BMJ Open

Telehealthcare for heart failure patients is highly cost-effective – results from the Danish TeleCare North Heart Failure trial

Journal:	*BMJ Open*
Manuscript ID	Draft
Article Type:	Research
Date Submitted by the Author:	n/a
Complete List of Authors:	Vestergaard, Anne; Aalborg Universitet, Department of Business and Management Hansen, Louise; Aalborg Universitet, Department of Business and Management Sørensen, Sabrina; Aalborg Universitet, Department of Business and Management Jensen, Morten; Aarhus University, Ehlers, Lars; Aalborg University, Danish Center for Healthcare Improvements, Department of Business and Management
Keywords:	HEALTH ECONOMICS, Heart failure < CARDIOLOGY, Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS

Title page

Title:

Telehealthcare for heart failure patients is highly cost-effective – results from the Danish TeleCare North Heart Failure trial

Authors:

- Anne Sig Sørensen (Vestergaard)[1], Ph.d
- Louise Hansen[1], Ph.d
- Sabrina Storgaard Sørensen[1], Ph.d
- Morten Berg Jensen[1,2], Ph.d
- Lars Holger Ehlers[1], Ph.d

Total word count: 4.441

Brief title: Cost-effectiveness of telehealthcare in HF

Affiliations:

[1]Danish Center for Healthcare Improvements, Dept. of Business and Management, Faculty of Social Sciences, Aalborg University, Aalborg, Denmark

[2]Department of Economics and Business Economics, Aarhus BSS, Aarhus University, Denmark

Address for correspondence

Lars Holger Ehlers

Aalborg University

Fibigerstræde 11, room 73

9220 Aalborg Øst

Denmark

Telephone: 0045 9940 8257

Fax: -

e-mail: lehlers@business.aau.dk

Suggested Keywords
Health Economics, Telemedicine, Heart Failure.

Abstract

Background. European guidelines for the treatment of patients with heart failure (HF) recommend telehealth as a means of monitoring patients' biomedical parameters to enable the detection of the development of complications and disease progression. There is, however, a lack of good economic evidence about the cost-effectiveness of telehealth in HF.

Methods. A cost-utility analysis was conducted alongside the TeleCare North trial. Patients in the intervention group were provided with a Telekit consisting of a tablet, a digital blood pressure monitor, and a scale and were instructed to perform measurements 1-2 times a week. The responsibility of the education, instructions and monitoring of the HF patients was placed on municipality nurses trained in HF and telemonitoring. A micro-costing approach was applied to evaluate the derived savings in the first year in the public health sector. Quality-adjusted life-years gained were estimated using the EQ-5D-3L questionnaire at baseline and at a one-year follow-up.

Results. Data for 274 patients were included in the main analysis. The telehealthcare solution provided a positive incremental NMB of £5164. The one-year adjusted QALY difference between the telehealthcare solution and the usual care group was 0.0034 [95% CI: -0.0711; 0.0780]. The adjusted difference in costs was -£5096 [95%CI: -8736;-1456]. All sensitivity analyses showed the main results were robust.

Conclusions. The TeleCare North solution for monitoring HF is highly cost-effective. There were significant costs savings on hospitalizations, primary care contacts, and total costs. Future economic research should focus on achieving a better understanding of the reasons for the changes in the demand for healthcare services among HF patients using telehealthcare.

Article summary

Strengths and limitations of this study

The present study is the first economic evaluation of telehealthcare in heart failure patients that strictly follows international guidelines for health economic evaluation alongside clinical trials

A broad healthcare and social sector perspective was chosen for the micro costing analyses based on patient specific data and detailed registration of operational and capital costs of telehealthcare.

This trial supports earlier findings that large savings can be obtained from telehealthcare in heart failure patients. However, the data collected in this trial provided limited explanation of what components of the intervention were actually effective or whether the effect is contingent on the intervention in its entirety.

1. Introduction

Heart failure (HF) is a common chronic disease with an estimated global prevalence of approximately two percent[1–3]. In Denmark, approximately 9000 patients are diagnosed with HF each year. The incidence increases with higher age, and it has been estimated that one in five individuals will develop HF during their lifetime[2–4]. In total, the condition is conservatively estimated to affect approximately 66,000 citizens in Denmark, and about five percent of all Danish citizens above the age of 75 have been diagnosed with HF[4,5]. The prevalence of HF is, however, expected to rise in the future due to, amongst others, a higher prevalence of predisposing factors, such as hypertension, diabetes, and obesity but also due to the increased longevity of patients with HF, which likely is the result of an improved treatment of the condition[1,2,6].

HF symptoms include dyspnea, fatigue, lethargy, and edema[3,4]. The severity of patients' HF is often described according to the New York Heart Association (NYHA) functional classification system, which may be used by patients to classify the severity of their HF according to their own experience of the condition. Class I indicates that the condition does not limit physical activity and that ordinary activity does not cause any symptoms. In higher classes, the symptoms reported are increasingly more severe; thus, in class IV, patients cannot perform physical activity without experiencing symptoms, or they experience symptoms even at rest[3,7]. HF is believed to impair patients' health-related quality of life (HRQoL) compared to individuals without the condition, and the condition entails a substantially increased mortality[2,8–10]. In addition to the personal burden that HF entails, the condition also causes a substantial burden on health care systems worldwide, accounting for approximately two percent of total health care expenditures[2,11]. Hospitalizations are recognized as the primary driver for the total costs related to HF, though outpatient visits also constitute a substantial part[2,12]. In 2016, the European Society of Cardiology published updated guidelines for the diagnosis and treatment of acute and chronic HF[13], emphasizing the beneficial impact of continuous monitoring of, amongst others, biomedical parameters to enable the detection of the development of complications and disease progression that may prompt changes to patients' disease management. In the guidelines, telehealthcare is mentioned as a possible means of monitoring patients[13]. Evidence suggests that telehealthcare in different forms may be beneficial in the management of HF, both for the improvement of patients' HRQoL but also in the prevention of, for example, hospitalizations and all-cause mortality[14–16]. Findings, however, are inconsistent[13,17], which might be ascribed to the fact that the components of the investigated telehealthcare solutions differ. Effectively, this heterogeneity makes the various telehealthcare solutions incomparable in terms of their design, effectiveness and, consequently, cost-effectiveness [15–17]. A number of reviews [16–18] have requested

more high-quality studies of the health economic consequences of telehealthcare interventions. To our knowledge, however, up until now, no cost-effectiveness analysis of telehealthcare in HF patients have been conducted according to international good practice guidelines for the economic evaluation alongside clinical trials[19,20].

