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Continuous monitoring of pulmonary artery pressure via an implanted leadless and battery less pressure sensor for the management of patients with moderate to severe heart failure (New York Heart Association class III)

A single technology assessment

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Norwegian Institute of Public Health
Oslo, October 2016

Executive summary

Background

In Norway the prevalence of chronic heart failure has been estimated to be 2 percent, meaning 80 000 – 100 000 people. Around 75 percent of heart failure patients are older than 75 years old. Furthermore, patients diagnosed with heart failure account for approximately 5 percent of all hospital admissions in Norway, and at any one time about 20 percent of patients on a medicine department consist of heart failure patients.

The New York Heart Association (NYHA) has categorized heart failure into four classes. Class I and class II are considered mild. Class III is considered moderate and class IV is considered severe. The CardioMEMS™ HF System implantable pulmonary artery pressure sensor is to be used by patients classified within class III, i.e. moderate heart failure.

The CardioMEMS™ HF System is only commercially available in the USA. In USA the CardioMEMS™ HF System was approved through the Premarket Approval (PMA) process by the U.S. Food and Drug Association (FDA) in May 2014. Approval was based upon one randomised, controlled clinical trial. The approved indication is: «This device is indicated for wirelessly measuring and monitoring pulmonary artery (PA) pressure and heart rate in New York Heart Association (NYHA) Class III heart failure patients who have been hospitalized for heart failure in the previous year. The hemodynamic data are used by physicians for heart failure management and with the goal of reducing heart failure hospitalisations».

Objective

This single technology assessment was commissioned by the The National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway. They wanted Norwegian Institute of Public Health to evaluate the efficacy, safety and health economic documentation for continuous monitoring of pulmonary artery pressure via an implanted leadless and battery less pressure sensor (CardioMEMS™ HF System) compared to standard treatment for the man-

agement of patients with New York Heart Association (NYHA) class III heart failure. We have evaluated the submitted documentation up towards available published documentation.

Evaluation of the documentation

Efficacy documentation

Evidence for the efficacy and safety came from the CHAMPION trial (NCT00531661) presented in two main publications. The CHAMPION trial was designed and powered to test, in home patients with NYHA Class III heart failure, the hypothesis that pulmonary artery pressure guided management with the CardioMEMS™ HF System would be a superior way to reduce the rate of heart-failure-related hospitalisations compared to current disease management systems relying on changes in weights, edema, or other symptoms.

From these two publications we have reviewed the randomised part of the trial for efficacy endpoints up to 18 months and safety endpoints up to 31 months. The randomised period ended after 18 months, after which the study went into an open access period for additional 13 months.

We have evaluated the quality of the evidence by GRADE (Grading of Recommendations Assessment, Development, and Evaluation). This is a system for grading the quality of evidence and strength of recommendations. The sponsor had not evaluated the quality of the evidence.

Health economic documentation

St. Jude Medical performed a cost-effectiveness analysis for evaluating the cost-effectiveness of CardioMEMS HF system. The sponsor considered variations in outcomes and costs depending on which treatment method a NYHA class III heart failure patient undergoes. By developing a Markov cohort model, they estimated the cost-effectiveness of the new technology compared to usual care strategies over a 10 years time horizon, for patients aged 70. The sponsor model considered just two health states “stable heart failure” and “death”. Other possible health states associated to complications were not modeled. However, the costs associated with the overall implant related complications were included in the evaluation.

In addition to presenting the results calculated by the sponsor, we have performed a separate analysis where we adjusted some of the input variables. We adjusted some of the variables because of deficient explanations from the sponsor on how they were estimated, or that we found a more reasonable assumption according to Norwegian conditions. We also performed a scenario analysis by changing the start age to 60 and 50 years, based on recommendation from the Norwegian clinical expert.

In the absence of the probabilities distributions for all the uncertain parameters, the uncertainties were assessed as one-way sensitivity analysis. We have presented the results of the sensitivity analyses as tornado diagrams.

Results

Efficacy results

Heart-failure-related hospitalisation: The intervention group had fewer heart-failure-related hospitalisation than the control group. The relative reductions were 28%, 37% and 33% respectively at 6, 15 and 18 months. We evaluated the quality of the evidence for this endpoint to be moderate.

Health related quality of life: Health related quality of life as measured with the Minnesota Living with Heart Failure Questionnaire both at 6 and 12 months was in favour of the intervention group. Mean and standard deviation were 45 (26) and 51 (25) at 6 months, and 47 versus 57 at 12 months, for the intervention and the control group respectively. We evaluated the quality of the evidence for these two endpoints to be moderate.

Mortality: The proportion of patients who died in the treatment group was smaller than in the control group with a nonsignificant relative risk reduction of 20% at 18 months. The mortality was 50/270 (19%) in the intervention group as compared to 64/280 (23%) in the control group, hazard ratio was 0.80 (0.95% CI 0.55-1.15). We evaluated the quality of the evidence for this endpoint to be low.

Safety: Generally there were few complications. Since both groups had the sensor implanted, we are interested in the safety data for the two groups together. We found that the overall combined device-related or system-related complication rate was 0.03 events per patient-year in the entire follow-up period (31 months). This represented a complication rate of 1.4% for the total population. This is comparable to the complication rate as reported for procedure-related serious adverse events (1.2%).

Health economic results

The calculated incremental cost-effectiveness ratio (ICER) based on the submitted economic model over 10 years time horizon was NOK 289,300 per quality adjusted life year (QALY) gained for patients aged 70. The corrected model gives a similar ICER as the result presented by the sponsor. By adjusting some of the input variables and assumptions, our calculated ICER became NOK 270,500 per QALY gained for patients aged 70.

In our scenario analyses we found that the ICERs were reduced when the patient group was younger, and the device will be more cost-effective if the patient group is younger.

The one-way sensitivity analysis showed that the results were most sensitive to changes in utility values both for treatment and control group at 12 months, efficacy data (mortality and HF hospitalisation), and costs related to standard heart failure care (excluding hospitalisation). Utility values at 12 month for treatment group had the largest uncertainty and the ICER varied between NOK 268,000 and NOK 485,000.

The sponsor estimated that the total added costs of implementing CardioMEMS in Norway would be about NOK 50,000,000 for the first five years.

Due to uncertainties associated with the number of patients (for both treatment strategies) and the yearly costs used in the calculation of budget impact by the sponsor, we re-calculated the additional costs of introducing the technology in Norway. The results of our budget impact analysis showed that assuming 100 new patients each year, the total added expected cost will be about NOK 89,000,000 for the first five years after adoption of CardioMEMS in Norway.

Discussion

Efficacy

The sponsor has submitted documentation supporting the selected PICO's, the literature search and the presentation of the evidence. However, we miss a critical appraisal from the sponsor of the quality of the evidence, both for the publications (risk of bias) and for the specific endpoints (GRADE).

There are reported data for efficacy and safety up to 18 and 31 months respectively. These time periods are relatively short. Further, all the available evidence came from only one trial (the CHAMPION trial) with few events. Therefore we cannot exclude that the evidence may change with further studies available.

Health economic

The sponsor performed economic evaluation by developing a simple model with only two health states. However, based on thorough review and input given by the clinical experts we think that the health economic model captured the outcomes that are clinically relevant to the defined population and intervention.

There were several uncertain points to consider regarding the submission. We performed some scenario analyses for younger patients (50 and 60 years), adjusted some input parameters (such as the costs related to implant procedure and the risk

rate of heart failure hospitalisation, and corrected some confidence intervals). However, these changes in the parameter values and assumptions did not have a great impact on the results.

Conclusion

Efficacy

The use of the CardioMEMS™ HF System is safe and probably reduces the heart-failure-related hospitalisation rate compared to standard treatment in heart failure patients with NYHA functional class III.

The evidence on efficacy and safety had relative short follow-up periods, 18 and 31 months respectively. Further, all the available evidence came from only one trial with few events. Hence the evidence may change with further studies available.

Cost-effectiveness

The use of the CardioMEMS device can most likely be considered cost-effective in heart failure patients with NYHA functional class III at what has normally been considered a cost-effective use of Norwegian health-care resources.

However, there are some uncertainties regarding the input parameters and assumptions. Long-term utility values, clinical efficacy data and costs related to standard heart failure care (excluding hospitalisation) group had the greatest impact on the results.

Sammendrag (norsk)

Tittel

Kontinuerlig monitorering av trykk i pulmonalarterien via en implantert trådløs sensor uten batteri for håndtering av pasienter med moderat til alvorlig hjertesvikt (New York Heart Association class III).

Bakgrunn

Forekomsten av kronisk hjertesvikt i Norge er anslått til 2 %, dvs. ca. 80 000 – 100 000 mennesker. Ca. 75 % av hjertesviktpasientene er over 75 år. Pasienter med hjertesvikt utgjør ca. 5 % av alle sykehusinnleggelsene i Norge, og til enhver tid er hjertesvikt det sentrale problem for ca. 20 % av pasientene på en indremedisinsk avdeling.

«The New York Heart Association (NYHA)» har kategorisert hjertesvikt i fire klasser. Klasse I og II betraktes som mild hjertesvikt. Klasse III betraktes som moderat og klasse IV som alvorlig. Den implanterte sensoren, som kalles «CardioMEMS™ HF System», brukes til monitorering av trykk i púlmonal arterien hos pasienter klassifisert i klasse III, dvs. moderat hjertesvikt.

“CardioMEMS™ HF System” er bare markedsført i USA.

I USA var “CardioMEMS™ HF System” godkjent i “The Premarket Approval (PMA) process” av “the U.S. Food and Drug Association” (FDA) i mai 2014. Godkjenningen var basert på en randomisert, kontrollert klinisk studie. Godkjent indikasjon er: «This device is indicated for wirelessly measuring and monitoring pulmonary artery (PA) pressure and heart rate in New York Heart Association (NYHA) Class III heart failure patients who have been hospitalized for heart failure in the previous year. The hemodynamic data are used by physicians for heart failure management and with the goal of reducing heart failure hospitalisations».

Problemstilling

Denne hurtigmetodevurderingen ble bestilt av Bestillerforum i “Nasjonalt system for innføring av nye metoder i spesialisthelsetjenesten” i Norge. De ønsket at Folkehelseinstituttet skulle evaluere dokumentasjonen for effekt, sikkerhet og helseøkonomi for kontinuerlig monitorering av trykk i púlmonal arterien via en implantert trådløs sensor uten batteri (CardioMEMS™ HF System) sammenliknet med standard behandling for håndtering av pasienter med moderat til alvorlig hjertesvikt (New York Heart Association class III).

Vi har vurdert den innsendte dokumentasjonen opp mot tilgjengelig publisert dokumentasjon.

Vurdering av dokumentasjonen

Dokumentasjon for effekt og sikkerhet

Dokumentasjonen for effekt og sikkerhet kom fra to hovedpublikasjoner fra CHAMPION studien (NCT00531661). CHAMPION studien var designet og styrkeberegnet for å undersøke pasienter med NYHA klasse III hjertesvikt, som ikke var hospitaliserte. Følgende forskningsspørsmål ble undersøkt: Om monitorering av trykk i púlmonal arterien via en implantert trådløs sensor uten batteri (CardioMEMS™ HF System) ville være bedre sammenliknet med standard behandling, basert på endringer i vekt, ødemer eller andre symptomer, med hensyn på å redusere hjertesviktrelaterte sykehusinnleggelseser.

Fra disse to publikasjonene har vi vurdert effektendepunktene opptil 18 måneder fra den randomiserte delen av studien, og endepunktene for sikkerhet opptil 31 måneder. Den randomiserte perioden endte etter 18 måneder, deretter fortsatte studien i en «open access» periode i ytterligere 13 måneder.

Vi har evaluert kvaliteten av dokumentasjonen ved hjelp av GRADE. Innsender hadde ikke vurdert kvaliteten på dokumentasjonen.

Helseøkonomisk dokumentasjon

St. Jude Medical presenterer en kostnadseffektivitetsanalyse der de evaluerer kostnadseffektiviteten knyttet til CardioMEMS HF system. Firmaet vurderte om de forskjellige behandlingsmetodene som utføres på pasienter diagnostisert med NYHA class III hjertesvikt ville gi ulike utfall og kostnader.

De utviklet en Markov-kohortmodell der de beregnet kostnadseffektiviteten av den nye intervensjonen sammenliknet med standard behandlingsstrategier over et tiårsperspektiv. Markovmodellen omfattet 70 år gamle pasienter. Den innsendte modellen tar utgangspunkt i kun to helsetilstander, «stabil hjertesvikt» og «død».

Andre eventuelle helsetilstander knyttet til komplikasjoner av hjertesvikt var ikke betraktet i modellen. Firmaet evaluerte imidlertid kostnadene av de generelle komplikasjonene som er knyttet til implanteringen av CardioMEMS HF system.

Nasjonalt Folkehelseinstitutt har i tillegg til å presentere resultater beregnet av sponsoren utført en egen analyse. Enkelte innsatsfaktorer kalkulert av firmaet manglet opplysninger på hvordan de var beregnet, og andre var ikke tilstrekkelig tilpasset Norske forhold. Vi justerte disse innsatsfaktorene i den separate analysen. I tillegg utførte vi en scenarioanalyse der vi endret startalderen til 60 og 50 år basert på anbefalinger fra vår norske kliniske ekspert.

Ettersom den innsendte modellen manglet sannsynlighetsfordelinger for alle de usikre parametrene ble usikkerheten vurdert i en enveis sensitivitetsanalyse. Vi har presentert resultatene av sensitivitetsanalysene som tornadodiagram.

Resultat

Effekt og sikkerhetsresultater

Hjertesviktrelaterte sykehusinnleggelse: Intervensjonsgruppen hadde færre hjertesviktrelaterte sykehusinnleggelse enn kontrollgruppen. Den relative reduksjonen var henholdsvis 28 %, 37 % og 33 % ved 6, 15 og 18 måneder. Vi vurderte kvaliteten på dokumentasjonen for dette endepunktet til å være moderat.

Helserelatert livskvalitet: Helserelatert livskvalitet, målt ved “the Minnesota Living with Heart Failure Questionnaire” både ved 6 og 12 måneder, var i favør av intervensjonsgruppen. Gjennomsnitt og standard avvik var henholdsvis 45 (26) and 51 (25) ved 6 måneder, og 47,0 versus 56,5 ved 12 måneder for intervensjons- og kontrollgruppen. Vi vurderte kvaliteten på dokumentasjonen for begge disse endepunktene til å være moderat.

Mortalitet: Ingen forskjell mellom gruppene. Ved 18 måneder var mortaliteten 50/270 (19 %) i intervensjonsgruppen sammenliknet med 64/280 (23 %) i kontrollgruppen, hazard ratio var 0,80 (0,95 %KIO,55-1,15). Vi vurderte kvaliteten på dokumentasjonen for dette endepunktet til å være lav ved 18 måneder.

Sikkerhet: Det var generelt få komplikasjoner. Siden begge gruppene hadde fått implantert sensoren, var vi interessert i sikkerhetsdata for de to gruppene samlet. Vi fant at den total kombinerte utstyr-relaterte eller system-relaterte komplikasjonsrate var 0,03 hendelser per pasient-år i løpet av hele oppfølgingsperioden (31 måneder). Dette representerer en komplikasjonsrate på 1,4 % for hele populasjonen. Dette er sammenlignbart med komplikasjonsraten rapportert for prosedyrerelaterte alvorlige bivirkninger (1,2 %).

