos | 1 |
| PubMed | 15 |
| NICE (National Institute for Health and Care Excellence) | 4 |
| PROSPERO | 0 |
| POP database (EUnetHTA database for planned and ongoing projects) | 0 |
| SBU (Swedish Agency for Health Technology Assessment and Assessment of Social Services) | 0 |
| Total | 168 |
| *Total unique hits, databases* | 118 |
| *Other source* | |
| ClinicalTrials.gov | 3 |
| WHO ICTRP | 1 |
| Trip, AETS, CADTH | 2 |
| *Total unique hits, other sources* | 6 |
| **Total, all sources** | **124** |

**Search in databases**

***Cochrane library***

Hits: 3
Search:

| ID | Search | Hits |
|---|---|---|
| #1 | MeSH descriptor: [Pacemaker, Artificial] explode all trees | 752 |
| #2 | MeSH descriptor: [Cardiac Pacing, Artificial] explode all trees | 1451 |
| #3 | MeSH descriptor: [Atrial Fibrillation] this term only | 3440 |
| #4 | MeSH descriptor: [Bradycardia] this term only | 434 |
| #5 | ((#1 or #2 or #3 or #4) and micra) | 1 |
| #6 | Micra transcatheter pacing system* | 1 |
| #7 | ((pac* or implant*) and micra) | 3 |
| #8 | ((atri* or bradycardi* or cardi* or heart*) and micra) | 1 |
| #9 | ((atri* or bradycardi* or cardi* or heart*) and micra) in Other Reviews, Trials, Technology Assessments and Economic Evaluations | 1 |
| #10 | #5 or #6 or #7 or #8 or #9 | 3 |

***Centre for Reviews and Dissemination***

Hits: 1
Search:

| ID | Search | Hits |
|---|---|---|
| 1 | (micra or Micra transcatheter pacing system*) | 1 |

***Embase*** *1974 to 2017 Week 33;* ***Ovid MEDLINE(R)*** *Epub Ahead of Print; In-Process & Other Non-Indexed Citations;* ***Ovid MEDLINE(R) Daily****;* ***Ovid MEDLINE(R)*** *1946 to Present*

Hits: 126 + 18
Search:

| ID | Search | Hits |
|---|---|---|
| 1 | (exp Pacemaker, Artificial/ or exp pacemaker implantation/ or exp heart ventricle pacing/ or exp Cardiac Pacing, Artificial/ or exp single chamber pacemaker/) and micra.ti,ab. | 56 |
| 2 | ((atri* or bradycardi* or cardi* or heart*) and micra).ti,ab. | 96 |
| 3 | ((pac* or implant*) and micra).ti,ab. | 152 |
| 4 | Micra transcatheter pacing system*.ti,ab. | 41 |
| 5 | or/1-4 | 187 |
| 6 | remove duplicates from 5 | 126 |
| 7 | 6 use ppez | 22 |
| 8 | 6 use oemez | 104 |

An additional search were performed in MEDLINE/Embase using micra as keyword (micra.kw) (Date: 2017.10.23)

| ID | Search | Hits |
|---|---|---|
| 1 | "Leadless Cardiac Pacemaker Implantation After Lead Extraction in Patients With Severe Device Infection.".m_titl. | 3 |
| 2 | (exp Pacemaker, Artificial/ or exp pacemaker implantation/ or exp heart ventricle pacing/ or exp Cardiac Pacing, Artificial/ or exp single chamber pacemaker/) and micra.ti,ab. | 69 |
| 3 | ((atri* or bradycardi* or cardi* or heart*) and micra).ti,ab. | 115 |
| 4 | ((pac* or implant*) and micra).ti,ab. | 173 |
| 5 | Micra transcatheter pacing system*.ti,ab. | 47 |
| 6 | or/2-5 | 209 |
| 7 | 1 and 6 | 0 |
| 8 | micra.kw. | 31 |
| 9 | 1 and 8 | 3 |
| 10 | 8 not 6 | 26 |
| 11 | remove duplicates from 10 | 18 |

Search guide: OVID search syntax

| | |
|---|---|
| pt. | denotes a Publication Type term |
| .ab. | denotes a word in the abstract |
| .fs. | denotes a 'floating' subheading |
| .sh. | denotes a Medical Subject Heading (MeSH) term |
| .ti. | denotes a word in the title. |
| * (asterisk) | denotes truncation (e.g. random* for random or randomised or randomized or randomly, etc) |