In Denmark, a national strategy has been formulated for the introduction of telehealthcare as a means of reducing healthcare costs while also providing patients with greater HRQoL and the feeling of improved control of their disease [21,22]. In this respect, the North Denmark Region has played a major role in the formulation of the national strategy by performing pre-launch, large-scale randomized controlled trials and health economic evaluations and national business cases as decision-support for the nationwide implementation[23,24]. In the wake of the first TeleCare North trial directed at patients suffering from chronic obstructive pulmonary disease (COPD), which was executed in 2014-2015[23,24], the TeleCare North Heart Failure (HF) trial was launched in 2016 with the purpose of evaluating the effectiveness and cost-effectiveness of a telehealthcare solution directed at patients with HF[25]. The purpose of this economic evaluation is to evaluate the cost-effectiveness of the TeleCare North HF solution, comparing the impact on costs and effects (i.e. quality-adjusted life years (QALYs)) with that of the usual practice for the treatment of HF in Denmark.

2. Methods

The cost-utility analysis was conducted in accordance with international guidelines for health economic evaluations alongside clinical trials[19,20,26]. All clinical and costs data for the analysis were collected alongside the TeleCare North HF trial, and the time horizon for the analysis was restricted to a one-year period. A Danish public healthcare sector perspective was applied, including costs accumulating under the auspices of the regional healthcare (i.e. pre-hospital and somatic and psychiatric in- and outpatient treatments), municipality-based health and social care (e.g. home care services and rehabilitation), and primary healthcare (e.g. general practice and physiotherapy) and costs associated with purchases of prescription medicine at Danish pharmacies. Costs associated with patient- or relative-paid transportation and productivity costs were not included.

The trial protocol presenting the design of the TeleCare North HF Trial and associated economic evaluation has previously been published[25]. The participants in the intervention group received patient education and telehealthcare equipment for continuous monitoring of physiological measurements. Patients in the intervention group were provided with a Telekit consisting of a tablet, a digital blood pressure monitor, and

a scale, and were instructed to perform measurements 1-2 times a week. The responsibility of the education, instructions and monitoring of the HF patients was placed on municipality nurses trained in HF and telemonitoring. The nurses were given the authority to intervene and change medication if, for instance, measurements indicated a deterioration in the patient's health. The specialized nurses could contact the heart failure clinic at the central university hospital for guidance regarding specific patient issues. Patients in the control group received the usual care, where general practitioners were responsible for the monitoring of the patients (see the appendix for elaboration).

The result of the economic evaluation is expressed as the incremental net monetary benefit (NMB) = ($\Delta QALY \times Rt - \Delta Cost$)[27], where ΔQALY is the incremental quality of life, and ΔCost is the incremental costs. Under the assumption of a cost-effectiveness threshold (Rt) of £20,000 per QALY gained, an incremental NMB > 0 indicates that the telehealthcare solution is cost-effective compared to the usual care [26].

The cost-effectiveness of the telehealthcare solution is estimated for a 12-month period starting 30 days after participant enrollment in the study. This 30-day 'blanking period' for both groups was introduced from the day of referral to accommodate that participants in the intervention group would only receive the telehealthcare solution belatedly compared to the referral date and therefore effectively did not receive any intervention in this period. The difference in follow-up length was accommodated for in the estimation of cost and effect accumulation by weighting the accumulation by the lengths of the follow-up of individual participants to represent a 12-month follow-up. The enrollment period started on September 1, 2016, and the follow-up period ended on March 4, 2018.

a. Cost accumulation

All costs are presented in 2018 values in British Pounds Sterling (£). The Danish consumer price index for health care products and services[28] was used to adjust the cost data from 2016 and 2017 to the price level in 2018. Costs were estimated in Danish Krone (DKK) and subsequently converted, based on a conversion rate of Danish Kroner (DKK) 827.19 per £100 from December 31, 2018[29].

i. Healthcare service use and healthcare costs

Patient-specific costs related to health care service use were estimated based on register data. In Denmark, all citizens are provided with a unique personal identification number at birth or immigration, which

enables the linkage of information from various registers at the individual level. Information on patients' gender, birthday, migration status, and vital status was retrieved from the Danish Civil Registration System[30].

Information on patients' use of prescription medicine was retrieved from the Danish National Prescription Registry. The costs related to prescription medicine were valued at pharmacy selling prices excluding VAT.

Patients' contacts with general practice were identified through the National Health Insurance Service Register[31,32]. The costs associated with the contacts to general practice are registered in the registry and based on fees quoted in a collective agreement negotiated with the Danish Medical Association[33].

Information on patient hospitalizations was retrieved from the Danish National Patient Registry, which holds information on all inpatient, outpatient, and emergency hospitalizations in somatic and psychiatric wards in Denmark[34]. In the registry, each contact is valued according to the designated diagnosis-related group used for reimbursement, the actual procedures performed, and the length of stay in relation to the contact.

Estimates of the resource consumption of community care services in the municipalities were based on detailed registrations from four of the 11 contributory municipalities. For patients in both groups, registrations included all local care activities, such as personal care, practical help, home nursing, rehabilitation, and telehealthcare activities. To increase generalizability to other settings in Denmark, the registered time consumption for standard care activities was valued using the national average effective hourly wage of the municipality nurses without managerial responsibility[35]. Time consumption in relation to rehabilitation consisting of physiotherapy was valued using the national average effective hourly wage of the municipality and regional physiotherapists without managerial responsibility[35]. Days of respite care in relation to rehabilitation were valued according to the estimated expenses of a day in care homes (see appendix) [36,37].

Information on trial participants' health care service use and health care costs was retrieved for 12 months following their individual study startup date (30 days after the date of their enrollment). Information on health service use and health care costs was retrieved for the participants from 12 months before the study start date for each participant (i.e. 30 days after the date of their enrollment) to control for differences in health care utilization before the start of the intervention.

i. Telehealthcare intervention costs

The administrative office for TeleCare North provided a detailed registration of all intervention costs (see appendix). Capital costs included the development of software and hardware modifications for the Telekit, the delivery of and the Telekit itself, and one-time start-up costs related to the education of patients and healthcare professionals. In the analysis, capital costs were annuitized over a period of five years with a discount rate of four per cent per annum and included as equivalent annual costs. The useful equipment lifetime and applied discount rate are in accordance with what applies for 'other IT equipment' in Danish capital accounting[38,39]. Operational costs included, among other things, maintenance, support, and licenses. The daily work with continuous monitoring of the patients was included in the municipalities' registrations of healthcare service use and healthcare costs described above.