Helseøkonomiske resultat

Sponsorens kalkulerte inkrementelle kostnadseffektivitetsratio (ICER) er NOK 289,300 per kvalitetsjusterte leveår (QALY) for pasienter med en alder av 70 år. Vi justerte noen av innsatsfaktorene og antakelsene. Deretter kalkulerte vi en ICER, ikke ulikt fra sponsoren sitt resultat, NOK 270,500 per QALY for pasienter med en alder av 70 år. I vår scenarionalyse fant vi at CardioMEMS vil være mer kostnadseffektiv for en yngre pasientgruppe ettersom ICER reduseres når pasientgruppen er yngre.

I vår enveis sensitivitetsanalyse ser vi at resultatene er mer sensitive til endringer i nytteverdier for både behandlings – og kontrollgruppen ved 12 måneder. Effektivitetsdata (mortalitet og hjertesviktinnleggelser) og kostnader knyttet til standard hjertesviktsbehandling (forutenom sykehusinnleggelser) er også sensitive variabler. Nytteverdiene ved 12 måneder for behandlingsgruppen viste mest usikkerhet og gir en ICER som varierte mellom NOK 268,000 og NOK 485,000.

Sponsoren utførte en fem års budsjettanalyse som viser at de totale ekstra kostnadene for å implementere CardioMEMS i Norge vil bli rundt NOK 50,000,000. På grunn av usikkerhet knyttet til antall pasienter (for begge behandlingsstrategier) og årlige kostnader som var brukt i de innsendte beregningene, omkalkulerte vi merkostnadene som vil forekomme dersom den nye metoden blir introdusert i Norge. Ved å anta 100 nye pasienter hvert år viser våre resultater av budsjettanalysen at man kan forvente at de totale ekstra kostnadene vil være omkring NOK 89,000,000 for de første fem årene etter å ha iverksatt CardioMEMS i Norge.

Diskusjon

Effekt og sikkerhet

Innsender har innsendt dokumentasjon som støtter de utvalgte PICO's, litteratursøket og presentasjonen av resultatene. Innsender har imidlertid ikke gjort en kritisk vurdering av kvaliteten av dokumentasjonen, verken for publikasjonene (risiko for skjevheter) eller for de spesifikke endepunktene (GRADE). Dette savnes.

For effekt og sikkerhet er det rapportert data opptil henholdvis 18 og 31 måneder. Disse tidsperiodene er relativt korte. Dessuten kommer all tilgjengelig dokumentasjon kun fra en studie (CHAMPION studien). Vi kan derfor ikke utelukke at de rapporterte resultater kan endres med ytterligere publiserte studier.

Helseøkonomi

Firmaet presenterte en enkel modell som kun inkluderte to helsetilstander. Denne modellen brukte de for å utføre en økonomisk evaluering. Basert på en grundig gjennomgang og innspill fra kliniske eksperter mener vi at den helseøkonomiske modellen fanger opp de utfallene som er klinisk relevante for den definerte populasjonen og intervensjonen.

Vi vurderte imidlertid flere usikre punkter angående den innsendte dokumentasjonspakken. Vi utførte ett par scenarioanalyser for yngre pasienter (50 og 60 åringer), justerte noen innsatsfaktorer (slik som kostnader knyttet til implanteringsprosedyren og risikorate for hjertesviktinnleggelse, og korrigererte noen konfidensintervaller). Våre endringer i parameterverdier og antakelser ga ingen store utslag på resultatene.

Konklusjon

Effekt og sikkerhet

Bruk av “CardioMEMS™ HF System” er sikker og reduserer sannsynligvis hjertesviktrelaterte sykehusinnleggelse sammenliknet med standard behandling hos hjertesviktspasienter med NYHA klasse III.

Dokumentasjonen for effekt og sikkerhet kommer fra relative korte oppfølgingsperioder, henholdsvis 18 og 31 måneder. I tillegg kommer all tilgjengelig dokumentasjon fra kun en studie med få hendelser. Vi kan derfor ikke utelukke at de rapporterte resultater kan endres med ytterligere publiserte studier.

Kostnadseffektivitet

Bruk av CardioMEMS HF system kan mest sannsynlig vurderes som kostnadseffektiv for pasienter diagnostisert med NYHA class III hjertesvikt. Konklusjonen tar utgangspunkt i hva som har blitt vurdert som kostnadseffektivt ved bruk av norske ressurser knyttet til helsevesenet.

Det finnes imidlertid noe usikkerhet angående innsatsfaktorer og antakelser. Langsiktige nytteverdier, kliniske effektdata og kostnader knyttet til standard hjertesviktbehandling (utenom sykehusinnleggelse) hadde størst betydning for resultatet.

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Preface

What is a single technology assessment

A single technology assessment (STA) is one of the products in The National System for Managed Introduction of New Health Technologies within the Specialist Health Service in Norway. The system has a website (<https://nyemetoder.no/>).

The Ordering Forum (Bestillerforum RHF) evaluates submitted suggestions and decides on which methods they need evaluated, and the type of evaluation they need. In a single health technology assessment, methods are evaluated based on documentation submitted by a company owning the method or their representatives. A template is available to aid the submission of necessary information and documentation (<https://nyemetoder.no/Documents/Administrativt%20%28brukes%20kun%20av%20sekretariatet%21%29/Template%20pharmaceuticals%20v3.pdf>)

Norwegian Institute of Public Health receives and evaluates the submitted documentation, but is not the decision-making authority. The single technology assessment from Norwegian Institute of Public Health will be available at our website. The Decision Forum (“Beslutningsforum RHF”), consisting of the directors for the four Health regions in Norway, makes the decision whether to introduce new methods or not.

Objective

In this single single technology assessment we will evaluate the efficacy, safety and health economic documentation for continuous monitoring of pulmonary artery pressure via an implanted leadless and battery less pressure sensor (CardioMEMS™ HF System) compared to standard treatment for the management of patients with New York Heart Association (NYHA) class III heart failure. Norwegian Institute of Public Health has evaluated the submitted documentation and additional available published documentation.

Logg

The Ordering Forum (“Bestillerforum RHF”) reviewed the suggestion regarding use of CardioMEMS™ HF System, ID2015_022, June 25th 2015. On August 24th 2015 “Bestillerforum RHF” requested Norwegian Knowledge Centre for the Health Services (now part of Norwegian Institute of Public Health) to perform a single single technology assessment on its use as an implanted sensor for the management of patients with moderate to severe heart failure (

<https://nyemetoder.no/metoder/implantert-sensor-for-handtering-av-pasienter-med-moderat-til-alvorlig-hjertesvikt>)

25.06.2015: Suggestion submitted

24.08.2015: The Ordering Forum (“Bestillerforum RHF”) commissioned a single technology assessment

September 2015-February 2016: dialogue and meeting with concerned company

17.03.1.2016: Valid submission

12.09.2016: End of 180 days evaluation period

Project group

The project group consisted of:

Project coordinator: Senior researcher Eva Pike

Senior researcher: Anne Mette Bjerkan

Health economists: Beate Charlotte Fagerlund and Vida Hamidi

Research librarian: Ingrid Harboe

Research director : Marianne Klemp

In addition, we have received help and feedback from the following persons:

Clinical expert: Reidar Bjørnerheim, MD, PhD, Head of Echocardiography, Oslo University Hospital.

Peer: Arne Westheim, MD, PhD, Cardiology department, Oslo University Hospital.

Signe Agnes Flottorp
Department director

Marianne Klemp
Research director

Eva Pike
Project coordinator

Background

Name of the device and the manufacturer who prepared the submission

Name of device: CardioMEMS™ HF System.

Name of the manufacturer which submitted the application: St. Jude Medical, International, Belgium.

Present approval

CardioMEMS™ HF System was CE marked in 2011. The CardioMEMS™ HF System is only commercially available in the USA.

In USA the CardioMEMS™ HF System was approved through the Premarket Approval (PMA) process by the U.S. Food and Drug Association (FDA) in May 2014 (1). Approval was based upon one randomised, controlled clinical trial (2). The approved indication is: «This device is indicated for wirelessly measuring and monitoring pulmonary artery (PA) pressure and heart rate in New York Heart Association (NYHA) Class III heart failure patients who have been hospitalized for heart failure in the previous year. The hemodynamic data are used by physicians for heart failure management and with the goal of reducing heart failure hospitalisations» (1). According to the FDA the CardioMEMS™ HF System is contraindicated for those patients who are unable to take two types of blood thinning medicines for one month after the sensor is implanted. The FDA gave the approval with some restrictions which can be read in detail in http://www.accessdata.fda.gov/cdrh_docs/pdf10/P100045a.pdf.

One example of the restrictions is that the labeling must specify the specific training or experience practitioners need in order to use the device. Further, continued approval of this PMA was contingent upon the following requirements to the manufacturer: submission of Annual Reports, as well as the requirements to conduct two post-approval studies, both will be conducted in USA, described below:

Study 1. *Newly Enrolled Champion*: This study will be conducted as per protocol dated March 21, 2014, Version 1.0. The study will be a prospective, multi-center,

open-label trial to examine the safety and effectiveness of CardioMEMS™ HF System. The study populations will be as in the CHAMPION study. The primary safety objectives are to evaluate 1) if device/system-related complication (DSRC)-free proportion of subjects is at least 80% at 24 months, and 2) if the pressure sensor failure-free proportion of subjects is at least 90% at 24 months. The primary effectiveness objective is to demonstrate that there is not a worsening in heart failure (HF) hospitalisation rate 1 year reported in the post-approval study reports (PAS) compared to 1 year prior to enrollment (based on hospitalisation records). Additional objectives will be to analyze 1-year mortality, compare the annualized HF hospitalisation or death rate at 1 year in study to the HF hospitalisation rate in the year prior to enrollment, and patient compliance.

Patients will be followed to 2-years post implant with follow-up visits at 1 month and every 6 months.

Study 2. Champion Substudy: This will be a prospective, multi-center, open-label trial to examine safety and compare the postmarket effectiveness of CardioMEMS™ HF System to premarket. The substudy patients will be all patients selected by independent committee from the PAS 1 (Main Cohort) who are optimally managed and are clinically similar to the Control group in CHAMPION based on preenrollment data. The primary safety objectives are similar as in the *Newly Enrolled Champion* study. The primary effectiveness objective is to demonstrate that there is not a worsening in heart failure (HF) hospitalisation rate 1 year in the PAS compared to the 1 year HF hospitalisation rate in the premarket control group.

Description of the technology

The monitoring system

The manufacturer of the CardioMEMS™ HF System describes the technology in the following way:

The CardioMEMS™ HF System system consists of a permanently implantable pressure sensor that is placed in the distal pulmonary artery using a guidewire compatible, catheter-based delivery system. The sensor is not battery driven and is interrogated by an electronic unit, which in turn uploads the measured pulmonary artery pressure waveform to a secure database. This database is accessible for medical professionals with the use of a secure web-based interface.

Observed changes in pulmonary artery pressure can be used in conjunction with heart failure signs and symptoms to guide HF management symptoms.

The CardioMEMS™ HF System is depicted in Figure 1 below.

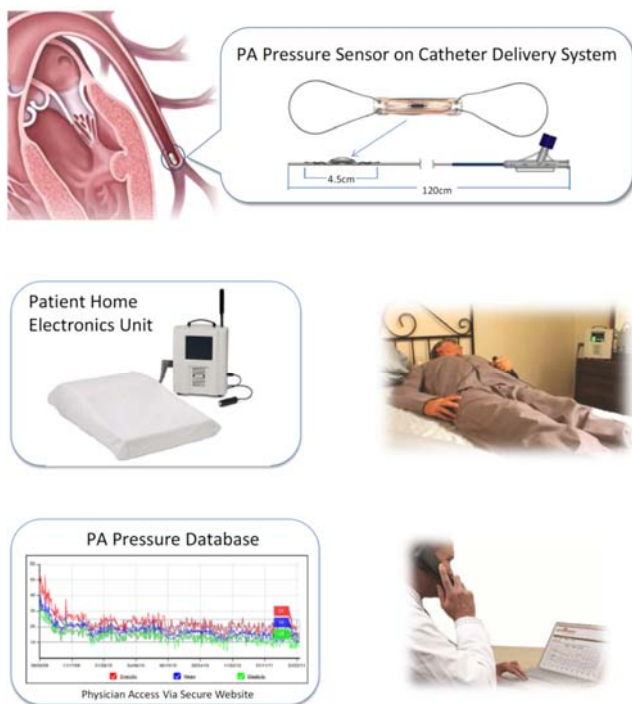


Figure 1. *The CardioMEMS™ HF System HF Monitoring system*

The sensor

The dimension of the sensor are 15 mm in length, 3,4 mm in width and 2 mm in thickness (see Figure 2).

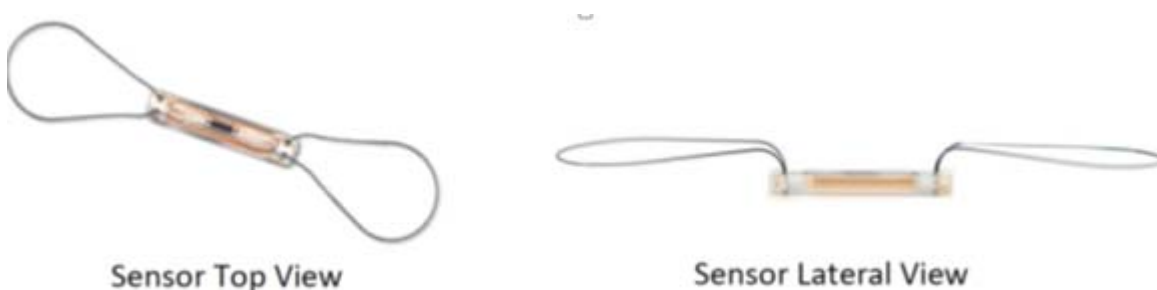


Figure 2. *The CardioMEMS™ HF System uses a minituarized wireless monitoring sensor that is implanted in the pulmonary artery*

The pressure sensor is permanently placed in the pulmonary artery during a right heart catheterisation procedure. The sensor does not require batteries or wires. The implanted sensor detects changes in pulmonary artery pressure.

Description, incidence and present treatment for heart failure patients (NYHA class III)

Description and incidence of heart failure NYHA class III

Heart failure is a complex clinical syndrome, and is a manifestation of the later stages of various cardiovascular diseases, including coronary artery disease, hypertension, valvular disease and primary myocardial disease (3). It is characterized by specific symptoms, such as dyspnea and fatigue, and signs related to fluid retention. The prevalence of heart failure has been estimated to 1-2 percent in the western world and the incidence approaches 5 – 10 per 1000 persons per year (4).

In Norway the prevalence of chronic heart failure has been estimated to be 2 percent, meaning 80 000 – 100 000 people (5). Around 75 percent of heart failure patients are older than 75 years old. Furthermore, patients diagnosed with heart failure accounts for approximately 5 percent of all hospital admissions in Norway, and any time about 20 percent of patients on a medicine department are heart failure patients (6). Additionally, a recent report from the Norwegian National Institute of Public Health showed that one in five re-hospitalisations were due to heart failure among older patients (7), which are associated with high cost.

Chronic heart failure is also a major cause of death and disability. It has been estimated that mortality rate approaches 20 percent per year in spite of current medical therapy (8). However, research has shown that close follow up of patients with severe heart failure especially after hospital discharge impacts both mortality and re-admission rates in this patient population (9). Patients with heart failure experience significant impairment in quality of life (10), and HF impairs quality of life to a greater extent than other serious chronic diseases (11).