***Epistemonikos***

Hits: 1
Search:

((title:(Micra transcatheter pacing system*) OR abstract:(Micra transcatheter pacing system*))) OR (title:((atri*OR bradycardi* OR cardi* OR heart*) AND micra)) OR abstract:((atri*OR bradycardi* OR cardi* OR heart*) AND micra))) OR (title:((pacemaker OR pacing OR implant) AND micra) OR abstract:((pacemaker OR pacing OR implant) AND micra))

***PubMed***

Hits: 15
Search:

Micra transcatheter pacing system[Title/Abstract]

**Search in other sources**

***ClinicalTrials.gov***

Hits: 3
Search:
Micra Transcatheter Pacing System; Micra Pacemaker Implant
Result:

| Study Title | Status | Conditions | Interventions |
|---|---|---|---|
| Micra Transcatheter Pacing System Post-Approval Registry | Recruiting | Bradycardia | Device: Micra Trans-catheter Pacing System |
| Micra Transcatheter Pacing System Continued Access Study Protocol | Completed | Bradycardia | Device: Micra Pacemaker Implant |
| Micra Transcatheter Pacing Study | Active, not recruiting Has Results | Class I or II Indication for Implantation of a Single Chamber Ventricular Pacemaker According to ACC/AHA/HRS 2001 Guidelines and Any National Guidelines | Device: Micra Pacemaker Implant |

***WHO ICTRP***

Hits: 1
Search:
Micra Transcatheter Pacing System; Micra Pacemaker Implant
Result:

| Public Title | Status | Main ID | Date of Registration | Prospective Registration |
|---|---|---|---|---|
| Micra Study - to evaluate the safety and effectiveness of the Micra pacemaker and to assess its long-term performance. | Not Recruiting | CTRI/2015/01/005445 | 22-01-2015 | Yes |

***Trip, AETS (Agencia de Evaluación de Tecnologias Sanitarias), CADTH (Canadian Agency for Drugs and Technologies in Health).***

Unique hits: 2
Search:
Micra Transcatheter Pacing System; Micra Pacemaker Implant
Result:

| Nr. | Study Title |
|---|---|
| 1 | Miniature Leadless Pacemaker; |
| 2 | Leadless Pacemakers for the Treatment of Cardiac Arrhythmias |

## Appendix 3. Excluded references

NOTE: We here only present excluded full text references. The excluded abstracts are not listed as they were excluded based on the format only.

| | | |
|---|---|---|
| 1. | Soejima K, Edmonson J, Ellingson ML, Herberg B, Wiklund C, Zhao J. Safety evaluation of a leadless transcatheter pacemaker for magnetic resonance imaging use. Heart Rhythm 2016;13(10):2056-63. | Pre-clinical study and case report. |
| 2. | Essandoh M. Perioperative Management of the Micra Leadless Pacemaker. Journal of Cardiothoracic and Vascular Anesthesia 2017. | Commentary. |
| 3. | Montgomery JA, Orton JM, Ellis CR. Feasibility of Defibrillation and Pacing Without Transvenous Leads in a Combined MICRA and S-ICD System Following Lead Extraction. Journal of Cardiovascular Electrophysiology 2017;28(2):233-4. | Case report. |
| 4. | El-Chami MF, Roberts PR, Kypta A, Omdahl P, Bonner MD, Kowal RC, et al. How to Implant a Leadless Pacemaker With a Tine-Based Fixation. Journal of cardiovascular electrophysiology 2016;27(12):1495-501. | Review of implantation technique. |
| 5. | Karjalainen PP, Nammas W, Paana T. Transcatheter leadless pacemaker implantation in a patient with a transvenous dual-chamber pacemaker already in place. Journal of electrocardiology 2016;49(4):554-6. | Case report. |
| 6. | Kerwin SA, Mayotte MJ, Gornick CC. Transcatheter pacemaker implantation in a patient with a bioprosthetic tricuspid valve. Journal of interventional cardiac electrophysiology : an international journal of arrhythmias and pacing 2015;44(1):89-90. | Case report. |
| 7. | Koay A, Khelae S, Wei KK, Muhammad Z, Mohd Ali R, Omar R. Treating an infected transcatheter pacemaker system via percutaneous extraction. HeartRhythm Case Rep 2016;2(4):360-2. | Case report. |
| 8. | Kypta A, Blessberger H, Kammler J, Lambert T, Lichtenauer M, Brandstaetter W, et al. Leadless Cardiac Pacemaker Implantation After Lead Extraction in Patients With Severe Device Infection. Journal of cardiovascular electrophysiology 2016;27(9):1067-71. | Outcome not relevant. |