Software development and hardware configuration were valued as prices paid to an external supplier, reflecting actual tenders. The Telekit was valued based on the expected purchase price if the intervention were to be implemented and used in real-life practice following the results of the TeleCare North HF trial. The delivery of hardware, running costs related to licenses, handling of assets, data charges, and substitution of malfunctioning equipment were valued as the price negotiated and paid to the external supplier.

Before the trial, various meetings and educational seminars were held to train healthcare professionals in the use of the telehealthcare solution and monitoring duties and to increase their general knowledge on the management of HF, rehabilitation, and palliation. Participants in these meetings and seminars included general practitioners and regional and municipality nurses. In addition, meetings were held informing project managers, key persons, and healthcare professionals on the telehealthcare solution and the implementation of the intervention. The per-patient costs of educating health care professionals and others were estimated based on the planned time spent in the meetings, the number of participants at the meetings, and the average effective hourly wage of the participants. The applied average effective hourly wages were estimated based on national average wages to increase generalizability to the other Regions in Denmark[35].

Costs of modifications of the hardware, software development, and education for healthcare professionals and management staff were allocated to all HF patients who would be offered the telehealthcare solution in the North Denmark Region. The number of HF patients in the North Denmark Region was estimated to be 6700, given an estimated prevalence of 66,000 HF patients in Denmark[4] and that approximately 10% of the Danish population resides in the North Denmark Region.

The annual operational costs of telehealthcare were allocated to the estimated number of HF and COPD patients in the North Denmark Region (10,500 patients[24]). The operational costs were valued as prices paid.

b. Measure of effectiveness

Information on patients' HRQoL was collected from questionnaires at baseline and at the end of the follow-up. Index scores for participants' HRQoL were estimated based on the EuroQol-5Dimensions-5Levels (EQ-5D-5L) questionnaire. Currently, however, there are no Danish societal weights estimated for the EQ-5D-5L questionnaire for which reason the responses in the EQ-5D-5L questionnaire were used to predict responses in the EuroQol-5Dimensions-3Levels (EQ-5D-3L) questionnaire by applying a response mapping approach[40,41]. Danish societal weights for the EQ-5D-3L questionnaire were subsequently applied[42]. Information on mortality was retrieved from the Danish Registry of Causes of Death, which holds information on all causes of death in Denmark. Information on participants' HRQoL and relevant demographic characteristics were collected at baseline at participant enrollment in the outpatient clinics or after the participant returned home, if preferred by the patient[25]. Irrespective of where the data were collected, the time of collection was dated to be 30 days after the date of their enrollment. At the end of the follow-up, the EQ-5D-5L questionnaire was sent in paper form to patients' home addresses from the trial administration office and included a prepaid return envelope. The response was dated to the end of follow-up (March 4, 2018). [43].

Linear interpolation of the utility scores from baseline to follow-up was performed to estimate the QALY gain and was scaled to represent the QALY gain within one year. The utility score for patients who died during follow-up was set to zero at the time of death.

3. Analysis

a. Missing data management

In accordance with good research practice guidelines within effectiveness and cost-effectiveness studies, the primary analysis was performed according to the intention-to-treat principle and imputation was performed to account for missing data [19,20,44,45]. Imputations of missing data for the primary analysis was performed in accordance with the methods for multiple imputations described by Faria et al. [20]. A full description of the imputation approach is provided in the appendix.

In total, 299 participants were enrolled in the trial (intervention group n=145, control group n=154) (see Figure 1). One patient was enrolled but was never randomized to any treatment group and, therefore, not included in the study. Four patients did not return questionnaires at either baseline or follow-up due to withdrawal shortly after enrollment for which reason no data were available on them except basic registry information. As no effectiveness data were available for these patients and they did, de facto, not participate in the study, they were excluded from analyses in accordance with guidelines on post-randomization exclusion[46]. Furthermore, 21 patients with a self-reported NYHA I classification were wrongfully included in the randomization. Given the eligibility criteria of the trial, these patients were excluded from the primary analysis. For the primary analysis, the intervention group included 134 patients, and the control group included 140 patients.

b. Cost-utility analysis

For descriptive statistics, all data are reported as means and standard errors, and differences in means between the intervention and the control group are presented as raw, unadjusted differences. *P* values for between-group differences have been evaluated by a Student's t-test for continuous variables and a Pearson's Chi-square test for binary and multinomial variables. Statistical significance was assumed for *P* values < 0.05, and all significance tests were two-tailed.

The estimates of incremental costs and QALYs between the intervention group and the control group were based on a seemingly unrelated regression analysis. In the primary analysis, both total costs and QALYs were adjusted for group allocation, age, gender, baseline EQ-5D-3L summary score, total costs in the year preceding the study start date, self-reported NYHA classification at baseline, the self-reported length of HF diagnosis at study start, education level, relationship status, and the presence of self-reported smoking, diabetes mellitus, psychological disorder, COPD, cancer, and musculoskeletal disorder. The estimations were performed using the *mi estimate, cmdok: sureg* command in STATA.

The deterministic incremental NMB was estimated using the treatment beta coefficients from the seemingly unrelated regressions, and a probabilistic sensitivity analysis was performed to evaluate the decision uncertainty. A scatter plot of incremental cost-effectiveness was generated based on 10,000 simulations. The simulations were based on random draws from the estimated treatment effect on cost and QALY accumulation and their associated standard errors. The incremental costs were expected to assume a gamma distribution and the QALYs were expected to assume a Gaussian distribution.

All statistical analyses were performed in STATA, version 15.1.

c. Sensitivity analyses

Both the primary analysis and sensitivity analyses were performed with and without adjustment. For deterministic sensitivity analyses, three different scenarios were investigated;

Scenario I: A complete case analysis, that is, an analysis in which information on all outcome variables and variables used for adjustment were available.

Scenario II: An analysis including all patients that were enrolled in the study, including patients with a self-reported NYHA classification of I.

Scenario III: To evaluate whether results were driven by a minority of patients with very high resource consumption, a sensitivity analysis was performed in which the upper ten percent of patients with the highest resource consumption before imputation were excluded before imputation.

Scenario analysis II and III were both based on imputed data sets.

4. Results

There were no statistically significant differences in baseline characteristics between the two groups, and missingness in variables was also fairly distributed between them (Table 1).

Within the one-year follow-up, the group receiving the telehealthcare solution had a consistently lower resource consumption across all health care cost categories compared to the group receiving usual care, leading to a total raw difference of -£5,668 (Table 2). This lower mean cost per patient was primarily driven by lower costs associated with hospitalizations (intervention group £5,055 vs. control group £9,064, *p*-value=0.01). Notably, the costs accumulating in the municipalities were also lower for the group receiving the telehealthcare solution (intervention group £682 vs. control group £1,247, *p* value=0.25), even though, for the intervention group, this cost category also included costs associated with the monitoring in relation to the telehealthcare solution.