The New York Heart Association (NYHA) has categorized heart failure into four classes. Class I and class II are considered mild. Class III is considered moderate and class IV is considered severe. The CardioMEMS™ HF System heart sensor is to be used by patients classified within class III, i.e. moderate heart failure.

Present treatment for patients with heart failure NYHA class III

Usual standard treatment is to treat in response to patients' clinical signs and symptoms. The pharmacology treatment is treatment with different drugs as ACE-inhibitors, diuretics, beta- receptor antagonists' (metoprolol and bisoprolol), and the alpha-1/beta receptor antagonist carvediol, digitalis and nitrates (5).

The main research questions

Based on the original suggestion and subsequent commission from The Ordering Forum (“Bestillerforum RHF”), the main research questions are shown in Table 1 below. The main research questions are organised according to the relevant PICO’s (P= Population, I= Intervention, C= Comparator, O=Outcomes (Endpoints)).

Table 1. The main research questions in this single single technology assessment

Patient group:	Patients with a diagnosis of moderate heart failure (NYHA class III) for 3 months, on a stable and optimised medication regimen, who have had a HF-related hospitalisation within the previous 12 months
Intervention:	Using an implanted wireless pulmonary artery pressure monitor to enable out of hospital pulmonary artery pressure monitoring to guide future medical therapy
Comparator:	Patient monitoring with usual care
Outcomes:	Heart Failure related hospitalisations Device and implant procedure safety Mortality Quality of life

Comments from the Norwegian Institute of Public Health

We have consulted with our clinical expert who agreed to the above PICO’s (Population, Intervention, Comparator and Outcomes).

Evaluation of the clinical documentation

Literature searches and identification of relevant published literature

Literature searches

St. Jude Medical's literature searches to identify clinical documentation

St. Jude Medical's literature searches were done in August 2015. The searches were performed with the aim to identify all randomised clinical trials or systemic reviews evaluating the performance of the CardioMEMS™ HF System within the bounds described in the PICO definition. The searches were conducted in Embase, the Cochrane Library, Clinicaltrials.gov and the NIHR/Centre for Reviews and Dissemination (CRD) database. St. Jude Medical's search strategies can be seen in Appendix 1.

The Norwegian Institute of Public Health's literature searches to identify clinical documentation

We wanted to perform our own searches, both to control the searches done by St. Jude Medical, as well as to get a more updated search.

Our searches were performed with the aim to identify all randomised trials, controlled trials, systematic reviews (SR's) and Health Technology Assessments (HTA's) evaluating the performance of the CardioMEMS™ HF System within the bounds described in the PICO definition. We systematically searched for literature in the following databases May 2, 2016:

- Ovid Embase 1974 to 2016 April 29
- Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
- Cochrane Library: Cochrane Database of Systematic Reviews, Central Register of Controlled Trials, Health Technology Assessment (HTA) Database

- Centre for Reviews and Dissemination: Database of Abstracts of Reviews of Effect, HTA Database , NHS Economic Evaluation Database

We searched for ongoing clinical trials in WHO ICTRP (International Clinical Trials Registry Platform) and ClinicalTrials.gov. August 18, 2016.

The research librarian Ingrid Harboe planned and executed all the searches. The complete search strategy can be seen in Appendix 2.

Identification of relevant published literature

St. Jude Medical's identification of relevant published literature

Their literature searches identified one randomised controlled trial of continuous pulmonary artery pressure monitoring to guide heart failure treatment:

Abraham, W. T. *et al.* Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: A randomised controlled trial. *The Lancet* 377, 658-666 (2011). This is the CHAMPION trial, NCT00531661.

Appendix 3 gives a summary of the identification of randomised controlled trials (RCT's) following St. Jude Medical's literature searches.

The Norwegian Institute of Public Health's identification of relevant published literature

The Norwegian Institute of Public Health also identified only one trial, the Champion trial, NCT00531661. We found that this trial was published in 12 publications (2, 12-22). Two of the publications used the total population from the CHAMPION trial (2, 14), the other 10 publications had data from subgroup analyses only. A flow chart of our selection of literature is shown in Figure 3.

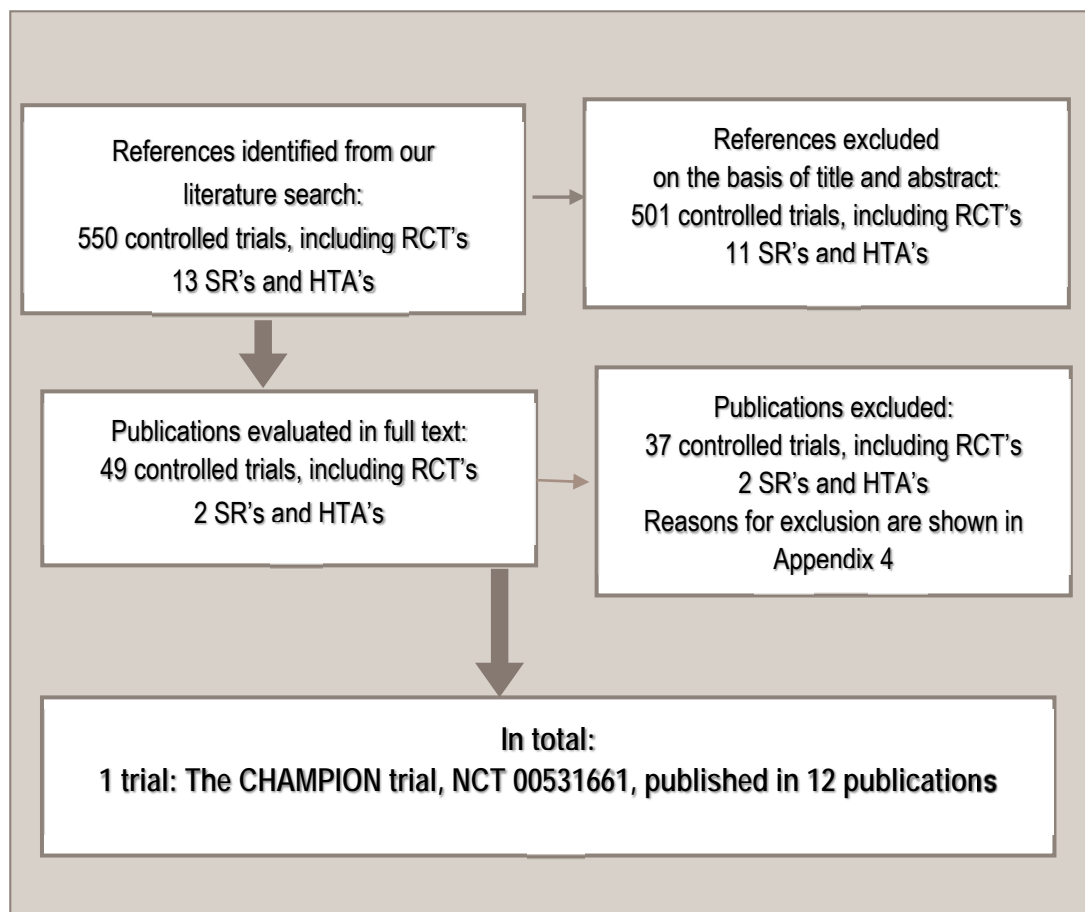


Figure 3. A flow chart of our selection of literature

Identification of ongoing trials

St. Jude Medical's identification of ongoing trials

After a request from us, the sponsor informed us that 2 trials are currently enrolling patients using the CardioMEMS HF System:

- CardioMEMS HF System Post Approval Study (NCT02279888); enrolling; expected publication Q1 2020
- CardioMEMS European Monitoring Study for Heart Failure (MEMS-HF); NCT02693691; enrolling; expected publication; Q1 2019.

The Norwegian Institute of Public Health's identification of ongoing trials

We identified on August 18, 2016, a total of 13 possibly ongoing trials, eight from ClinicalTrials.gov and five from WHO ICTRP (International Clinical Trials Registry Platform). These are listed in Appendix 5.

Comments from the Norwegian Institute of Public Health on the literature searches and identification of relevant published literature.

Literature searches

Available publications

St. Jude Medical performed their literature searches in August 2015. Our literature search was of a newer date, May 2016. In their submission, St. Jude Medical stated that they searched for randomised trials and systematic reviews. However, in the actual search they also searched for controlled trials. In our search we searched for randomised controlled trials, controlled trials, systematic reviews (SR's) and health technology assessments (HTA's). With the exception of the need for updating, we considered their searches to be sufficient.

Ongoing trials

The two ongoing studies the sponsor informed about, were also identified by us through our ClinTrials search. We assume that the Post Approval Study (NCT02279888); was one of the studies requested by FDA.

Identification of relevant literature

According to the submission from St. Jude Medical, they identified one randomised controlled trial, the CHAMPION trial, NCT00531661. From their searches from 2015, they were however able to identify only one (2) of the now 12 (2, 12-22) available publications from this trial. This was the first published main study from the CHAMPION trial, published in 2011. This may partly be explained by the date when the searches were performed. This shows that the updated searches we did in May 2016 were needed. Ten of our 12 publications were however substudies from the CHAMPION trial, those were published from 2010-2015.

Description of included trials

The Norwegian Institute of Public Health's description of their included publications

We identified 12 publications (2, 12-22) with data from the Champion trial, NCT00531661. These were two publications that use the total population from the CHAMPION trial (2, 14), and 10 publications with data from subgroup analyses (12, 13, 15-22). The trials were published from 2010 to 2016.

The CHAMPION trial was designed and powered to test, in home patients with NYHA Class III heart failure, the hypothesis that pulmonary artery pressure guided heart failure management with the CardioMEMS™ HF System would be a superior way to reduce the rate of heart-failure-related hospitalisations compared to current

disease management systems relying on changes in weights, edema, or other symptoms (2, 23).

Description of the CHAMPION Trial, NCT NCT00531661

The CHAMPION trial was a prospective, parallel, single-blinded, multicentre study undertaken in the USA. A total of 550 patients ≥ 18 years with New York Heart Association (NYHA) class III heart failure, irrespective of the left ventricular ejection fraction, and with a previous hospital admission for heart failure were randomly assigned (1:1) to either the treatment group, or to the control group. Before randomisation all patients got the CardioMEMS™ HF System implanted. All patients took daily pressure readings. The difference between the treatment group (n=270) and the control group (n=280) in the randomised part of the study (2, 14) was that the pulmonary artery pressure data from the sensor was only available to the physician for patients in the treatment group. In the treatment group the treatment was based upon these monitored data in addition to standard of care (patients' signs and symptoms). The management of the patients in the control group was only based upon standard of care. Patients then remained masked in their randomised study group until the last patient enrolled completed at least 6 months of study follow-up (randomised access period) for an average of 18 months (2, 14). At the conclusion of randomised access, investigators had access to pulmonary artery pressure for all patients (open access period) averaging an additional 13 months of follow-up (14). Analyses were by intention to treat.

Description of the included publications covering the total population

Abraham 2011 (2):

This publication described the randomised controlled part of the CHAMPION trial (2). All patients remained in their assigned group until the last patient completed 6 months of follow-up. The mean follow-up time was 15 months (SD 7). The primary efficacy endpoint was the rate of heart-failure-related hospitalisation. The two primary safety endpoints were: device-related or system-related complications; and pressure-sensor failures. Both the efficacy and safety endpoints were during the 6 months after insertion of the implant in the treatment group versus the control group.

Secondary endpoints which are of interest according to the PICO in the submission, were: Patient survival rates at 6 months (analysed by use of the Kaplan-Meier method and the log-rank test); and the quality of life at 6 months (by use of the total Minnesota Living with Heart Failure Questionnaire (MLHFQ)).

Prespecified supplementary analyses included heart-failure-related hospitalisation during the entire randomisation follow-up.

Abraham 2016 (14):

This publication described follow-up results from the CHAMPION randomised trial published by Abraham 2011 (2). In Abraham 2016 (14) these results were reported in two ways:

- 1) Present data for an average follow-up of 18 months (end of the randomised period).
- 2) After the end of the randomised period (after 18 months follow-up), investigators had access to pulmonary artery pressure for all patients. The trial now entered the open access period, with an average of 13 months additional follow up.

The primary endpoint was the rate of hospital admissions between the treatment group and control group in both the randomised and open access period.

From the randomised period: This publication reported heart-failure-related hospitalisation and mortality for the average entire follow-up of 18 months as well as quality of life at 12 months.

Analyses for heart-failure-related hospitalisation and mortality were done by intention to treat. Quality of life at 12 months were done by a last observation carried forward technique.

From the open access period: This publication reported heart-failure-related hospitalisation and mortality; as well as pressure-sensor failures for the average follow-up of 31 months (18 months from the RCT period and 13 from the open access period). The safety data at 31 months was only reported, not analysed.

Our comments to this publication (14): In the open access period, the investigators had access to pulmonary artery pressure for all patients. In our opinion, this design will be of no interest to test the efficacy of the CardioMEMS™ HF System. Hence, from the open access period, we will only use the data for safety.

We consider the evidence from the randomised part of the CHAMPION trial to be the main evidence in our evaluation for efficacy. In addition we use safety data for the entire follow-up period (31 months: 18 months randomised period + 13 months open access). Abraham et al, 2011 (2) reported up to an average of 15 months follow-up for the randomised period; and Abraham et al, 2016 (14) reported up to an average of 18 months follow-up for the randomised period.

Table 2 below gives more information about the available evidence. In this table we have chosen to present:

- Heart-failure-related hospitalisation at 6 months (primary endpoint) (2), as well as the follow-up results at 15 (2) and 18 months (14). The follow-up results were pre-specified supplementary analyses.
- The safety endpoints: Device-related or system-related complications at 6 (2) and 31 months (14), pressure-sensor failures at 6 (2) and 31 months (14), and procedure-related adverse events at 6 months (2) (we have assumed that procedure-related

events means events related to the right heart catheter procedure used to implant the CardioMEMS system). We report the complications present for the combined groups (the intervention and the control group together). This was done since both groups underwent right heart catheterisation and implantation of the pulmonary artery pressure sensor before randomisation.

-Mortality at 18 months (end of the randomization period) (14).

-Quality of life measured with Minnesota Living with Heart Failure Questionnaire at 6 months (2) and at 12 months (14).

Table 2. Overview of the available evidence from the randomised period of the CHAMPION trial for the *total population*

Endpoints	Average follow-up time (months)	Publication
Efficacy: Heart-failure-related hospitalisation	6 months	Abraham 2011 (2)
	15 months (SD 7)	Abraham 2011 (2)
	18 months	Abraham 2016 (14)
Minnesota Living with Heart Failure Questionnaire	6 months	Abraham 2011 (14)
	12 months	Abraham 2016 (14)
Safety: Device-related or system-related complications	6 months	Abraham 2011 (2)
	31 months	Abraham 2016 (14)
Pressure- sensor failures	6 months	Abraham 2011 (2)
	31 months	Abraham 2016 (14)
Procedure- related adverse events	6 months	Abraham 2011 (2)
Mortality	18 months	Abraham 2016 (14)
Minnesota Living with Heart Failure Questionnaire	6 months	Abraham 2011 (2)
	12 months	Abraham 2016 (14)

A more detailed study description, data extraction and risk of bias for the included publications is shown in Appendix 6.