## Appendix 4. Included reference result for NIPH and submitter

| | Reference | NIPH | Submitter |
|---|---|---|---|
| 1. | Ritter P, Duray GZ, Steinwender C, Soejima K, Omar R, Mont L, et al. Early performance of a miniaturized leadless cardiac pacemaker: The Micra Transcatheter Pacing Study. European Heart Journal 2015;36(37):2510-9. | Included. | Included. |
| 2. | Pachon M, Puchol A, Akerstrom F, Rodriguez-Padial L, Arias MA. Implantation of the Micra Transcatheter Pacing System: Initial Experience in a Single Spanish Center. Rev Esp Cardiol (Engl Ed) 2016;69(3):346-9. | Included. | Included. |
| 3. | Reynolds D, Duray GZ, Omar R, Soejima K, Neuzil P, Zhang S, et al. A Leadless Intracardiac Transcatheter Pacing System. New England Journal of Medicine 2016;374(6):533-41. | Included. | Included. |
| 4. | Da Costa A, Axiotis A, Romeyer-Bouchard C, Abdellaoui L, Afif Z, Guichard JB, et al. Transcatheter leadless cardiac pacing: The new alternative solution. International Journal of Cardiology 2017;227:122-6. | Included. | Not included. Published after search. |
| 5. | Duray GZ, Ritter P, El-Chami M, Narasimhan C, Omar R, Tolosana JM, et al. Long-term performance of a transcatheter pacing system: 12-Month results from the Micra Transcatheter Pacing Study. Heart Rhythm 2017;14(5):702-9. | Included. | Included after the literature search in Nov 2016. |
| 6. | Grubman E, Ritter P, Ellis CR, Giocondo M, Augostini RS, Neuzil P, et al. To retrieve, or not to retrieve: System revisions with the micra transcatheter pacemaker. Heart Rhythm 2017;14:S245-S6. | Included. | Not included. Published after search. |
| 7. | Lloyd M, Reynolds D, Sheldon T, Stromberg K, Hudnall JH, Demmer WM, et al. Rate adaptive pacing in an intracardiac pacemaker. Heart Rhythm 2017;14(2):200-5. | Included. | Not included. Published after search. |
| 8. | Martinez-Sande JL, Garcia-Seara J, Rodriguez-Manero M, Fernandez-Lopez XA, Gonzalez-Melchor L, Redondo-Dieguez A, et al. The Micra Leadless Transcatheter Pacemaker. Implantation and Mid-term Follow-up Results in a Single Center. Revista Espanola de Cardiologia 2017;70(4):275-81. | Included. | Not included. Published after search. |

| | | | |
|---|---|---|---|
| 9. | Piccini JP, Stromberg K, Jackson KP, Laager V, Duray GZ, El-Chami M, et al. Long-term outcomes in leadless Micra transcatheter pacemakers with elevated thresholds at implantation: Results from the Micra Transcatheter Pacing System Global Clinical Trial. Heart Rhythm 2017;14(5):685-91. | Included. | Not included. Published after search. |
| 10. | Roberts PR, Clementy N, Al Samadi F, Garweg C, Martinez-Sande JL, Iacopino S, et al. A leadless pacemaker in the real-world setting: The Micra Transcatheter Pacing System Post-Approval Registry. Heart Rhythm 2017;11:11. | Included. | Not included. Published after search. |
| 11. | Simmers TA, Bonner MD, Fale B, Eggen MD, Ritter P, Reynolds D. How robust is the Micra transcatheter pacemaker fixation? Europace 2015;17:iii26. | Excluded based on abstract criteria. | Included. |
| 12. | Kuhne, M., Reichlin, T., Muehl, A., Knecht, S., Celikyurt, U., Schaer, B., Osswald, S., and Sticherling, C., 2016, Leadless transcatheter VVI-Pacing (MicraTM) compared to standard transvenous VVI-Pacing: European Heart Journal, v. 37, p. 1305. | Not found in search. | Included. |
| 13. | Kowal, R., Soejima, K., Ritter, P., Duray, G. Z., Hudnall, J. H., Stromberg, K., and Reynolds, D., 2016, Relationship between operator experience and procedure outcomes with the micra transcatheter leadless pacing system: Heart Rhythm, v. 13, p. S169. | Excluded based on the abstract criteria. | Included. |
| 14. | Kypta, A., Blessberger, H., Kammler, J., Lambert, T., Lichtenauer, M., Brandstaetter, W., Gabriel, M., and Steinwender, C., 2016, Leadless Cardiac Pacemaker Implantation After Lead Extraction in Patients With Severe Device Infection: J.Cardiovasc. Electrophysiol., v. 27, p. 1067-1071. | Excluded based on population criteria (patients in need for revision because of infection). | Included. |