In the primary analysis, the one-year adjusted QALY difference between the telehealthcare solution and the usual care group was 0.0034 [95% CI: -0.0711; 0.0780], indicating an insignificant gain in HRQoL for patients receiving the telehealthcare solution (Table 3). The adjusted difference in costs was -£5096 [95%CI: -8736; -1456], indicating a significantly lower total mean cost per patient in the telehealthcare solution group. Based on the incremental cost and QALY estimates and an assumed cost-effectiveness threshold of £20,000 per QALY[27], the telehealthcare solution provides a positive incremental NMB of £5164, indicating that the telehealthcare solution is cost-effective. The unadjusted analysis also indicates that the telehealthcare solution provides a significant cost saving (-£5539 [95% CI: -9483; -1595]) and an insignificant impact on patients' QALY gain (-0.0005 [95% CI: -0.0723; 0.0714]) and therefore is cost-effective (NMB = £5530). The result of the probabilistic sensitivity analysis is shown in the incremental cost-effectiveness scatter plot in Figure 2. The incremental cost-effectiveness distribution disperses across the southwest and southeast quadrant of the incremental cost-effectiveness plane in agreement with the QALY gain associated with the telehealthcare solution being insignificant but the incremental negative cost being significant.

All scenario analyses showed the same result with telehealthcare associated with lower costs and an insignificant impact on patients' health-related quality of life (Table 3). Across the adjusted and unadjusted sensitivity analyses, the cost-effectiveness result is relatively robust, with all analyses indicating a positive incremental NMB of the telehealthcare solution compared to usual practice.

5. Discussion

The principal finding of this study is that the investigated telehealthcare solution is highly cost-effective for the treatment of HF patients in the Danish setting. High-quality economic evaluations of telehealthcare solutions in the management of HF have been requested[16–18] and, to our knowledge, the present study is the first economic evaluation of telehealthcare in HF patients that strictly follows international guidelines for health economic evaluation alongside clinical trials[19]. Thus, a particular strength of this study was the micro-costing approach, including the availability of information on patient-specific resource usage from the Danish registers. The majority of information on patients' resource consumption was retrieved from well-validated Danish registers, ensuring the validity of the registrations with no missing data in these parameters. For the resource consumption in the municipalities, data from four out of the 11 participatory municipalities were applicable. The four municipalities were relatively large (making for approximately 50% of the total participant sample), and thus, the representativeness of their organization and consequently costs for smaller municipalities is debatable. However, municipality costs only constitute a minor share of the total costs (cf. Table 3); for which reason it could be suspected that even if the estimate of municipality costs is not representative for all participatory municipalities, the cost-effectiveness conclusion would not be markedly affected.

In the present cost-utility analysis, the impact on patients' QALY gain was insignificant across all analyses. The increased sensitivity, which could have been achieved by using the 5L questionnaire[19], may effectively have been watered down when predicting the 3L responses from the 5L responses and applying the 3L weights. This might provide an explanation of why it was not possible to observe any substantial differences in QALY accumulation between the two intervention groups, which could otherwise have been expected given findings in previous studies[16].

In general, telehealthcare interventions and the studies of them are relatively heterogeneous, making a comparison of them difficult[15,16]. In a Cochrane review from 2015[16], structured telephone support and telemonitoring for HF patients were found to reduce all-cause mortality and HF-related hospitalizations. In addition, the impact on patients HRQoL and cost accumulation was inconsistent, emphasizing the difficulties of evaluating and comparing the cost-effectiveness of telehealthcare interventions aggregately.[16]

Only a few papers report on cost savings in relation to telehealthcare within this field. These studies do not have economic evaluation as their primary aim and do not strictly follow proper practice guidelines for economic evaluations[19,26]. Nevertheless, they all point in the same direction of potentially huge savings [16–18]. Frederix et al.[48] reported insignificant long-term savings of approximately 27% from an initial 6-month telehealthcare intervention. Jiménez-Morrero et al.[49] report savings of approximately 38% for a

subgroup of HF patients with a left ventricular ejection fraction >40. Comín-Colet et al. [50] report savings of approximately 45%, mainly driven by a significant reduction in hospitalizations between the telehealthcare group and control group. An economic modeling study by Liu et al. [51] also points in the same direction of possible savings from telehealthcare interventions directed at intermediate- and high-risk patients over a 1- to 5-year window. Their results suggest the economic viability of telehealthcare programs for the management of chronic HF, but emphasized the importance of risk stratification in such programs[51]. In our study, however, the severity of HF did not seem to be important, as there appeared to be only minor differences in cost savings depending on whether patients reporting being in NYHA class I were included or not. A particular difference between our study and other studies may also have been the level of organizational learning and knowledge management, as the TeleCare North trial builds upon many years of experience with telehealthcare solutions from previous trials[23,24] as well as the national implementation of telehealth program for COPD in Denmark decided in 2015[22].

As the design of the TeleCare North HF trial and the components of the telehealthcare intervention was somewhat similar to that of the TeleCare North COPD trial[23,25], the present study anticipated that the economic evaluation would essentially produce results similar to that of Udsen et al.[24]. In agreement with the economic evaluation by Udsen et al.[24], no significant difference in QALY accumulation between the intervention groups was observed in this study. In contrast, the present study found telehealthcare to produce substantial cost savings, which contrasts with the added costs associated with telehealthcare found by Udsen et al.[24]. The difference is that telehealthcare is cost-effective for HF patients but not all COPD patients. This discrepancy indicates that the cost-effectiveness of telehealthcare interventions, to a large degree, depends on the recipient patient group, making it difficult to comment on the cost-effectiveness of telehealthcare interventions as a whole. The characteristics of specific patient groups ought, therefore, to be incorporated when telehealthcare interventions are designed and implemented.

The impact of the TeleCare North solution of patients Qol measured with the Short-Form 36 (SF-36) questionnaire's physical and mental component summary scores and the Kansas City Cardiomyopathy Questionnaire 12 score are published elsewhere[52]. It was only possible to detect a small but significant positive change in the SF-36 mental component summary score. Thus, with respect to the impact on patients' HRQoL, the telehealthcare solution cannot be characterized as an unqualified success. It could, however, be hypothesized that the currently applied methods of measurement of effect are too insensitive to detect any beneficial impact especially on patients' mental well-being, as suggested by the positive impact on the SF-36 mental component summary score but none of the other measures. It is possible that

the positive impact of telehealthcare does not manifest itself as an impact on patients' HRQoL but rather their sense of security, which subsequently affects their healthcare-seeking behavior.