Description of the included publications for subgroup analyses of the CHAMPION trial

We have identified ten publications (12, 13, 15-22) that give data from different subgroups of the patient population included in the CHAMPION trial. All data were from the randomised part of the trial. The subgroups with available evidence are patients with preserved ejection fraction (15, 16); with reduced ejection fraction (15); with reduced ejection fraction and with/without cardiac resynchronization therapy (CRT) (22); patients with/or without a history of myocardial infarction (21); with atrial fibrillation (20); with comorbid chronic obstructive pulmonary disease (18),

with chronic kidney disease (13); with/or without chronic obstructive pulmonary disease (COPD) (19); patients with cardiac resynchronizatin therapy (CRT) or implantable cardioverter defibrillator (12) and patients with/or without WHO group II pulmonary hypertension (17). Only the patients with preserved and reserved ejection fraction were prespecified as supplementary analyses (2). The endpoints studied were heart-failure-related hospitalisation in all the ten publications, and mortality in two of the publications (12, 17).

More information about these publications (study description and data extraction) is presented in Appendix 6.

St. Jude Medical's description of their included publications

In their submission St. Jude Medical gives a description of the CHAMPION trial based upon the publication from 2011 (2). They describe the randomised period with an average follow-up time of 15 months (SD 7). They do however, both describe and report from the other main publication from CHAMPION (14), without giving the references (most probably not published at the time of writing the submission). Here they report from the last part of the randomised period, an average of 18 months, as well as from the open access period, an additional 13 months, after the conclusion of the randomised period. Further, they also describe and report from one of the substudies (patients with preserved ejection fraction) that we we also identified (15).

Critical appraisal of included publications

According to the submission template, the company should critically appraise all included studies. We cannot see that this have been done, we find no risk of bias evaluations or other evaluations of the quality of the included study.

We have assessed the included publications (2, 14) for possible risk of bias according to our Handbook (24).

Clinical results

St. Jude Medical's description of the clinical results

The sponsor claimed that:

Heart-failure-related hospitalisation had a 33% relative risk reduction in the intervention group as compared to the control group at 18 months (HR 0.67 (95% CI 0.55-0.80), better quality of life in the treatment group than in the control group (average scores 45.2 ±26.4 and 50.6 ±24.8) respectively at 6 months, and no difference in mortality at 18 months.

Safety was reported from the total safety population (575 patients). Of these

567 (98.6%) were free from device-and system-related complications at 31 months (average total follow-up of the CHAMPION trial). No sensor failures occurred after 31 months of average follow up.

Norwegian Institute of Public Health’s description of the clinical results from their included studies

The data for all the endpoints except complications are taken from the randomised period for the total population in the CHAMPION trial (2, 14). Complications were reported both from the randomised period, as well as after 31 months (total follow-up: 18 months average from the randomization period + 13 months from the open access period). Since both groups had the sensor implanted, we are interested in the safety data for the two groups together.

Evidences for the total population from the randomised period

The results for the total population from the randomised period from the CHAMPION trial are shown in Table 3 below.

Table 3. The Summary of Findings Table

Endpoints	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Risk with standard treatment	Risk with CardioMEMS™ HF System			
Heart-failure-related hospitalisations:					
6 months	429 per 1 000	332 per 1 000 (285 to 379)	HR 0.72 (0.60 to 0.85)	550 (1 RCT) ¹	⊕⊕⊕○ MODERATE ²
mean 15 months*	907 per 1 000	776 per 1 000 (709 to 840)	HR 0.63 (0.52 to 0.77)	550 (1 RCT) ¹	⊕⊕⊕○ MODERATE ³
mean 18 months*	996 per 1 000	977 per 1 000 (955 to 989)	HR 0.67 (0.55 to 0.80)	550 (1 RCT) ⁵	⊕⊕⊕○ MODERATE ³

Endpoints	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)
	Risk with standard treatment	Risk with CardioMEMS™ HF System			
Health related quality of life (Minnesota Living with Heart Failure Questionnaire) at 6 months	The mean health related quality of life in the intervention group was 6 SD lower (10,27 lower to 1,73 lower) than the control group, which means better quality of life in the treatment group		-	550 (1 RCT) ¹	⊕⊕⊕○ MODERATE ³
Mortality at 18 months	229 per 1 000	187 per 1 000 (133 to 258)	HR 0.80 (0.55 to 1.15)	550 (1 RCT) ⁵	⊕⊕○○ LOW ⁴

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: Confidence interval; HR: Hazard Ratio; RR: Risk ratio; MD: Mean difference

1. Abraham 2011 (2)
2. Few events and only one study (n=550)
3. Only one study
4. Very few events and only one study
5. Abraham 2016 (14)

GRADE Working Group grades of quality of evidence (25)

High quality: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Heart-failure-related hospitalisation: The intervention group had fewer heart-failure-related hospitalisation than the control group. This was reduced by 28%, and 37% and 33% respectively at 6, 15 and 18 months. We evaluated the quality of the evidence for this endpoint to be moderate.

Health related quality of life: Health related quality of life as measured with the Minnesota Living with Heart Failure Questionnaire) both at 6 and 12 months was in favour of the intervention group. Mean and standard deviation were 45 (26) and 51 (25) at 6 months, and 47 versus 57 at 12 months respectively for the intervention and the control group. We evaluated the quality of the evidence for both these endpoints to be moderate.

Mortality: No difference between the groups. At 18 months the mortality was 50/270 (19%) in the intervention group as compared to 64/280 (23%), hazard ratio

was 0.80 (0.95% CI 0.55-1.15). We evaluated the quality of the evidence for this endpoint to be low at 18 months.

Safety evidences for the total population from the entire follow-up period (31 months)

The safety endpoints were either device-related or system-related complications, pressure-sensor failures or procedure-related adverse events. Generally there were few complications. Since both groups had the sensor implanted, we are interested in the safety data for the two groups together. We found that the overall combined device-related or system-related complication rate was 0.03 events per patient-year in the entire follow-up period (31 months). This represented 1.4% of the total population. This is comparable to the complication rate as reported for procedure-related serious adverse events (1.2%) (2).

Critical appraisal of the results

We find that the submission presents the evidence for the requested endpoints in agreement with our findings.

The submission did not report on quality of neither the publications, nor the endpoints.

One weakness is that all the results came from one study, the CHAMPION trial.

Evidence from subpopulations from the randomised period in the CHAMPION trial

All the ten publications (12, 13, 15-22) had examined heart-failure-related- hospitalisation, and they all showed fewer hospitalisations in the treatment group as compared to the control group. Two of the publications examined mortality. Patients with cardiac resynchronization therapy (CRT) or implantable cardioverter defibrillator (12) had a lower mortality at 18 months in the treatment group as compared to the control group (HR: 0.47 (0.26-0.87). For patients with/without WHO group II pulmonary hypertension there was however no difference in survival at 15 months, but the confidential interval was wide (HR:0.78, 95%CI 0.50-1.22)) (17).

More information about these publications (study description and data extraction) is presented in Appendix 6.

Cost-effectiveness

General

St. Jude Medical has submitted a cost-effectiveness analysis where the CardioMEMS HF System technology for measuring and monitoring pulmonary artery pressure in NYHA class III hearth failure patients is compared with usual care.

The sponsor mentioned two published cost effectiveness analysis related to CardioMEMS. One analysis by the manufacturer (26) has not yet been published in a peer reviewed journal. The second analysis, by Sandhu et al (27), is a recently published analysis from a US based academic group. Both analyses were designed to evaluate the technology within the US healthcare system and employed different structures and assumptions leading to variations in results.

Table 4. The published economic studies

Study	Year	Country	Type of model analysis	Patient population	Comparison	Incremental effect (QALY)**	Incremental costs	ICER***
Adamson (Abstract) (26)	2015	USA	Cost-effectiveness analysis	Patients with NYHA class III HF *** (> 18 years, > 3 months heart failure)	Usual care	0.4	\$ 11,939	\$ 30,167 (5 year time horizon)
Sandhu (27)	2015	USA	Cost-effectiveness analysis	Patients with NYHA class III HF *** (Average 62 years)	Usual care	0.24	\$ 20,079	\$ 28,301 (reduced ejection fraction) \$ 47,768 (preserved ejection fraction)

*QALY: Quality adjusted life years

**ICER: Incremental cost effectiveness ratio

***NYHA class III HF: New York Heart Association (NYHA) Class III Heart Failure

The cost-effectiveness analysis by the manufacturer (26), assessed the long term cost-effectiveness of HF therapy with and without CardioMEMS HF system guidance. The perspective of the analysis was the health care payer. They developed a Markov model with four states (stable, hospitalized of HF, hospitalized for other, and death), with monthly patient transition, incurring costs for hospitalisations for outpatient care with (intervention group) or without (control group) guidance by the CardioMEMS HF System for 5 years. The input data were submitted from the CHAMPION (CardioMEMS Heart Sensor Allows Monitoring of Pressure to Improve Outcomes in NYHA Class III Heart Failure Patients) trial: Transition probabilities between the Markov states, quality of life (QoL) and age distribution. The reimbursement costs were derived from a national administrative claims database. Costs and QoL are discounted at 3% per year. Their model suggested that pulmonary artery pressure guided management of HF using the CardioMEMS HF System is cost-effective. The ICER of \$30,167 is below the conventional US acceptability threshold of \$50,000.

In the cost-effectiveness study by Sandu et al (27), 550 patients with NYHA class III HF and a hospitalisation for heart failure within the previous year underwent artery implantation. Patients were randomized to the treatment group or the control group. In the treatment group providers were given access to the pressure readings and in the control group the provider could not access the pressure readings. The CardioMEMS were shown to reduce hospitalisations for heart failure and improve QoL in the CHAMPION trial.

The analysis included a Markov model to determine the hospitalisations, survival, QoL, costs and ICER of CardioMEMS implantation compared with usual care among a CHAMPION trial cohort of patients with heart failure. By using a probabilistic sensitivity analysis, they found that 17.3% of simulations showed that CardioMEMS was the preferred intervention at a willingness-to-pay threshold of \$50,000, 76.9 % at a threshold of \$100,000, and 95.1% at a threshold of \$150,000. Their conclusion claims that in populations similar to that of the CHAMPION trial, the CardioMEMS device is cost-effective if the trial effectiveness persists for longer periods (after 18 months). Post-marketing surveillance data on durability will further clarify its value.

Comments from the Norwegian Institute of Public Health

Both studies compared pulmonary artery pressure guided management of heart failure comparing the CardioMEMS with usual care. However, we were able to read just one of the studies because the analysis by (26) was not published in a peer reviewed journal, only the abstract was available. The studies were both based on US conditions, in that way they are not representative of the Norwegian population.

Patient population

The patient population are patients with a diagnosis of moderate and severe HF (NYHA class III). These patients have marked limitation of physical activity and are not comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea. They are prescribed with a stable and optimised medical treatment plan. The patients have been admitted to hospital for the treatment of heart failure within the previous 12 months.

The sponsors assumed that patients entering the submitted model were 70 years old, the average age for heart failure patients.

Comments from the Norwegian Institute of Public Health

Expert opinion suggested that the average age on 70 years for heart failure patients also applies to Norwegian conditions. However, monitoring will also particularly be relevant for the few, but relatively young individuals (40-60 years) surviving larger myocardial infarcts. These patients experience both reduced quality and length of life.

Choice of comparator

According to the sponsor the management of the patients in the control group was standard care. Usual standard treatment includes drug changes in response to patients' clinical signs and symptoms (2).

Comments from the Norwegian Institute of Public Health

We have consulted with our clinical expert who agreed in the above PICO's (Population, Intervention, Comparator and Outcomes.)

Type of analysis and decision model

In the submitted report, cost-effectiveness is measured as the incremental cost per QALY gained. By developing a Markov cohort model in TreeAge 2015, they estimated the cost-effectiveness of pulmonary artery pressure guided treatment of heart failure using the CardioMEMS (St. Jude Medical Inc.) implantable pressure sensor compared to usual care strategies.

The submitted Markov model considered two health states: 1) Stable heart failure and 2) Dead (Figure 4). The cycle length was fixed one month and half cycle correction applied.

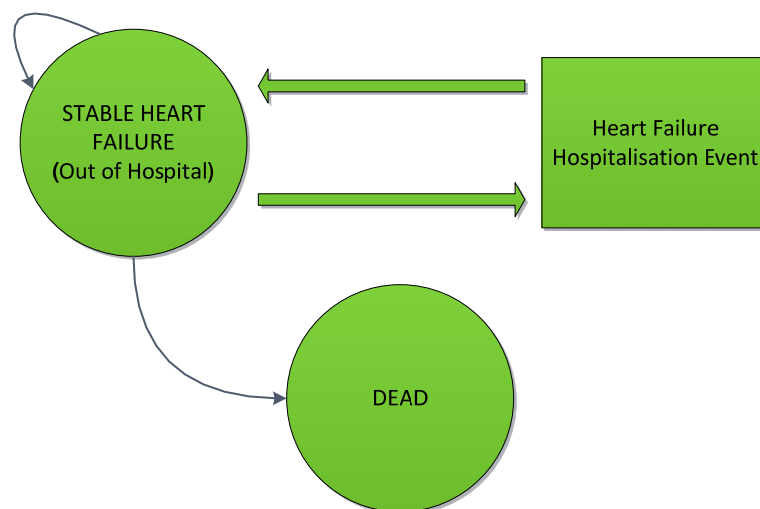


Figure 4. *State transition diagram as illustrated in the submission dossier*

The sponsor described in the submission that patients are assigned a monthly probability of death based on their age and whether they have received the intervention. In each period, the patients who are alive are under the risk of an average number of monthly heart failure re-hospitalisations. Each patient then accrue QALYs and healthcare costs according to their hospitalisation and treatment status. The average age of 70 years was considered and the submitted model used a ten-year time horizon. The costs and QALYs were discounted at an annual discount rate of 4%. The sponsor claimed that the economic perspective of the model is that of the Norwegian health care system.

Comments from the Norwegian Institute of Public Health

The submitted model considered just two health states “stable heart failure” and “death”. Peri-procedural complications, as procedure–related serious adverse events and major bleeding, and post-procedural placement failure were not modeled. However, the costs associated with the overall implant related complications were included in the evaluation.

Based on our expert opinion, the likelihood of implant related complications are very small and may not be considered more frequent than by other catheter-based procedures. Bleeding is most common, but hardly ever fatal. Bleedings can prolong hospital stay a few days, but they are unlikely to require surgery.

We have also run the model for the younger patients (separate analyses for patients of 50 and 60 years), as recommended by Norwegian experts. Due to uncertainty

regarding long-term effects of the treatment (average follow-up time is 18 months), the mortality and hospitalisation effectiveness were considered at 5 and 10 years, respectively, after which we assumed that the mortality risks and hospitalisation rates were the same for both cohorts within the model.

The clinical and epidemiological data

In the submitted report from the sponsor, the baseline risk of hospital admission (for the control group) was estimated based on the result of a meta-analysis study reported by Klersy et al (28). The baseline rate of hospitalisation was estimated at 0.035 by the sponsor.

There is an assumption that mortality within a UK population of heart failure patients is similar to that of Norwegian heart failure patients.

Comments from the Norwegian Institute of Public Health

The rate of hospitalisation in the submission dossier was estimated based on a meta-analysis of 20 studies from 2009 (28). Only 54% of patients in the RCTs included in the meta-analysis were of NYHA class III to IV. In addition, further explanation about the estimation of the baseline hospitalisation rate, based on the meta-analysis by (28), was not presented in the submitted report. We used the reported risk of heart failure hospitalisation for the comparator, “usual care”, found in the CHAMPION trial.