# Appendix 5. Critical assessment of the methodology and risk of bias of included studies

### *The Micra TP Study and Micra TPS Post Approval Registry – without comparator*

Two reviewers (TET, LG) critically assessed the methodology of the included studies which did not include controls. We used a checklist from Anon 2017 New York Department of Health Evidence-based Review Process for Coverage Determinations.

| Adapted from Anon 2017 New York Department of Health Evidence-based Review Process for Coverage Determinations https://www.health.ny.gov/health_care/medicaid/redesign/docs/dossier_submission_form.pdf | | Quality Appraisal Checklist: Case Series | |
|---|---|---|---|
| *Study identification (as given in the report)*<br>Micra TP Study: Ritter2015, Reynolds 2016, Duray 2017, Lloyd 2017, Piccini 2017<br>Micra TPS Post Approval Registry: Roberts 2017 | | | |
| Checklist completed by: Torunn E Tjelle and Liv Giske | | | Date: 8. Feb, 2018 |
| SECTION 1: INTERNAL VALIDITY | | MICRA TP STUDY | MICRA TPS POST APPROVAL REGISTRY |
| | | YES / NO / UNCLEAR / NA | |
| 1.1 | The study addresses an appropriate and clearly focused question. | YES | YES |
| SELECTION OF SUBJECTS | | | |
| 1.2 | Were the patient characteristics clearly described? | YES | YES |
| 1.3 | Was the likelihood that some eligible subjects might have the outcome at the time of enrolment assessed and accounted for in the analysis (pertinent for screening and diagnostic topics)? | N/A<br>The outcomes were any adverse events in an already diseased population. The diagnosis were recorded before enrolment. | N/A<br>The outcomes were any adverse events in an already diseased population. The diagnosis were recorded before enrolment. |
| 1.4 | Was the study based on a consecutive sample or other clearly defined relevant population? | UNCLEAR | UNCLEAR |
| 1.5 | Did all of the individuals enter the study at a similar point in their disease progression? | YES | NO<br>This study also included patients with revisions. |
| ASSESSMENT AND FOLLOW-UP | | | |
| 1.6 | Were outcomes assessed using objective criteria (i.e., medical records) or was blinding used? | NO<br>Criteria for adverse event: longer hospitalization or re-hospitalization. No blinding. | NO<br>Criteria for adverse event: longer hospitalization or re-hospitalization. No blinding. |
| 1.7 | Was follow-up long enough for important events to occur? | YES | YES |
| 1.8 | Was there a low dropout or withdrawal rate (<20%)? | YES | YES |
| CONFOUNDING | | | |
| 1.9 | Were the main potential confounders identified and taken into account in the design and analysis? | UNCLEAR<br>Crude patient population and no confounders taken into account.<br>Funding by manufacturer. | UNCLEAR<br>Crude patient population and no confounders taken into account.<br>Funding by manufacturer. |
| CONFLICT OF INTEREST | | | |
| 1.10 | Have competing interests of members have been recorded and addressed? | YES<br>Financed by Medtronic | YES<br>Financed by Medtronic |
| 1.11 | Have views of funding body influenced the content of the study? | UNCLEAR | UNCLEAR |

NIPH

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