Given the complexity and multiple purposes of the intervention under investigation[25], it is possible that conventional measures of effectiveness, such as HRQol and QALY, do not sufficiently capture all potential effects. It is possible that impacts on other parameters could have been observed, such as patients' satisfaction, sense of security, comfort, ability to reduce anxiety through telephone contact with a well-known local nurse, and an increased sense of capability among others. It could be considered whether the slightly narrow focus on patients' HRQoL and QALY in the present analysis represent an appropriate evaluation approach to this particular kind of complex intervention.

Though the present economic evaluation found the telehealthcare solution to be highly cost-effective, questions remain as to why this result was achieved. Thus, it remains unclear what components of the intervention were actually effective or whether the effect is contingent on the intervention in its entirety. In the design phase of future trials on the effectiveness and cost-effectiveness of complex interventions such as telehealthcare, early consideration of mechanisms of action and programme theory [53] ought to be introduced to improve our understanding of why some interventions may prove effective and cost-effective and others not. This may increase the cost-effectiveness of future telehealth solutions.

Acknowledgments: The authors would like to thank all of the participants in TeleCare North Heart Failure for their time and effort when filling out questionnaires and reporting physical measurements. Likewise, a thank you goes out to all healthcare professionals involved in the execution of the trial, the North Denmark Region, and the municipalities for their goodwill in making this trial possible. A special thank you to Kuno Strand Kudajewski, project manager for the TeleCare North Heart Failure Trial at the North Denmark Region for helping with information on cost data and for proof-reading the manuscript, and to Simon Lebech Cichosz for the lengthy keying of the EQ-5D questionnaire data.

Author contributions: LHE is the primary investigator for economic evaluation in the TeleCare North Heart Failure Trial; LHE planned the design of the economic evaluation and stands as a guarantor of the statistical quality for the evaluation as a whole. LHE, LH, MBJ, and ASV contributed equally to the detailed planning and design of the analyses in the economic evaluation. LH was mainly responsible for data management. All analyses were performed by collaboration by all authors, and ASV drafted the paper in collaboration with the other authors. All authors had full access to the data and accept responsibility for the integrity of the data and the data analyses. All authors met regularly during the data analysis period and contributed equally to the interpretation and presentation of data. All authors reviewed and approved the manuscript prior to submission.

Ethics: The trial has been authorized by the Danish Data Protection Agency. The study is being conducted in accordance with the Helsinki declaration. The trial has been presented to the Ethical Committee for Medical Research in the North Denmark Region; this committee decided that no ethical approval was necessary.

Trial registration number: ClinicalTrials.gov: NCT02860013

Competing interests: None

Funding: The study was funded by the Danish Agency for Digitalisation under the Danish Ministry of Finance the North Denmark Region.

Patient content: not required

Patient and Public Involvement: Local politician decided to perform and fund the trial. The local patient organization was involved in the design fg the trial. The TeleCare North management team designed a web page https://rn.dk/sundhed/til-sundhedsfaglige-og-samarbejdspartnere/telecare-nord/om-telecare-nord to inform patients, clinicians etc. about the trial. At recruitment, patients were informed about the

potential burden of participating in the trial. A national conference was held at the end of the trial to inform the public about the results from the trial and to discuss the next step in the implementation of telehealth care in the region.

References

[1] Savarese G, Lund LH. Global Public Health Burden of Heart Failure. *Card Fail* Rev 2017;03:7. doi:10.15420/cfr.2016:25:2.

[2] Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. *Nat Rev Cardiol* 2011;8:30–41. doi:10.1038/nrcardio.2010.165.

[3] Inamdar A, Inamdar A. Heart Failure: Diagnosis, Management and Utilization. *J Clin Med* 2016;5:62. doi:10.3390/jcm5070062.

[4] Madelaire C, Gislason G. Hjertesvigt i Danmark 2017 - socioøkonomiske forskelle i forekomst, dødelighed og behandling [Heart Failure in Denmark 2017 - socioeconomic differences in prevalence, mortality, and treatment]. 2017.

[5] Dansk Selskab for Almen Medicin. Kronisk hjertesvigt/kronisk systolisk hjerteinsufficiens [Chronic heart failure/chronic systolic heart failure]. *DSAM Guidel* 2013. https://vejledninger.dsam.dk/hjerteinsufficiens/?mode=visKapitel&cid=597&gotoChapter=597 (accessed November 7, 2018).

[6] Roger VL. Epidemiology of Heart Failure. *Circ Res* 2013;113:646–59. doi:10.1161/CIRCRESAHA.113.300268.

[7] Dansk Cardiologisk Selskab. Behandlingsvejledning, 5. Kronisk hjertesvigt [Treatment Guidelines, Chronic Heart Failure] 2017. https://www.cardio.dk/chf#55-behandling (accessed November 16, 2018).

[8] Polikandrioti M. Health Failure and Health Related Quality of Life. *Heal Sci J* 2008;3:119–20.

[9] Juenger J, Schellberg D, Kraemer S, Haunstetter A, Zugck C, Herzog W, et al. Health related quality of life in patients with congestive heart failure: comparison with other chronic diseases and relation to functional variables. *Heart* 2002;87:235–41. doi:10.1136/heart.87.3.235.

[10] Comín-Colet J, Anguita M, Formiga F, Almenar L, Crespo-Leiro MG, Manzano L, et al. Health-related Quality of Life of Patients With Chronic Systolic Heart Failure in Spain: Results of the VIDA-IC Study. *Rev Española Cardiol* (English Ed 2016;69:256–71. doi:10.1016/j.rec.2015.07.030.

[11] Shafie AA, Tan YP, Ng CH. Systematic review of economic burden of heart failure. *Heart Fail Rev* 2018;23:131–45. doi:10.1007/s10741-017-9661-0.

[12] Brorholt G, Jakobsen M, Hauge AM, Kjellberg Med Bidrag Fra J, Grønbaek M, Terkelsen CJ, et al. En helhjertet indsats – En artikelbaseret klinisk, patientnær og sundhedsøkonomisk kortlægning af hjerte-kar-området [A whole-hearted effort - a paper-based clinical, patient-relevant and health economic survey of the cardiovascular area]. København K: 2018.

[13] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2016;37:2129–200. doi:10.1093/eurheartj/ehw128.

[14] Bashi N, Karunanithi M, Fatehi F, Ding H, Walters D. Remote Monitoring of Patients With Heart Failure: An Overview of Systematic Reviews. *J Med Internet Res* 2017;19:e18. doi:10.2196/jmir.6571.