We did not find Norwegian mortality risk data for the defined population. Based on the expert opinion, the age related mortality risk used in the submitted model was a reasonable assumption. However, one can argue that the Norwegian mortality risk may be slightly lower, as the risk of death due to cardiovascular disease has decreased in the recent years. We considered the uncertainty regarding these estimates in the sensitivity analysis.

The efficacy

The sponsors derived the clinical efficacy of pulmonary artery pressure guided treatment from the CHAMPION trial on US patients, which showed a significant decrease in hospitalisations related to heart failure, no effect on non-heart failure hospitalisations and a small trend towards a mortality benefit.

In addition, the model submitted by the manufacturer used an implant related complication rate at about 3% based on the CHAMPION trial data. The sponsor did

not present further explanation regarding estimation of the implant related complications.

Table 5. Efficacy parameters used in the model

Endpoint	Value	Ref.
Heart-failure-related hospitalisation	HR 0.67	CHAMPION trial
Mortality	HR 0.80	CHAMPION trial
Device-related complication	Rate 0.0296	CHAMPION trial

Comments from the Norwegian Institute of Public Health

We present estimates for heart failure related hospitalisations and mortality in Table 3 and estimates for complications in Appendix 6. Our finding based on the systematic review is in agreement with the estimates for clinical efficacy and safety used in the submitted model. The uncertainty around the clinical efficacy parameters were modelled based on the reported confidence interval in the CHAMPION trial.

Based on the opinion of the Norwegian expert, the likelihood of implant related complication is low. Therefore the uncertainty associated with this input may not have great impact on the results. This is also showed in the sensitivity analysis.

The costs

The sponsor included the health care costs only. The estimates were based on UK reference costs, Norwegian DRGs and the Norwegian cardiovascular disease model. All costs were expressed in 2016 Norwegian kroner (NOK).

Resources used in the submission file

- CardioMEMS device– NOK 143,165. The price was given by the manufacturer, St. Jude Medical. This price was assumed to be fixed and not subject to uncertainty.
- Heart failure hospitalisation – NOK 47,299. The sponsor based this cost on the DRG 127: «Heart failure & non- traumatic shock» (ISF regulation, 2016).

- Implant procedure – in the model, the sponsor used 22,410 NOK. The sponsor claimed that it is associated with a simple diagnostic heart catheterisation which is almost an identical procedure to the implantation procedure for CardioMEMS.
- Implant complication – NOK 21,305. The sponsor based this cost on UK reference costs. This cost is a weighted average of the eight complications in the CHAMPION trial mapped to NHS reference costs and is calculated at £1,630.32. This cost has been converted from UK to Norway because the sponsor did not find any clear individual complications in the Norwegian DRG tables. The sponsor stated that the rate of complications is very low and so inaccuracies in this input will have very minimal effect on the model results.
- Deliver medical care – NOK 12,125 (monthly cost). This cost was taken from the Norwegian cardiovascular disease model (29). The sponsor claimed that the cost of one month's standard heart failure was applied to stable heart failure patients in both cohorts.

Comments from the Norwegian Institute of Public Health

We agree with the sponsor that the simple diagnostic cardiac catheterisation procedure is almost an identical procedure to the implantation procedure concerning costs. Based on the ISF regulation 2016 (DRG 125), the costs were estimated to be NOK 22,219.

The implant related complication costs have been converted from UK to Norway. Fifteen serious adverse events were reported for device-related or procedure-related complications in the CHAMPION trial (2). As further information about the kind of these complications was not presented, it was not possible for us to re-calculate the implant related complication costs based on the Norwegian unit prices. However, based on the opinion of the Norwegian expert, we agree with the sponsor that the likelihood of implant related complication is low, and as a one-way sensitivity analysis has showed, the uncertainty associated with this input may not have great impact on the results.

Monthly cost of standard heart failure care was estimated based on the Norwegian study (NOK 12,125) (29). However, in the submission file it was not further discussed how it was estimated. Based on the same reference, we have calculated that the costs related to standard care for heart failure patients (excluding hospitalisations) may be approximately NOK 10,000. The uncertainty associated with utility values was considered in the sensitivity analysis.

Health related quality of life

The sponsor modelled the utilities based on patient-level data recorded within the CHAMPION trial at one month, three months, six months and twelve months (not published data). They calculated mean utility values over time for each patient profile, because the economic model doesn't include mutually exclusive health states (other than the stable heart failure and dead). Patients in the treatment group had 0.026 higher utility compared with usual care at month one – 0.755 among patients in the treatment group and 0.729 among patients in the control group. At 12 months the utility difference increased to 0.082 – 0.732 among patients in the treatment group and 0.65 among patients in the control group.

The sponsor wanted to apply a decrement in utility over time in order to reflect the real world impact of heart failure where patients face a decline in quality of life as the disease progresses. According to NICE's guidance for sacubitril valsartan, they assumed that after 12 months the utility values will decrement at a rate of 0.008 QALYs per year (30).

After 12 months a disutility for each heart failure hospitalisation of -0.1 is applied to reflect the impact of hospitalisation on quality of life. The sponsor assumed that the disutility for each hospitalisation apply for a whole year. This assumption was based on the cost-effectiveness analysis written by Yao et al. 2008 (31). In this analysis the risk of a cardiovascular hospitalisation increases with NYHA class, and a disutility of -0.1 is applied for that event, which is equivalent to a utility of 1 health state lower in terms of NYHA class. This is similar to disutilities applied to hospitalisations from previous cost-utility analysis for heart failure technologies as Thokela et al. 2013 (32), Griffiths et al. 2014 (33) and more recently NICE's guidance for sacubitril valsartan (30).

Comments from the Norwegian Institute of Public Health

The utilities for usual care used in the submitted model were considered reasonable based on "A review of health utilities using the EQ-5D in studies of cardiovascular disease" by Dyer et al. 2010 (34). The review presented an average utility score of 0.60 for HF patients after 12 months.

The disutility for each heart failure hospitalisation of -0.1, based on the analysis by Yao et al. 2010, was considered a decent assumption (31). In Yao et al. 2008, 2,135 patients were enrolled from eleven countries and all the patients were aged 70 or older.

The utility values were modelled based on patient-level data recorded within the CHAMPION trial (not published data). The sponsor used higher utility values for the CardioMEMS group due to lower risk of hospitalisation. There is some uncertainty as the utility values were just based on one trial with short follow-up duration. However, we agree that some additional utility benefit for patients having CardioMEMS could be plausible. The uncertainty associated with utility values was considered in the sensitivity analysis.

Sensitivity analysis

The uncertainties around the input parameters were modelled as probability distributions for some of the parameters (such as the effectiveness estimates and the risk of mortality) and the other parameters were just modelled as point estimates.

In the absence of the probability distributions for all the uncertain parameters, we performed one-way sensitivity analyses, as a form of tornado diagram, to show which variable had the greatest impact on the results.

Cost-effectiveness results and sensitivity analysis

The sponsor provided a base case analysis over a time horizon of 10 years. Their analysis showed an increase in costs by 192,478 NOK of the pulmonary artery pressure guided heart failure therapy compared with usual care. Their analysis also showed an increase in effect, 0.66 QALYs over 10 years, by using pulmonary artery pressure monitoring compared with usual care. Their calculated ICER was NOK 289,300 per QALY gained (Table 6).

Table 6. Base-case results based on the submitted model

Intervention	Costs (NOK)	Incremental cost (NOK)	Effects (QALY)	Incremental effect (QALYs)	ICER (NOK/QALY)
Usual care	779,099		2.85		
Pulmonary artery pressure-monitoring	971,577	192,478	3.51	0.66	289,276

Comments from the Norwegian Institute of Public Health

The sponsor has constructed a straightforward and simple model. However, we adjusted some variables, which are mentioned in the earlier sections. We changed the cost variables related to implant procedure, the monthly rate of hospitalisations due to heart failure and we corrected some confidence intervals.

Table 7. Base-case results with our corrections in the model

Intervention	Costs (NOK)	Incremental cost (NOK)	Effects (QALY)	Incremental effect (QALYs)	ICER (NOK/QALY)
Usual care	812,239		2.79		
PAP monitoring	994,204	181,965	3.46	0.67	270,460

The corrected model gives a similar ICER as the result presented by the sponsor, NOK 270,500 per QALY gained (Table 7).

Scenario analysis for varying age based on our corrections

The sponsor based the submitted model on patients who were aged 70. We examined what impact the start age had on the model outcomes. We changed the start age to 60 and 50 years (based on recommendation from the Norwegian clinical expert) and performed a scenario analysis (Table 8). The ICERs were reduced in the younger patient group.

Table 8. Results for patients of 70, 60 and 50 years

Age	PAP monitoring		Usual care		Incremental effect (QALYs)	Incremental cost (NOK)	ICER (NOK/QALY)
	Effect (QALYs)	Costs (NOK)	Effect (QALYs)	Costs (NOK)			
70	3.46	994,204	2.79	812,239	0.67	181,965	270,460
60	4.44	1,231,362	3.70	1,088,380	0.74	142,982	193,061
50	5.03	1,379,155	4.25	1,265,259	0.78	113,896	146,286

Sensitivity analysis

To explore the uncertainty of the different included parameters, we used one-way sensitivity analyses. Each parameter estimate was varied, individually, within reasonable bounds in order to investigate the impact on costs or QALYs. We have presented the results of the sensitivity analyses as tornado diagrams that show the top five variables which have a large potential impact on the ICER estimates.

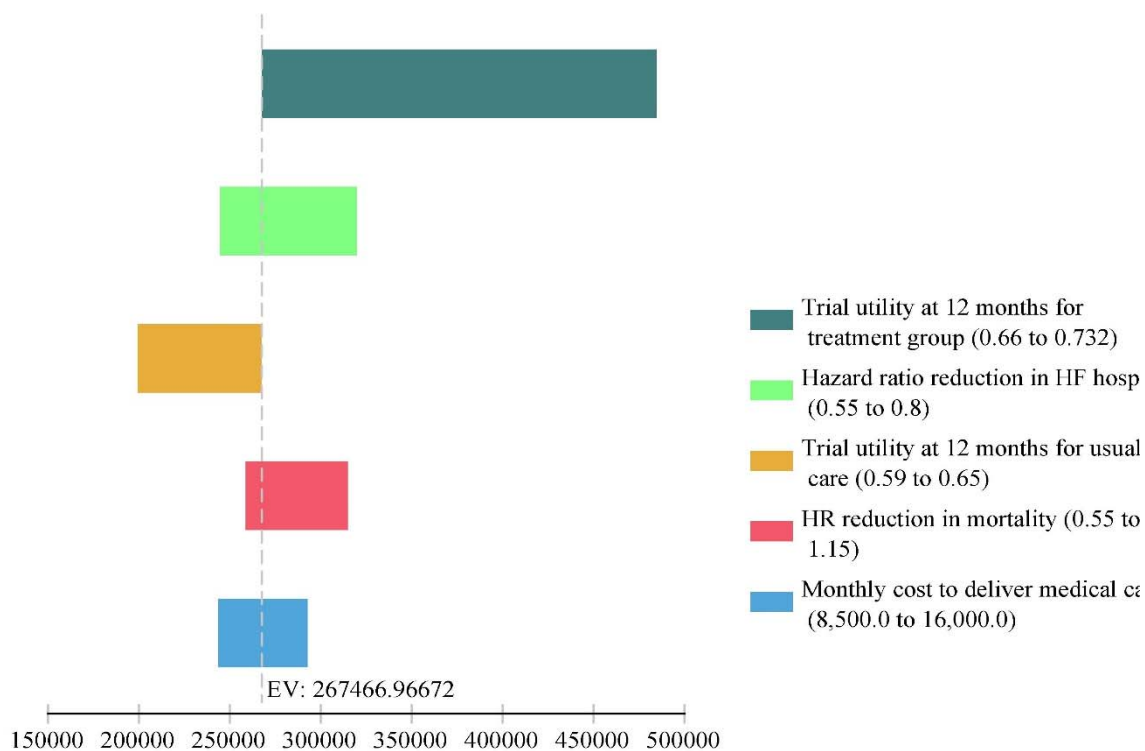


Figure 5. One-way sensitivity analysis (the top five variables in tornado diagram)

The results were most sensitive to changes in utility values both for the treatment and the control group at 12 months, efficacy data (mortality and HF hospitalisation), and costs related to standard heart failure care (excluding hospitalisation) (Figure 5). Utility values at 12 month for the treatment group had the largest uncertainty and the ICER varied between NOK 268,000 and NOK 485,000.

Budget impact analysis

The sponsor calculated the budget impact by using the incidence rate for NYHA class III patients across the general population from OECD statistics for 2016. They pointed out that this was a basic assumption because not all of the patients will have experienced a heart failure hospitalisation in the last 12 months.

Table 9 shows the population shares per year treated by pulmonary artery pressure monitoring (implanted CardioMEMS HS system) or usual care if the new technology, CardioMEMS HF system, is adopted. If the new technology is not adopted all the patients will undergo usual care.

Table 9. Number or shares of patients if the new technology is adopted (St. Jude Medical)

	Year 1	Year 2	Year 3	Year 4	Year 5
Implanted with CardioMEMS	57	109	156	198	237
Usual Care	12,998	16,923	20,384	23,435	26,125

Table 10 shows the budget impact calculated by the sponsor. The budget impact included two scenarios: 1. Cost related to adoption of the CardioMEMS HF system and 2. Cost without adoption of the CardioMEMS HF system. The calculations showed the difference between the two scenarios in each of the five years of the analysis. The comparisons between the two scenarios showed an increase in total added costs for each year. The sponsor estimated that the total added costs would be about NOK 50,000,000 for the first five years after adoption of CardioMems in Norway.

Table 10. Budget impact (St. Jude Medical)*

Budget Impact	Year 1	Year 2	Year 3	Year 4	Year 5
Cost if the New technology is adopted (NOK)	1,788,349,340	2,467,409,054	3,066,304,763	3,594,504,163	4,060,356,370
Cost without adoption of the New Technology, i.e. Current situation (NOK)	1,778,521,009	2,457,678,273	3,056,470,195	3,584,406,485	4,049,871,559
Total added cost (NOK)	9,828,332	9,730,781	9,834,568	10,097,678	10,484,811

* Based on number of patients estimated in Tabel 9.

Comments from the Norwegian Institute of Public Health

Due to uncertainties associated with the number of patients (for both treatment strategies) and the yearly costs used in the calculation of budget impact by the sponsor, we re-calculated the additional costs of introducing the technology in Norway.

According to the clinical experts, each year about 100 new heart failure patients in Norway would be eligible for this procedure.

In addition, we considered the probabilities predicted in the model for being in the stable heart failure health state for each treatment strategy and the costs associated with these strategies. The results showed that assuming 100 new patients each year, the incremental cost of implementing CardioMEMS in Norway will be from NOK 16,800,000 to NOK 18,900,000 each year during five years time horizon (Table 11). This gives a total added expected cost of about NOK 89,000,000 for the first five years after adoption of CardioMems in Norway.

Table 11. The results of the budget impact analysis (based on 100 new patients per year)

Budget Impact	Year 1	Year 2	Year 3	Year 4	Year 5
Implanted with CardioMEMS (NOK)	32,914,704	45,702,326	56,816,175	65,617,645	74,012,514
Usual Care (NOK)	16,094,651	28,399,152	38,827,124	47,664,752	55,154,575
Total added cost (NOK)	16,820,053	17,303,173	17,989,050	17,952,893	18,857,939

Discussion

We have performed a single technology assessment of the use of CardioMEMS™ HF System as an implanted sensor for the management of patients with moderate to severe heart failure (NYHA class III).