[15] Dierckx R, Inglis SC, Clark RA, Prieto-Merino D, Cleland JGF. Telemedicine in heart failure: new insights from the Cochrane meta-analyses. *Eur J Heart Fail* 2017;19:304–6. doi:10.1002/ejhf.759.

[16] Inglis SC, Clark RA, Dierckx R, Prieto-Merino D, Cleland JG. Structured telephone support or non-invasive telemonitoring for patients with heart failure. Cochrane Database Syst Rev 2015. doi:10.1002/14651858.CD007228.pub3.

[17] Gensini GF, Alderighi C, Rasoini R, Mazzanti M, Casolo G. Value of Telemonitoring and Telemedicine in Heart Failure Management. *Card Fail Rev* 2017;3:1. doi:10.15420/cfr.2017:6:2.

[18] Grustam AS, Severens JL, van Nijnatten J, Koymans R, Vrijhoef HJM. Cost-effectiveness of telehealth interventions for chronic heart failure patients: A literature review. *Int J Technol Assess Health Care* 2014;30:59–68. doi:10.1017/S0266462313000779.

[19] Ramsey SD, Willke RJ, Glick H, Reed SD, Augustovski F, Jonsson B, et al. Cost-effectiveness analysis alongside clinical trials II - An ISPOR good research practices task force report. *Value Heal* 2015;18:161–72. doi:10.1016/j.jval.2015.02.001.

[20] Faria R, Gomes M, Epstein D, White IR. A Guide to Handling Missing Data in Cost-Effectiveness Analysis Conducted Within Randomised Controlled Trials. *Pharmacoeconomics* 2014;32:1157–70. doi:10.1007/s40273-014-0193-3.

[21] Digitaliseringsstyrelsen. Telemedicin - en nøgle til fremtidens sundhedsydelser. National handlingsplan for udbredelse af telemedicin - kort fortalt [Telehealthcare - a key to future healthcare services. A national action plan for the introduction of telehealthcare - in brief]. København K: 2012.

[22] Sundhedsdatastyrelsen. Telemedicin og telesundhed [Telemedicine and telehealth] 2018. https://sundhedsdatastyrelsen.dk/da/rammer-og-retningslinjer/telemedicin-og-telesundhed (accessed December 21, 2018).

[23] Udsen FW, Lilholt PH, Hejlesen O, Ehlers LH. Effectiveness and cost-effectiveness of telehealthcare for chronic obstructive pulmonary disease: Study protocol for a cluster randomized controlled trial. *Trials* 2014;15:1–7. doi:10.1186/1745-6215-15-178.

[24] Witt Udsen F, Lilholt PH, Hejlesen O, Ehlers L. Cost-effectiveness of telehealthcare to patients with chronic obstructive pulmonary disease: results from the Danish 'TeleCare North' cluster-randomised trial. *BMJ* Open 2017;7:e014616. doi:10.1136/bmjopen-2016-014616.

[25] Cichosz SL, Ehlers LH, Hejlesen O. Health effectiveness and cost-effectiveness of telehealthcare for heart failure: Study protocol for a randomized controlled trial. *Trials* 2016;17:4–9. doi:10.1186/s13063-016-1722-5.

[26] Drummond MF, Schulpher M, Claxton K, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. 4th ed. Oxford: Oxford University Press; 2015.

[27] Devlin N, Parkin D. Does NICE have a cost-effectiveness threshold and what other factors influence its decisions? A binary choice analysis. *Health Econ* 2004;13:437–52. doi:10.1002/hec.864.

[28] Statistics Denmark. Pris111: Consumer price index ((2015=100) by commodity group and unit 2018. http://www.statistikbanken.dk/PRIS8 (accessed December 5, 2018).

[29] EUROinvestor. Valutakurser [Exchange rates] 2018. https://www.valutakurser.dk/ (accessed February 15, 2019).

[30] Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014:541–9. doi:10.1007/s10654-014-9930-3.

[31] Sundhedsdatastyrelsen. Sygesikringsregisteret (SSR) [National Health Insurance Service Register] 2017. https://sundhedsdatastyrelsen.dk/da/registre-og-services/om-de-nationale-sundhedsregistre/sundhedsoekonomi-og-finansiering/sygesikringsregisteret (accessed November 20, 2018).

[32] Sahl Andersen J, De Fine Olivarius N, Krasnik A. The Danish national health service register. *Scand J Public Health* 2011;39:34–7. doi:10.1177/1403494810394718.

[33] Danish Medical Association. Honorartabel 01-10-2018 [Fee table 2018-10-01] 2018.

https://www.laeger.dk/sites/default/files/honorartabel_2018_oktober_web.pdf.

[34] Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: A review of content, data quality, and research potential. *Clin Epidemiol* 2015;7:449–90. doi:10.2147/CLEP.S91125.

[35] Statistics Denmark. Statistikbanken - LONS20: Løn efter arbejdsfunktion, sektor, aflønningsform, lønmodtagergruppe, lønkomponenter og køn [Statistikbanken - LONS20: Wages estimated based on job function, sector, payment form, employment group, wage component and gender]○ 2018. http://statistikbanken.dk/statbank5a/default.asp?w=1920 (accessed November 19, 2018).

[36] Ministry of Finance. Frit valg og kvalitet - afregningsmodeller på de kommunale serviceområder [Liberty of choice and quality - models of settlements in the municipal service areas]. Ministry of Finance; 2003.

[37] Jakobsen M, Klausen E, Kolodziejczyk C. Omkostninger ved blodprop i hjernen og blødninger blandt patienter med atrieflimren i Danmark - en registerbaseret 'cost of illness'-analyse [The costs of stroke and hemorrhages amongst patients with atrial fibrillation - a register-based cost of illness. Copenhagen: KORA; 2014.

[38] Agency for Modernisation - Ministry of Finance. Levetider [Service lives]. Den Økonomiske Adm Vejl [Economic Adm Instr 2018. https://modst.dk/oekonomi/oeav/regnskabsregler/generelle-bogfoeringsbestemmelser/levetider/ (accessed November 7, 2018).

[39] Ministry of Finance. Den samfundsøkonomiske diskonteringsrente [The economic discount rate] 2018:1–19.

[40] Van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Heal* 2012;15:708–15. doi:10.1016/j.jval.2012.02.008.

[41] The EuroQol Group. EQ-5D-5L Crosswalk Index Value Calculator for Windows 2018.

[42] Wittrup-Jensen KU, Lauridsen J, Pedersen KM, Gudex C. Generation of a Danish TTO value set for EQ-5D health states. *Scand J Public Health* 2009;37:459–66. doi:10.1177/1403494809105287.

[43] Sundhedsdatastyrelsen. Dødsårsagsregisteret (DAR) [Danish Registry of Causes of Death] n.d. https://sundhedsdatastyrelsen.dk/dar (accessed November 12, 2018).

[44] Gupta SK. Intention-to-treat concept: A review. *Perspect Clin Res* 2011;2:109. doi:10.4103/2229-

3485.83221.

[45] Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;338:b2393–b2393. doi:10.1136/bmj.b2393.

[46] Fergusson D. Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. *BMJ* 2002;325:652–4. doi:10.1136/bmj.325.7365.652.

[47] Nixon RM, Thompson SG. Methods for incorporating covariate adjustment, subgroup analysis and between-centre differences into cost-effectiveness evaluations. *Health Econ* 2005;14:1217–29. doi:10.1002/hec.1008.

[48] Frederix I, Vanderlinden L, Verboven A-S, Welten M, Wouters D, De Keulenaer G, et al. Long-term impact of a six-month telemedical care programme on mortality, heart failure readmissions and healthcare costs in patients with chronic heart failure. *J Telemed Telecare* 2018;0:1357633X1877463. doi:10.1177/1357633x18774632.

[49] Jiménez-Marrero S, Yun S, Cainzos-Achirica M, Enjuanes C, Garay A, Farre N, et al. Impact of telemedicine on the clinical outcomes and healthcare costs of patients with chronic heart failure and mid-range or preserved ejection fraction managed in a multidisciplinary chronic heart failure programme: A sub-analysis of the iCOR randomized trial. *J Telemed Telecare* 2018. doi:10.1177/1357633X18796439.

[50] Comín-Colet J, Enjuanes C, Verdú-Rotellar JM, Linas A, Ruiz-Rodriguez P, González-Robledo G, et al. Impact on clinical events and healthcare costs of adding telemedicine to multidisciplinary disease management programmes for heart failure: Results of a randomized controlled trial. *J Telemed Telecare* 2016;22:282–95. doi:10.1177/1357633X15600583.

[51] Liu SX, Xiang R, Lagor C, Liu N, Sullivan K. Economic Modeling of Heart Failure Telehealth Programs: When Do They Become Cost Saving? *Int J Telemed Appl* 2016;2016:1–9. doi:10.1155/2016/3289628.

[52] Cichosz SL, Udsen FW. Hejlesen OK. The impact of telehealth care on health-related quality of life of patients with heart failure: Results from the Danish TeleCare North heart failure trial. *J Telemed Telecare* [accepted April 2019].

[53] Pawson R, Tilley N. Realistic Evaluation. London: Sage; 1997.

Table 1. Participant baseline characteristics. P-values for differences have been evaluated by Student's t-test for continuous variables and Pearson's Chi-square test for binary and multinomial variables. *Variable has no missing values. COPD: Chronic Obstructive Pulmonary Disease, HF: Heart failure, NYHA: New York Heart Association.

Study population	Telehealthcare solution	Control group	Raw between-group difference	P-value for difference
No of patients, n (%)	134 (49 %)	140 (51 %)		
Age, mean (SD), y*	67.21 (11.51)	67.30 (11.78)	-0.09	0.95
Sex, female, %*	18.91 (n=24)	20.71 (n=29)	-1.8	0.56
Relationship status				0.14
- *Missing, %*	1.49 (n=2)	0.71 (n=1)		
- Living with somebody, %	75.76 (n=100)	67.63 (n=94)	8.13	
- Living alone, %	24.24 (n=32)	32.37 (n=45)	-8.13	
Education				0.67
- *Missing, %*	2.23 (n=3)	1.43 (n=2)		
- Primary (<3 years), %	65.65 (n=86)	68.12 (n=94)	-2.47	
- Secondary (>3 years), %	34.35 (n=45)	31.88 (n=44)	2.47	
Smoking, (yes)* %	23.31 (n=31)	17.14 (n=24)	6.17	0.20
Self-reported duration of HF				
- *Missing, %*	5.97 (n=8)	6.43 (n=9)		
- Mean (SD), y	5.27 (7.45)	5.47 (7.13)	-0.20	0.82
- Median, y	2	2	0	
NYHA score at baseline, mean (SD)	2.55 (0.69)	2.50 (0.61)	0.05	0.53
- *Missing, %*	4.48 (n=6)	5.00 (n=7)		
- NYHA class II, %	56.25 (n=72)	56.39 (n=75)	-0.14	
- NYHA class III, %	32.81 (n=42)	37.59 (n=50)	-5.41	
- NYHA class IV, %	10.94 (n=14)	6.02 (n=8)	4.92	
Self-reported comorbidity, %*	41.04 (n=55)	41.43 (n=58)	-0.39	0.95
- Diabetes, %	13.43 (n=18)	19.29 (n=27)	-5.86	0.19
- COPD, %	16.42 (n=22)	15.71 (n=22)	0.71	0.87

- Psychological disorder, %	2.24 (n=3)	2.14 (n=3)	0.10	0.96
- Musculoskeletal disorder, %	16.42 (n=22)	15.71 (n=22)	0.71	0.87
- Cancer, %	6.72 (n=9)	7.14 (n=10)	-0.42	0.89
Baseline EQ-5D-3L index score, mean (SD)	0.7073 (0.1514)	0.7078 (0.1465)	0	0.98
- *Missing, %*	5.22 (n=7)	0.7 (n=1)		
Baseline historical costs excl. municipality costs (£), mean (SD)*	18,587.52 (21,605.38)	19,560.00 (23,491.52)	-972.48	0.72
Baseline historical municipality costs (£), mean (SD)	122.24 (303.18)	479.88 (1585.97)	-357.64	0.07
- *Missing, %*	49. 25 (n=66)	50.71 (n=71)		

Table 2. Unadjusted mean costs per patient in the intervention group and the control group, respectively, partitioned into cost categories over the 12-month follow-up (2018 £). For all cost categories, data are complete except for the municipality costs of which 50% missing (N=137). The costs associated with the telehealthcare solution is based on deterministic estimates. SE: Standard error of the mean.

*Annuitized over a 5-year period with a discount rate of 4 per cent,

**Costs divided amongst the expected number of HF patients in the North Denmark Region (6700 patients).

***Costs divided amongst the expected number of HF and COPD patients in the North Denmark Region (10,500 patients[24]). See appendix for further information.