The submission came from St. Jude Medical. We have reviewed the submission file and evaluated it towards the applied PICO's (Population, Intervention, Comparator and Outcomes/endpoints), our own searches for literature, selection of studies, quality assessment of the included studies, data extraction, GRADE assessment of the quality of the evidence for the effect estimates of the endpoints, as well as health economic evaluations.

Efficacy

The evidence for the efficacy and safety came from the CHAMPION trial (NCT00531661) presented in two main publications (2, 14). The CHAMPION trial was designed and powered to test, in home patients with NYHA Class III heart failure, the hypothesis that pulmonary artery pressure guided management with the CardioMEMS™ HF System would be a superior way to reduce the rate of heart-failure-related hospitalisations compared to current disease management systems relying on changes in weights, edema, or other symptoms (2, 23).

From these two publications we have reviewed the randomised part of the trial for efficacy endpoints up to 18 months and safety endpoints up to 31 months. The randomised period ended after 18 months, after which the study went into an open access period for additional 13 months.

Our single technology assessment shows a heart-failure-related hospitalisation probably in favour of the treatment group (hazard ratio of 0.72 (0.95%CI 0.60-0.85) and 0.67 (0.95%CI 0.55-0.80) respectively at 6 and 18 months). We evaluated the quality of the evidence for this endpoint to be moderate. The safety endpoints were either device-related or system-related complications, pressure–sensor failures or procedure-related adverse events. Generally there were few complications. Since both groups had the sensor implanted, we were interested in the safety data for the two groups together. We found that the overall combined device-related or system-related complication rate was 0.03 events per patient-year in the entire follow-up

period (31 months). This represented 1.4% of the total population. This is comparable to the complication rate as reported for procedure-related serious adverse events (1.2%) (2). We have assumed that procedure-related events were events related to the right heart catheter procedure used to implant the CardioMEMS system. This was in agreement with reported serious adverse events associated with right heart catheterization (35).

For the endpoint mortality there may be no difference between the groups at 18 months (Hazard ratio 0.80 (0.95% CI 0.55-1.15). We evaluated the quality of the evidence for this endpoint to be low.

Health related quality of life was probably in favour of the intervention group both at 6 and 12 months. We evaluated the quality of the evidence for both these endpoints to be moderate.

The sponsor have submitted documentation supporting the selected PICO's, the literature search and the presentation of the evidence. However, we missed a critical appraisal from the sponsor of the quality of the evidence, both for the publications (risk of bias) and for the specific endpoints (GRADE).

Weaknesses of the CHAMPION trial are:

-The selection of patients: Both the American College of Cardiology's clinical guideline (ACC) and the American Heart Association guideline (AHA) (36) regard it as important that the patients with heart failure follow a disease management program. In the latest guideline from the European Society of Cardiology (ESC) the treatment in an outpatient clinic for heart failure has a 1A recommendation (37). Evidence from the Norwegian heart failure registry (38) indicates that treatment/follow-up of heart failure patients in 24 hospital outpatient clinics in Norway led to a reduction in the number of hospital admissions for cardiovascular reasons when comparing the six month periods before visit 1 and after visit 2. Both the main publications from the CHAMPION trial (2, 14) lack information on whether the patients had gone through a disease management program before they were included in the trial.

-Monitoring of patients with heart failure: Natriuretic peptides can be used in the monitoring of patients with heart failure, especially patients with reduced ejection fraction (37). In the publications from the CHAMPION trial (2, 14) it is unclear if such monitoring was used.

-New medications after the end of the CHAMPION trial: A study published in 2014 (39) with more than 8000 heart failure patients with NYHA class II-IV and ejection-fraction $\leq 40\%$, examined the efficacy of a new drug, an angiotensin receptor neprilysin inhibitor (sacubitril/valsartan) compared to an ACE-inhibitor (enalapril). The new drug demonstrated better effect both on cardiovascular mortality and heart-failure-related hospitalisation. This can mean that the standard drug treatment used in the CHAMPION trial is not quite relevant for the Norwegian setting today.

There are reported data for efficacy and safety up to 18 and 31 months respectively. These time periods are relatively short. Further, all the available evidence came from only one trial (the CHAMPION trial). Therefore we cannot exclude that the evidence may change with further studies available.

CardioMEMS™ HF System was approved by FDA in 2014 for the now submitted indication in Norway. The approval by FDA had a requirement of performing two post-approval studies. We have identified 13 ongoing studies of potential interest. Upon our request to the sponsor, they were not able to identify any ongoing trials, therefore we do not know if the requested post-approval studies from FDA have been started.

Cost-effectiveness

The sponsor performed economic evaluation by developing a simple model with only two health states. However, based on thorough review and input given by the clinical experts we think that the health economic model captured the outcomes that are clinically relevant to the defined population and intervention.

The sponsor provided a base case analysis over a time horizon of 10 years. The sponsor calculated that the base-case incremental cost-effectiveness ratio for CardioMEMS compared with standard treatment would be around NOK 289,000 per QALY gained.

However, there were several uncertain points to consider regarding the submission. First, we considered the age of patients entering the economic model. In the submitted model, the mean baseline age of 70 years was considered. As recommended by the clinical experts, the intervention may also be appropriate for younger patients. We changed the start age to 60 and 50 years (based on recommendation from the Norwegian clinical expert) and performed two scenario analyses where the mean age of 50 and 60 years, respectively, were considered. The results showed that the device probably will be more cost-effective if the patient group is younger.

Further, as discussed in the earlier sections, we adjusted some input parameters (such as the cost variables related to the implant procedure and the monthly risk rate of heart failure hospitalisation, and corrected some confidence intervals). However, we concluded that changes in the parameter values and assumptions did not have a great impact on the results. The corrected model gave an ICER about NOK 270,500 per QALY gained.

In the absence of the probability distributions for all the uncertain parameters, the uncertainties were assessed as one-way sensitivity analysis. The results were most sensitive to changes in utility values both for the treatment and the control group at

12 months, efficacy data (mortality and heart failure hospitalisations), and costs related to standard heart failure care (excluding hospitalisations). The incremental cost-effectiveness ratios varied between NOK 268,000 and NOK 485,000.

The sponsor estimated that the total added costs of implementing CardioMEMS in Norway would be about NOK 50,000,000 for the first five years.

Due to uncertainties associated with the number of patients (for both treatment strategies) and the yearly costs used in the calculation of budget impact by the sponsor, we re-calculated the additional costs of introducing the technology in Norway. The results of our budget impact analysis showed that assuming 100 new patients each year, the total added expected cost will be about NOK 89,000,000 for the first five years after adoption of CardioMEMS in Norway.

Conclusion

Efficacy

The use of the CardioMEMS™ HF System is safe and will probably reduce the heart-failure-related hospitalisation rate compared to standard treatment in heart failure patients with NYHA functional class III.

The evidence on efficacy and safety endpoints has a relatively short follow-up period, 18 and 31 months respectively. Further, all the available evidence came from only one trial. Hence the evidence may change with further studies available.

Cost-effectiveness

The use of the CardioMEMS device can most likely be considered cost-effective in heart failure patients with NYHA functional class III at what has normally been considered a cost-effective use of Norwegian health-care resources.

However, there are some uncertainties regarding the input parameters and the assumptions. Long-term utility values, clinical efficacy data and costs related to standard heart failure care (excluding hospitalisations) had the greatest impact on the results.

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29. Wisløff T, Selmer R, Halvorsen S, Kristiansen IS. Norwegian cardio vascular disease model- a simulation mode for estimating health benefits and cost consequences of cardiovascular interventions Rapport fra Kunnskapssenteret: 2008. (23).
30. National Institute for Health and Care Excellence. Sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction. National Institute for Health and Care Excellence; 2016
31. Yao G, Freemantle N, Flather M, Tharmanathan P, Coats A, Poole-Wilson PA, et al. Long-term cost-effectiveness analysis of nebivolol compared with standard care in elderly patients with heart failure: an individual patient-based simulation model. *Pharmacoeconomics* 2008;26(10):879-889.

32. Thokala P, Baalbaki H, Brennan A, Pandor A, Stevens JW, Gomersall T, et al. Telemonitoring after discharge from hospital with heart failure: cost-effectiveness modelling of alternative service designs. *BMJ Open* 2013;3(9):e003250.
33. Griffiths A, Paracha N, Davies A, Branscombe N, Cowie MR, Sculpher M. The cost effectiveness of ivabradine in the treatment of chronic heart failure from the U.K. National Health Service perspective. *Heart* 2014;100(13):1031-1036.
34. Dyer MT, Goldsmith KA, Sharples LS, Buxton MJ. A review of health utilities using the EQ-5D in studies of cardiovascular disease. *Health Qual Life Outcomes* 2010;8:13.
35. Hoepfer MM, Lee SH, Voswinckel R, Palazzini M, Jais X, Marinelli A, et al. Complications of right heart catheterization procedures in patients with pulmonary hypertension in experienced centers. *J Am Coll Cardiol* 2006;48(12):2546-2552.
36. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;62(16):e147-239.
37. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016;37(27):2129-2200.
38. Grundtvig M, Gullestad L, Hole T, Flonaes B, Westheim A. Characteristics, implementation of evidence-based management and outcome in patients with chronic heart failure: results from the Norwegian heart failure registry. *Eur J Cardiovasc Nurs* 2011;10(1):44-49.
39. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;371(11):993-1004.

Appendix

Appendix 1. St. Jude Medical's search strategies

Database	Search Terms	Results	Final number excluding duplicates
EMBASE Embase includes MEDLINE references (search conducted on 10 August 2015)	#1:- 'heart failure/exp OR 'heart failure'	377901	36
	#2:- chronic AND heart AND failure	72771	
	#3:- congestive AND heart AND failure	94826	
	#4:- #1 OR #2 OR #3	393051	
	#5:- new AND york AND heart AND association AND class AND 3	16327	
	#6:- #4 OR #5	11011	
	#7:- haemodynamic OR hemodynamic	151468	
	#8:- #7 AND sensor	675	
	#9:- #7 AND device	6800	
	#10:- pulmonary AND arter* AND pressure	57430	
	#11:- pulmonary AND arter* AND pressure AND sensor	182	
	#12:- pulmonary AND arter* AND pressure AND device	2422	
	#13:- pulmonary AND arter* AND pressure AND monitor*	6916	
	#14:- #7 AND monitor*	29023	
	#15:- #10 OR #11 OR #12 OR #13 OR #14	39072	
	#16:- .rct	20593	
	#17:- 'randomised controlled trial' OR 'randomised controlled trial'	463713	
	#18:- 'controlled trial'	480367	
	#19:- 'systematic review'	126686	
	#20:- #16 OR #17 OR #18	587839	
	#21:- #6 OR #15 OR #20	36	
Cochrane Library (searched on 10/08/2015)	#1:- heart failure	19006	15
	#2:- new york heart association class 3	1372	
	#3:- #1 and #2	1178	
	#4:- haemodynamic or hemodynamic	14729	
	#5:- #4 and sensor	48	
	#6:- #4 and device	617	
	#7:- #4 and monitor	320	
	#8:- pulmonary artery pressure	2345	

	#9:- #5 or #6 or #7	904	
	#10:- #3 and #8 and #9	18	
Clinicaltrials.gov	heart failure "hemodynamic sensor" OR "hemodynamic monitor" OR "hemodynamic device"	10	10
NIHR Centre for reviews and dissemination	1:- (hemodynamic) OR (haemodynamic)	271	
	2:- (heart failure)	1572	
CRD Database managed by York university Database of HTA reports and economic analyses	3:- #1 AND #2	38	38

Appendix 2. Norwegian Institute of Public Health's search strategies

Cardiomems - Literature search

Databases: Cochrane Library, Ovid Embase and MEDLINE, Centre for Reviews and Dissemination

Study design: Systematic Review, Health Technology Assessment, Controlled trial

Searched by: Ingrid Harboe, research librarian

Peer review: Gyri Straumann, research librarian

Results: 13 Systematic Reviews, Health Technology Assessments
550 Controlled trials

Search strategies

Database: Cochran Library

Results: Cochrane Reviews (3), Trials (326), Technology Assessments (3)

ID	Search	Hits
#1	MeSH descriptor: [Heart Failure] explode all trees	6456
#2	heart failure:ti,ab,kw	18243
#3	"new york heart association class 3" or "new york heart association class III":ti,ab,kw	163
#4	(NYHA Class III):ti,ab,kw	794
#5	#1 or #2 or #3 or #4	18357
#6	cardiomems:ti,ab,kw	8
#7	((haemodynamic or hemodynamic) near/6 (device* or monitor* or sensor* or tool*)):ti,ab,kw	1165

#8	((pulmonar* arter* or PA) near/6 (device* or measur* or monitor* or sensor* or system or tool*)):ti,ab,kw	885
#9	(implant* near/6 (measur* or pressure)):ti,ab,kw	1217
#10	(wireless near/6 (device* or implant* or monitor* or sensor* or system or tool*)):ti,ab,kw	146
#11	(systolic near/6 artery pressure):ti,ab	295
#12	(diastolic near/6 artery pressure):ti,ab	176
#13	#6 or #7 or #8 or #9 or #10 or #11 or #12	3699
#14	#5 and #13	332

Databases: Embase 1974 to 2016 April 29,

Epub Ahead of Print, In-Process & Other Non-Indexed Citations,

Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

1	Heart Failure/	269435
2	heart failure.tw.	315793
3	("new york heart association class 3" or "new york heart association class III").tw.	1947
4	NYHA Class III.tw.	4932
5	or/1-4	409988
6	cardiomems.tw.	52
7	((haemodynamic or hemodynamic) adj6 (device* or monitor* or sensor* or tool*)).tw.	13122
8	((pulmonar* arter* or PA) adj6 (device* or tool* or measur* or monitor* or sensor* or tool*)).tw.	21080
9	(implant* adj6 (measur* or pressure)).tw.	19944
10	(wireless adj6 (device* or implant* or monitor* or sensor* or system or tool*)).tw.	8513
11	(systolic adj6 arter* pressure).tw.	11176
12	(diastolic adj6 arter* pressure).tw.	5774
13	or/6-12	74609
14	5 and 13	4936
15	limit 14 to "reviews (maximizes specificity)"	13
16	14 and (systematic* review* or technology assessment*).tw.	13

17	15 or 16	15
18	remove duplicates from 17	12
19	limit 14 to "therapy (maximizes specificity)"	293
20	randomised controlled trial.pt.	414579
21	controlled clinical trial.pt.	90600
22	randomi*ed.ab.	990235
23	placebo.ab.	399483
24	clinical trials as topic/	217996
25	randomly.ab.	569599
26	control group.tw.	716980
27	or/20-26	2497356
28	news.pt.	176355
29	editorial.pt.	909701
30	exp Animals/	41726453
31	Humans/	27837811
32	30 not (30 and 31)	13891831
33	or/28-29,32	14833976
34	27 not 33	1761191
35	14 and 34	479
36	or/19,35	547
37	remove duplicates from 36	409

Database: Centre for Reviews and Dissemination

1	MeSH DESCRIPTOR Heart Failure EXPLODE ALL TREES	819
2	(heart failure)	1601
3	("new york heart association class 3" or "new york heart association class III")	13
4	((NYHA Class III))	33
5	#1 OR #2 OR #3 OR #4	1608

6	(cardiomems)	2
7	((haemodynamic near6 (device* or monitor* or sensor* or tool*)))	18
8	((hemodynamic near6 (device* or monitor* or sensor* or tool*)))	3
9	((((pulmonar* arter* or PA) near6 (device* or measur* or monitor* or sensor* or system or tool*)))	18
10	((implant* near6 (measur* or pressure)))	30
11	((wireless near6 (device* or implant* or monitor* or sensor* or system or tool*)))	13
12	((systolic near6 artery pressure))	0
13	((diastolic near6 artery pressure))	0
14	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	79
15	#5 AND #14	11
16	(#15) IN DARE, HTA	9
17	(#15) IN NHSEED	2

Searching ongoing trials

Source: ClinicalTrials.gov

Date: 2016.08.17

Results: 69 trials

Searches: cardiomems (basic search)

heart failure AND wireless monitoring

heart failure AND Hemodynamic monitor*

Source: WHO International Clinical Trials Registry Platform

Date: 2016.08.17

Results: 43 records of 42 trials

Basic search: cardiomems

Advanced search:

Condition: heart AND failure

Intervention: wireless AND monitor OR Hemodynamic AND monitor* OR cardiomems

Appendix 3. A summary of the identification of RCTs following St. Jude Medical's literature searches

	EMBASE (includes medline)	The Cochrane library	clinicaltrials.gov	NIHR CRD
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Number of Results	36	17	12	38
Citations excluded after title / abstract review				
Wrong Intervention	23	9	5	38
Wrong Population	1	0	1	0
Wrong Intervention and population	4	7	5	0
Wrong publication type (review, editorial etc...)	5	0	0	0
Wrong Study type	0	0	1	0
Total number excluded	32	16	12	0
Number of Citations excluded after full text review				
Wrong Intervention	0	0	0	0
Wrong Population	1	0	0	0
Wrong Intervention and population	1	0	0	0
Wrong publication type (review, editorial etc...)	0	0	0	0
Wrong Study type	0	0	0	0
Total number excluded	2	0	0	0
Number of citations of direct randomised trials included	1	0	0	0
Consolidated citations (excluding duplicates)	1			
Number of additional citations included by manual searches of references	0			
Number of published direct RCTs including study reports	1			
Number of published systematic reviews included	0			

Appendix 4. Excluded trials from our search, and the reasons for the exclusions

Controlled trials, including RCT's

Abraham W, Adamson P, Bourge R. **Erratum:** Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: A randomised controlled trial (The

Lancet (2011) 377 (658-666). Lancet2012. p. 412.

Reason for exclusion: Comments to: *Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: A randomised controlled trial. The Lancet 2011;377(9766):658-666.* We take care of this in our report under «Comments to the description of the included trials»

Abraham W, Adamson P, Raval N, Stevenson L, Bauman J, Neville S, et al. The malignant effect of acute decompensation in patients with chronic heart failure: Insights from the CHAMPION trial. *Eur Heart J* 2012;33:962.

Reason for exclusion: Have the same data in the full text: *Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: A randomised controlled trial. The Lancet 2011;377(9766):658-666.*

Abraham WT. Disease management: remote monitoring in heart failure patients with implantable defibrillators, resynchronization devices, and haemodynamic monitors. *Europace* 2013;15 Suppl 1:i40-i46.

Reason for exclusion: Overview, not SR. No new data.

Abraham WT, Adamson P, Packer M, Bauman J, Yadav J. Impact of introduction of pulmonary artery pressure monitoring for heart failure management: Longitudinal results from the champion trial. *J Am Coll Cardiol* 2014;1):A766.

Reason for exclusion: Have the same data in the full text: *Abraham WT, Stevenson LW, Bourge RC, Lindenfeld JA, Bauman JG, Adamson PB. Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: Complete follow-up results from the CHAMPION randomised trial. The Lancet 2016;387(10017):453-461.*

Abraham WT, Adamson PB, Hasan A, Bourge RC, Pamboukian SV, Aaron MF, et al. Safety and accuracy of a wireless pulmonary artery pressure monitoring system in patients with heart failure. *Am Heart J* 2011;161(3):558-566.

Reason for exclusion: Inappropriate population

Adamson P, Abraham W, Stevenson L, Bourge R, Raval N, Bauman J, et al. Targeting pulmonary artery pressures in the treatment of chronic heart failure: Insights from the CHAMPION trial. *Eur Heart J* 2012;33:650-651.

Reason for exclusion: Inappropriate outcome

Adamson P, Gold M, Bennett T, Bourge R, Stevenson L, Trupp R, et al. Continuous hemodynamic monitoring in patients with mild to moderate heart failure: results of The Reducing Decompensation Events Utilizing Intracardiac Pressures in Patients With Chronic Heart Failure (REDUCEhf) trial. *Congestive heart failure (Greenwich, Conn)*2011. p. 248-254.

Reason for exclusion: Inappropriate population and intervention

Adamson P, Henderson J, Ginn G, Neville S, Abraham W. Pulmonary artery pressure guided heart failure management during a 'real-world' clinical setting follow-up period demonstrated even greater improvement in clinical outcomes than that achieved in the champion randomised controlled trial. *J Card Fail* 2015. p. S118-s119. **Reason for exclusion:** Have the same data in the full text: *Abraham WT, Stevenson LW, Bourge RC, Lindenfeld JA, Bauman JG, Adamson PB. Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: Complete follow-up results from the CHAMPION randomised trial. The Lancet 2016;387(10017):453-461.*

Adamson PB. Ambulatory hemodynamics in patients with chronic heart failure: implications for volume management in elderly patients. *The American journal of geriatric cardiology* 2005;14(5):236-241. **Reason for exclusion:** No results

Adamson PB, Abraham W, Stevenson L, Neville S, Cowart P, Yadav J. Benefits of pulmonary artery pressure monitoring extend to reduction of all-cause rehospitalisation. *J Am Coll Cardiol* 2014;1):A746. **Reason for exclusion:** Have the same data in the full text: *Abraham WT, Stevenson LW, Bourge RC, Lindenfeld JA, Bauman JG, Adamson PB. Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: Complete follow-up results from the CHAMPION randomised trial. The Lancet 2016;387(10017):453-461.*

Adamson PB, Abraham WT, Aaron M, Aranda Jr JM, Bourge RC, Smith A, et al. CHAMPION trial rationale and design: The long-term safety and clinical efficacy of a wireless pulmonary artery pressure monitoring system. *J Card Fail* 2011;17(1):3-10. **Reason for exclusion:** No results. This publication gives the rationale and the design for the CHAMPION trial.

Adamson PB, Zile MR, Cho YK, Bennett TD, Bourge RC, Aaron MF, et al. Hemodynamic factors associated with acute decompensated heart failure: part 2--use in automated detection. *J Card Fail* 2011;17(5):366-373. **Reason for exclusion:** Inappropriate population

Anonymous. Late-Breaking Clinical Trial Presentations 14th Annual Scientific Meeting, Heart Failure Society of America. *Journal of Cardiac Failure Conference: 14th Annual Scientific Meeting, Heart Failure Society of America San Diego, CA United States Conference Start* 2010;16(11). **Reason for exclusion:** No results

Aronson D, Eitan A, Dragu R, Burger AJ. Relationship between reactive pulmonary hypertension and mortality in patients with acute decompensated heart failure.[Erratum appears in *Circ Heart Fail*. 2012 Jan 1;5(1):e18]. *Circ Heart Fail* 2011;4(5):644-650. **Reason for exclusion:** Inappropriate intervention

Baumert J, Falter F, Eletr D, Hecker K, Reyle-Hahn M, Rossaint R. Xenon anaesthesia may preserve cardiovascular function in patients with heart failure. *Acta Anaesthesiol Scand* 2005. p. 743-749. **Reason for exclusion:** Inappropriate intervention

Benza R, Bourge R, Adamson P, Abraham W, Yadav J. Heart failure hospitalisations are reduced in heart failure patients with comorbid pulmonary hypertension using a wireless implanted pulmonary artery pressure monitoring system. *J Card Fail* 2012;1):S99. **Reason for exclusion:** Have the same data in the included full text:

Benza RL, Raina A, Abraham WT, Adamson PB, Lindenfeld J, Miller AB, et al. Pulmonary hypertension related to left heart disease: insight from a wireless implantable hemodynamic monitor. J Heart Lung Transplant 2015;34(3):329-337.

Costanzo MR, Abraham WT, Adamson PB, Cowart PA, Corcoran KM, Ginn GL. Medical management guided by pulmonary artery pressures in NYHA functional class III heart failure patients. *J Card Fail* 2011;1):S93.

Reason for exclusion: Inappropriate outcome

Costanzo MR, Adamson PB, Abraham WT, Bradley J, Neville S, Cowart P, et al. Vasodilator use guided by wireless pulmonary artery hemodynamic monitoring reduces heart failure hospitalisations in both african american and non-african american heart failure patients: Results from the champion trial. *Circulation Conference: American Heart Association* 2012;126(21 SUPPL. 1).

Reason for exclusion: Inappropriate outcome

Costanzo MR, Stevenson LW, Adamson PB, Desai AS, Heywood JT, Bourge RC, et al. Interventions Linked to Decreased Heart Failure Hospitalisations During Ambulatory Pulmonary Artery Pressure Monitoring. *JACC Heart Failure* 2016;2:2.

Reason for exclusion: Inappropriate outcome

Desai A, Bauman J, Abraham W, Adamson P, Costanzo M, Heywood J, et al. Clinical outcomes and benefit of ambulatory pulmonary artery pressure monitoring in heart failure patients according to initial pulmonary artery diastolic pressure. *Eur Heart J* 2015. p. 1045-1046.

Reason for exclusion: The results were not specified for the intervention and the control group.

Feldman D, Moazami N, Bauman J, Naka N. A wireless implantable hemodynamic monitor in advanced heart failure patients needing ventricular support device therapy. *European Heart Journal: Acute Cardiovascular Care* 2014. p. 32.

Reason for exclusion: Inappropriate population

Feldman D, Naka Y, Cabuay B, Takayama H, Bauman J, Cowart P, et al. A wireless hemodynamic pressure sensor before and after ventricular assist device placement: A sub-study of the CHAMPION Trial. *J Heart Lung Transplant* 2011;1):S86.

Reason for exclusion: Inappropriate outcome

Frantz RP, Benza RL, Kjellstrom B, Bourge RC, Barst RJ, Bennett TD, et al. Continuous Hemodynamic Monitoring in Patients With Pulmonary Arterial Hypertension. *J Heart Lung Transplant* 2008;27(7):780-788.

Reason for exclusion: Inappropriate intervention

Goldberg L, Desai A, Costanzo M, Stevenson L, Adamson P, Heywood J, et al. Pressure for action: Implantable pulmonary artery pressure sensor measurements alone beat clinical signs to guide prevention of heart failure hospitalisations. *Heart Rhythm* 2015. p. S82-s83.

Reason for exclusion: Inappropriate outcome

Hoppe UC, Vanderheyden M, Sievert H, Brandt MC, Tobar R, Wijns W, et al. Chronic monitoring of pulmonary artery pressure in patients with severe heart failure: multicentre experience of the monitoring Pulmonary Artery Pressure by Implantable device Responding to Ultrasonic Signal (PAPIRUS) II study. *Heart* 2009;95(13):1091-1097.

Reason for exclusion: Inappropriate population and intervention

Martinez F, Bourge R, Benza R, Abraham W, Adamson P, Yadav J, et al. Respiratory event hospitalisations are reduced in heart failure patients with comorbid chronic obstructive pulmonary disease using a wireless implanted pulmonary artery pressure monitoring system. *European Respiratory Journal Conference: European Respiratory Society Annual Congress 2012*;40(no pagination).

Reason for exclusion: Inappropriate outcome

Maurer M, Adamson P, Costanzo M, Eigler N, Gilbert J, Gold M, et al. Rationale and design of the left atrial pressure monitoring to optimize heart failure therapy study (LAPTOP-HF). *J Card Fail* 2015. p. 479-488.

Reason for exclusion: Inappropriate intervention

Miller AB, Gilbert EM, Chung ES, Levy WC, Teerlink JR, Carson P, et al. Implantable hemodynamic monitoring reduces heart failure hospitalisations due to congestion regardless of perfusion status. *Circulation Conference: American Heart Association's 2015*;132(no pagination).

Reason for exclusion: Have the same data in the full text: *Abraham WT, Stevenson LW, Bourge RC, Lindenfeld JA, Bauman JG, Adamson PB. Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: Complete follow-up results from the CHAMPION randomised trial. The Lancet 2016;387(10017):453-461.*

Raina A, Abraham WT, Adamson PB, Bauman J, Benza RL. Limitations of right heart catheterization in the diagnosis and risk stratification of patients with pulmonary hypertension related to left heart disease: insights from a wireless pulmonary artery pressure monitoring system. *J Heart Lung Transplant* 2015;34(3):438-447.

Reason for exclusion: Not our focus

Raval N, Abraham W, Adamson P, Chronos N, Sachar R, Ginn G. Long-term effects of implantable hemodynamic monitoring in patients with moderate heart failure. *Eur Heart J* 2011;32:298.

Reason for exclusion: Have the same data in the full text: *Abraham WT, Stevenson LW, Bourge RC, Lindenfeld JA, Bauman JG, Adamson PB. Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: Complete follow-up results from the CHAMPION randomised trial. The Lancet 2016;387(10017):453-461.*

Shah M, O'Connor C, Sopko G, Hasselblad V, Califf R, Stevenson L. Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE): design and rationale. *Am Heart J* 2001. p. 528-535.

Reason for exclusion: Inappropriate population

Shil AB. Wireless pulmonary artery haemodynamic monitoring. *Lancet* 2011;377(9784):2176; author reply 2177.

Reason for exclusion: No result data

Siminiak T, Jerzykowska O, Woloszyn M, Smuszkiewicz P, Manicki M, Kalmucki P, et al. Percutaneous repair of functional mitral regurgitation using CARILLONTM Mitral Contour System. POZNAN single center registry in consecutive patients. *Am J Cardiol* 2009;1):51D.

Reason for exclusion: Not relevant

Ståhlberg M, Hilpisch K, Reiters P, Linde C, Braunschweig F. Haemodynamic effects of different basic heart rates in ambulatory heart failure patients treated with car-

diac resynchronization therapy. *Europace : European pacing, arrhythmias, and cardiac electrophysiology : journal of the working groups on cardiac pacing, arrhythmias, and cardiac cellular electrophysiology of the European Society of Cardiology* 2013. p. 1182-1190.

Reason for exclusion: Inappropriate intervention

Verdejo H, Castro P, Concepción R, Ferrada M, Alfaro M, Alcaíno M, et al. Comparison of a radiofrequency-based wireless pressure sensor to swan-ganz catheter and echocardiography for ambulatory assessment of pulmonary artery pressure in heart failure. *J Am Coll Cardiol* 2007. p. 2375-2382.

Reason for exclusion: Inappropriate population

Wadas TM. The implantable hemodynamic monitoring system. *Crit Care Nurse* 2005;25(5):14-16, 18-20, 22-14; quiz 27.

Reason for exclusion: Overview, not SR; inappropriate intervention

Zile MR, Bourge RC, Bennett TD, Stevenson LW, Cho YK, Adamson PB, et al. Application of Implantable Hemodynamic Monitoring in the Management of Patients With Diastolic Heart Failure: A Subgroup Analysis of the COMPASS-HF Trial. *J Card Fail* 2008;14(10):816-823.

Reason for exclusion: Inappropriate population

SR's and HTA's

Hayes, Inc. Wireless pulmonary artery pressure monitoring with CardioMEMS™ HF System HF System (St. Jude Medical) for management of chronic heart failure (Structured abstract). *Health Technology Assessment Database HAYES, Inc;* 2015.

Reason for exclusion: We were unable to get his, too high cost.

Nihr H. CardioMEMS™ HF System HF System for heart failure (Structured abstract). *Health Technology Assessment Database NIHR Horizon Scanning Centre (NIHR HSC);* 2013.

Reason for exclusion: This is a Technology Alert from HORIZIN Scanning Center, October 2013. No data.

Appendix 5. Ongoing trial of possible interest

From ClinTrials:

Recruitment status	Main ID	Public Title	Date of registration
Recruiting, No results available	NCT02693691	CardioMEMS™ HF System European Monitoring Study for Heart Failure	20/02/2016
Recruiting, No results available	NCT02279888	CardioMEMS™ HF System HF System Post Approval Study	29/10/2014
Recruiting, No results available	NCT02489370	CHF Home Telemonitoring: A Home Telemonitoring Service for Chronic Heart Failure Patients on Trial	/10/2014

Not yet recruiting	NCT02048748	Congestive Heart Failure Home Tele-monitoring	30/10/2013
Not yet recruiting	NCT00893685	Randomised Controlled Trial of Home Telemonitoring for Elderly People	22/04/2009
Enrolling by invitation No Results Available	NCT02729922	Registry of Patients With CardioMEMS™ HF System	31/03/2016
Active, not recruiting No Results Available	NCT02115620	Telemedicine Technology Demonstration Project for Heart Failure	14/04/2014
Completed, No Results Available	NCT01162707	Wireless, Intermittent Monitoring of Right Heart Pressures in HF	13/06/2010

From WHO ICTRP:

Recruitment status	Main ID	Public Title	Date of registration
Recruiting	NCT02729922	Registry of Patients With CardioMEMS™ HF System	31/03/2016
Recruiting	NCT02693691	CardioMEMS™ HF System European Monitoring Study for Heart Failure	20/02/2016
Recruiting	NCT02279888	CardioMEMS™ HF System HF System Post Approval Study	29/10/2014
Not recruiting	NCT02126254	Optimization of the Treatment of Acute HF by a Non Invasive Cardiac System-a Randomised Control Trial	22/04/2014
Not recruiting	ACTRN12612000789864	Comparison of Pressure Difference Measurements Across Narrowed Diseased Arteries Using a New Pressure Sensor Compared to a Commercially Available Pressure Sensor	25/07/2012

Appendix 6. Trial description, data extraction and Risk of Bias tables for the included trials

In the following tables we used these abbreviations:

HFH: Heart-failure-related-hospitalisation

CRT: Cardiac Resynchronization Therapy

LVEF: Left ventricular ejection fraction

RRR: Relative risk reduction rate

COPD: Chronic Obstructive Pulmonary Disease

QoL: Quality of Life

PH: Pulmonary hypertension

HR: Hazard ratio

RR: Relative risk

CI: Confidential interval

NNT: Number Needed to Treat

Study description: Publications from the CHAMPION trial (NCT00531661) that include **the whole population in the randomised period:** Abraham 2011 (2); Abraham 2016 (14)

Trials:

1) Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, et al. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: A randomised controlled trial. *The Lancet* 2011;377(9766):658-666.

2) Abraham WT, Stevenson LW, Bourge RC, Lindenfeld JA, Bauman JG, Adamson PB. Sustained efficacy of pulmonary artery pressure to guide adjustment of chronic heart failure therapy: Complete follow-up results from the CHAMPION randomised trial. *The Lancet* 2016;387(10017):453-461.

Both: NCT00531661, (CHAMPION trial)

Design: Randomised, prospective, single-blind (patients blinded) trial double-blind, multicentre clinical trial conducted at 64 sites in the U.S. The patients were randomly assigned between Sept 6, 2007, and Oct 7, 2009.

One of the publications (Abraham 2011) describes the randomised period, with an average follow-up period of 15 months.

The other publication (Abraham 2016) describes the randomised period, with an average follow-up period of 18 months. Further, this publication described the open access period that follow after the end of the randomisation period. The total randomisation period lasted for an average of 18 months (then the last patient enrolled completed at least 6 months of study follow-up). The open access period had an additional averaging 13 months of follow-up. In the open access period the investigators had access to pulmonary artery pressure for all the patients. From the open access period, we only report safety data.

Population: 550 patients ≥ 18 years with New York Heart Association (NYHA) Class III heart failure, regardless of left ventricular ejection fraction or cause, who had been admitted to hospital for heart failure in the previous year were eligible for the study.

Before randomisation, all patients underwent right heart catheterisation with haemodynamic assessment and implantation of the pulmonary artery sensor (CardioMEMS™ HF System sensor).

Intervention/comparators: 550 patients randomised 1:1 to either the

Treatment group: in which daily uploaded pulmonary artery pressures were used to guide medical therapy, or to the

Control group: in which daily uploaded pulmonary artery pressures were *not* made available to investigators. Patients in the control group received all standard medical, device, and disease management strategies available.

Endpoints:

Primary:

<p><i>Efficacy:</i> The rate of heart-failure-related hospitalisations during the 6 months after insertion of the implant in the treatment group versus the control group.</p> <p><i>Safety:</i> Device-related or system-related complications (DSRC) defined as an adverse event that was definitely or possibly related to the wireless pressure sensor or external electronics, and was treated with invasive means other than intramuscular administration of drugs or a right-heart catheterization; and pressure –sensor failure defined as an inability to obtain readings.</p> <p><i>Secondary:</i> Patients survival rates. Days alive outside hospital. Quality of life by use of MLHFQ (Minnesota Living with Heart Failure Questionnaire at 6 months).</p> <p><i>Prespecified supplementary analyses:</i> Includes heart-failure-related hospitalisations during the entire randomised follow-up, quality of life analysis at 12 months. Safety analyses over the randomised and open access periods.</p> <p>All analyses were by the intention to treat..</p>
<p><i>Follow-up:</i> All patients remained in their assigned group until the last patient completed 6 months of follow-up. The average follow-up for efficacy from the randomised period was 15 months (SD) (Abraham 2011), and 18 months (Abraham 2016).</p> <p>Safety was reported at 6 months, at 18 months and at 31 months (18 months in the randomised period + 13 in the open access period).</p>
<p><i>Funding source:</i> St. Jude Medical</p>

Data extraction: Publications from the CHAMPION trial (NCT00531661) that **include the whole population in the randomised period:** Abraham 2011 (2); Abraham 2016 (14)

Endpoints	Intervention Investigator has access to pulmonary artery pressure data (n=270)	Control: Standard care (n=280)	Risk (95% CI), p-values
<p>HFH</p> <p>6 months (Abraham 2011)</p>	84 (0-32)	120 (0-44)	HR: 0.72 (28%RRR; 95%CI 0.60-0.85)
<p>15 months (SD 7) (Abraham 2011)</p>	158	254	HR: 0.63 (37%RRR; 95%CI 0.52-0.77)
<p>18 months (Abraham 2016)</p>	182	279	HR: 0.67 (33%RRR; 95%CI 0.55-0.80)
<p>Device-related or system- related complications 6 months (Abraham 2011)</p>	3 (1%)	3 (1%)	From study: HR not given, From our own RevMan calculations: RR: 1.04 (0.21 to 5.09)

Device-related or system- related complications 31 months (Abraham 2016)	Overall combined device-related or system-related complication rate was 0.02 events per patients-year in the entire follow-up period.		
Pressure –sensor failures: 6 months (Abraham 2011) 31 months (Abraham 2016)	0 0	0 0	
Procedure –related adverse events 6 months (Abraham 2011)	For the total group: 7/575		
Mortality at 18 months (Abraham 2016)	50 (19%)	64 (23%)	HR 0.80 (0.95%CI0.55-1.15)
QoL, measured with Minnesota Living with Heart Failure Questionnaire** at 6 months (mean, SD) (Abraham 2011)	45(26)	51(25)	Not given
QoL, measured with Minnesota Living with Heart Failure Questionnaire* at 12 months (mean, SD) (Abraham 2016)	47	56.5	Not given

* Minnesota Living with Heart Failure Questionnaire. Total possible score: Better quality with low score.

Risk of Bias: Publications from the CHAMPION trial (NCT00531661) that **include the whole population in the randomised period:** Abraham 2011 (2); Abraham 2016 (14)

Entry/Domain	Judgement	Description
Random sequence generation?	Low	“Randomisation was done by use of a computer-generated schedule stratified by study site, with block sizes of four..”, page 660
Allocation concealment?	Low	“Investigators enrolled patients who were randomly assigned in a 1:1 ratio by use of a centralized electronic system.”, p 660.
Blinding of participants and personnel?	?	The study is single-blinded (patient blinded). To maintain patient masking, all patients were asked to take pressure readings every day.

Blinding of outcome assessments?		
Heart-failure-related hospitalisation	Low	We do not think that any of the endpoints will be influenced by the lack of blinding of the investigators
Survival rates	Low	
Safety	Low	
Health related quality of life	Low	
Incomplete outcome data?		
Heart-failure-related hospitalisation	Low	All analyses were by intention to treat
Survival rates	Low	
Safety	Low	
Health related quality of life	Low	
Selective reporting?	Low	CHAMPION trials' rationale and design were published in a specific article (23). All endpoints were pre-specified, and reported on.
Other sources of bias?	Low	CardioMEMS™ HF System , Atlanta, GA, USA sponsored this study
Conclusions	Low risk of bias for all the endpoints	

Data extraction: Publications from the CHAMPION trial (NCT00531661) with substudies from the randomised period with heart-failure-related hospitalisation as endpoint: Adamson 2010 (16); Adamson 2014 (15); Weiner 2011 (22); Strickland 2016 (21); Miller 2016 (20), Criner 2012 (18); Abraham 2014 (13), Krahnke 2015 (19); Abraham 2015 (12); Benza 2015 (17)

Type of subpopulation /follow-up-period for HFH (Publication)	Intervention Investigator has access to pulmonary artery pressure data Number of events/ Total population	Control: Standard care Number of events/ Total population	Risk (95% CI)
<p>Patients with preserved ejection fraction*: HFH at 6 months (Adamson 2010): >6 months (Adamson 2014) at 15 months (Adamson 2010): at 17.6 months, average (Adamson 2014)</p>	<p>10/59, rate 0.17 11/62 rate 0.21 29/62</p>	<p>19/56, rate 0.34 19/57 rate 0.52 59/57</p>	<p>RRR 50% Incidence rate ratio: 0.54 (0.38-0.70) RRR 60% Incidence rate ratio: 0.50 (0.35-0.70)</p>
<p>Patients with reduced ejection fraction**: HFH >6 months (Adamson 2014) at 17.6 months, average (Adamson 2014)</p>	<p>73/208 153/208</p>	<p>101/222 220/222</p>	<p>Incidence rate ratio: 0.76 (0.61-0.91) Incidence rate ratio: 0.74 (0.63-0.89)</p>
<p>Patients with reduced ejection fraction and with/without Cardiac Resynchronization Therapy (CRT) HFH at 6 months, <i>with</i> CRT (Weiner 2011) HFH at 6 months, <i>without</i> CRT (Weiner 2011)</p>	<p>31/82 42/126</p>	<p>45/89 56/133</p>	<p>RRR: 24% 23%</p>
<p>Patients with/or without a history of Myocardial infarction (Strickland 2011) HFH <i>with</i> history of myocardial infarction: At 6 months Average 15 months:</p>	<p>46/134 -</p>	<p>67/137 -</p>	<p>RRR: 29.8% 46.3%</p>

HFH <i>without</i> history of myocardial infarction: At 6 months Average 15 months	38/136 -	53/143 -	25.3% 22.9%
Patients with atrial fibrillation HFH at: 6 months (Miller 2012) 15 months (Miller 2012)	Total N: 120 Hospitalisation rate: 0.36 0.54	Total N:135 Hospitalisation rate: 0.57 0.91	Hospitalisation rate: 37% lower in the treatment group 41% lower in the treatment group
Patients with comorbid chronic obstructive pulmonary disease (N=187) HFH at average of 15 months (Criner 2012)	Hospitalisation rate: 0.55	Hospitalisation rate: 0.96	Reduction in hospitalisation rate: 41%, HR: 0.59, 95%CI 0.44-0.81)
Patients with Chronic Kidney Disease HFH at 18 months (Abraham 2014)	Total N: 150 Hospitalisation rate: 0.48	Total N: 147 Hospitalisation rate: 0.83	HR: 0.58
Patients with/ or without Chronic Obstructive Pulmonary Disease (COPD) HFH at 15 months (Krahnke 2015): <i>with COPD</i> <i>without COPD</i>	66/91 92/179	110/96 144/184	HR (95%CI) 0.59 (0.44-0.81) 0.66 (0.51-0.85)
Patients with cardiac resynchronizatin therapy (CRT, n= 142 total) or implantable cardioverter defibrillator (ICD, n= 133 total). The results are for the two groups together (n=275) (Abraham 2015) HFH at average 18 months:	88/129	164/146	43% reduction. HR: 0.57 (0.44-0.74), NNT=4

Patients with/without WHO group II pulmonary hypertension*** (Benza 2015)			
HFH at average 15 months <i>With PH</i>	113/151	186/163	RRR: 36%; HR:0.64 (0.51-0.81)
<i>Without PH</i>	40/107	66/108	RRR: 40%; HR: 0.60 (0.41-0.89)

*Preserved ejection fraction: Defined at a previous hospitalisation as LVEF>40% (Adamson 2010); and as baseline ejection fraction ≥40% (Adamson 2016).

**Reduced ejection fraction: Defined as baseline ejection fraction <40% (Adamson 2016).

***Pulmonary arterie hypertension defined as >25 mm Hg.

Data extraction: Publications from the CHAMPION trial (NCT00531661) with substudies from the randomised period with mortality as endpoint: Abraham 2015 (12); Benza 2015 (17)

Type of subpopulation; /follow-up-period (Publication)	Intervention Investigator has access to pulmonary artery pressure data Number of events/ Total population	Control: Standard care Number of events/ Total population	Risk (95% CI)
Patients with cardiac resynchronizatin therapy (CRT, n= 142 total) or implantable cardioverter defibrillator (ICD, n= 133 total). The results are for the two groups together (n=275) (Abraham 2015)			
Mortality at average 18 months:	15/129	33/146	53% reduction. HR: 0.47 (0.26-0.87), NNT=13
Patients <i>with WHO group II pulmonary hypertension*</i> (Benza 2015)			
Survival at average 15 months			No difference in survival: HR:0.78, 95%CI 0.50-1.22)

* Pulmonary arterie hypertension defined as >25 mm Hg.

Data extraction: Publications from the CHAMPION trial (NCT00531661) with substudies from the randomised period with device safety: Benza 2015 (17) ().

Type of subpopulation; /follow-up-period (Publication)	Intervention Investigator has access to pulmonary artery pressure data Number of events/ Total population	Control: Standard care Number of events/ Total population	Risk (95% CI)
<p>Patients <i>with/without WHO group II pulmonary hypertension*</i> (Benza 2015)</p> <p>Device safety</p>	<p>1.4% of the patients having a complication. No procedure- related mortality. No events required removal of the sensor</p>		

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