	Mean costs (SE), £			
Cost category	Telehealthcare solution (n=134)	Control group (n=140)	Raw between-group difference (£)	P-value for difference
Hospital contacts				
- Hospitalizations	5055.13 (1027.31)	9063.65 (1217.95)	-4008.52	0.01
- Outpatient contacts	3163.53 (264.85)	4191.29 (644.82)	-1027.76	0.15
- Psychiatric outpatient contacts	13.72 (5.95)	62.46 (39.20)	-48.74	0.23
Primary care contacts	469.26 (44.37)	600.36 (40.43)	-131.10	0.03
Pharmacy purchases	972.25 (94.01)	1076.57 (81.31)	-104.32	0.40
Municipality costs (home care, rehabilitation, monitoring in relation to the telehealthcare solution, etc.)	681.61 (137.16)	1246.88 (461.78)	-565.27	0.25
Healthcare costs, excl. costs of the telehealthcare solution	10,355.50	16,241.21	-5,885.71	0.01
Costs of the telehealthcare solution, excl. costs of monitoring:				
Software development and support*/**	0.27	0	0.27	

Basic operation: surveillance, support of health professionals, server licenses, etc***	8.47	0	8.47	
Running development of apps, system updates, etc. ***	1.76	0	1.76	
Education of health care professionals*/**	3.04	0	3.04	
Telekit, including initial delivery and patient education*	122.36	0	122.36	
Annual operational costs: licenses, sim card data, substitution of faulty equipment, etc.	82.15	0	82.15	
Total costs (incl. costs of the telehealthcare solution)	10,573.55	16,241.21	-5,667.66	0.01

Table 3. Incremental costs (£) and quality-adjusted life years after 12-month follow-up. CI: confidence interval, QALYs: Quality-adjusted life-years.

*Estimated based on an expected cost-effectiveness threshold of £20,000 per QALY.

**Seemingly unrelated regression, adjustment for group allocation, age, gender, baseline EQ-5D-3L summary score, total costs in the year preceding the study start date, self-reported NYHA classification at baseline, the self-reported length of HF diagnosis, education level, relationship status, and the presence of self-reported smoking, diabetes mellitus, psychological disorder, COPD, cancer, and musculoskeletal disorder.

***Seemingly unrelated regression with intervention group as the only predictor.

Scenario	N	Incremental costs, £ (95% CI)	Incremental QALYs (95% CI)	Net monetary benefit, £*
Primary analysis, adjusted**	274	-5095.92 [-8736.33; -1455.51]	0.0034 [-0.0712; 0.0780]	5163.98
Primary analysis, unadjusted***	274	-5539.10 [-9483.26; -1594.95]	-0.0005 [-0.0723; 0.0714]	5530.04
Scenario I:				
Complete case analysis, adjusted**	89	-1609.85 [-7036.27; 3816.57]	-0.0239 [-0.0605; 0.0127]	1131.62
Complete case analysis, unadjusted***	94	-2752.84 [-8438.59; 2932.91]	-0.0157 [-0.0536; 0.0221]	3570.69
Scenario II:				
Incl. NYHA class I patients, adjusted**	295	-4572.69 [-8030.66; -1114.73]	-0.0037 [-0.0736; 0.0663]	4498.88
Incl. NYHA class I patients, unadjusted***	295	-4857.43 [-8587.98; -1126.88]	-0.0061 [-0.0730; 0.0609]	4736.20
Scenario III:				
Excl. top 10th percentile resource-heavy patients, leaving out municipality costs, adjusted**	247	-3060.50 [-4836.08; -1284.93]	-0.0096 [-0.0949; 0.0756]	2867.62

Excl. top 10th percentile resource-heavy patients, leaving out municipality costs, unadjusted***	247	-3181.34 [-5103.28; -1259.40]	-0.0130 [-0.0944; 0.0683]	2921.12

Figure 1. Flowchart of exclusion of patients for the economic evaluation.

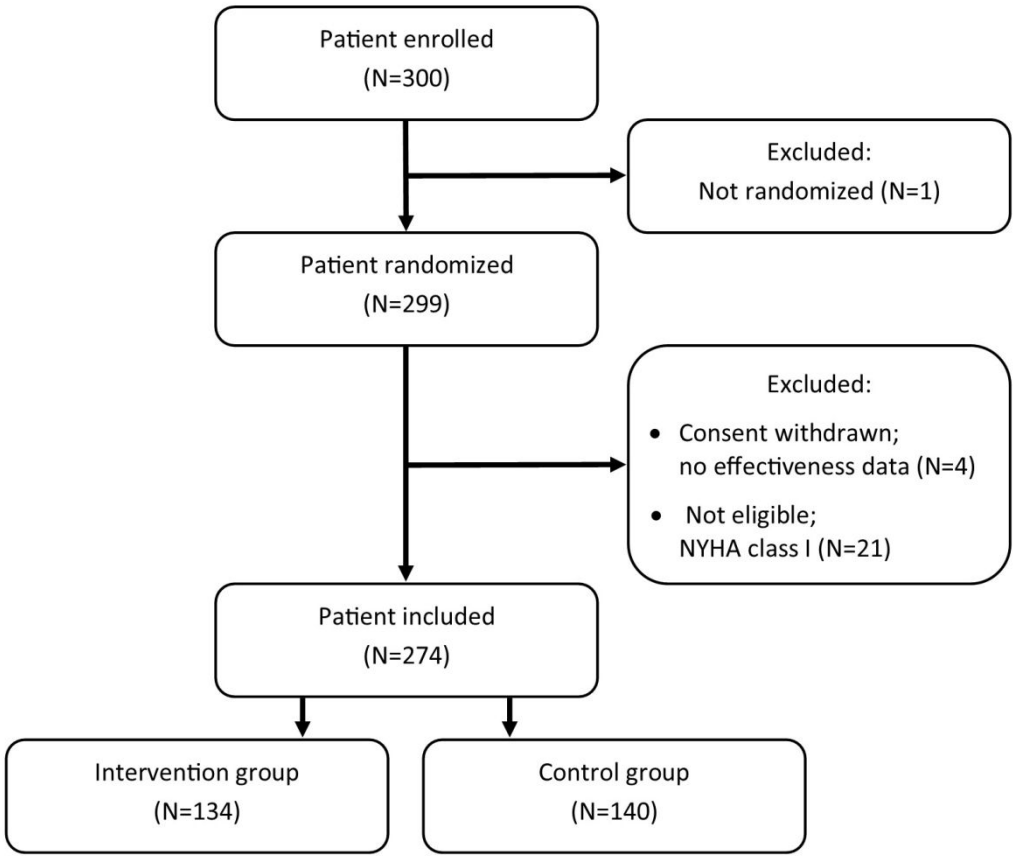
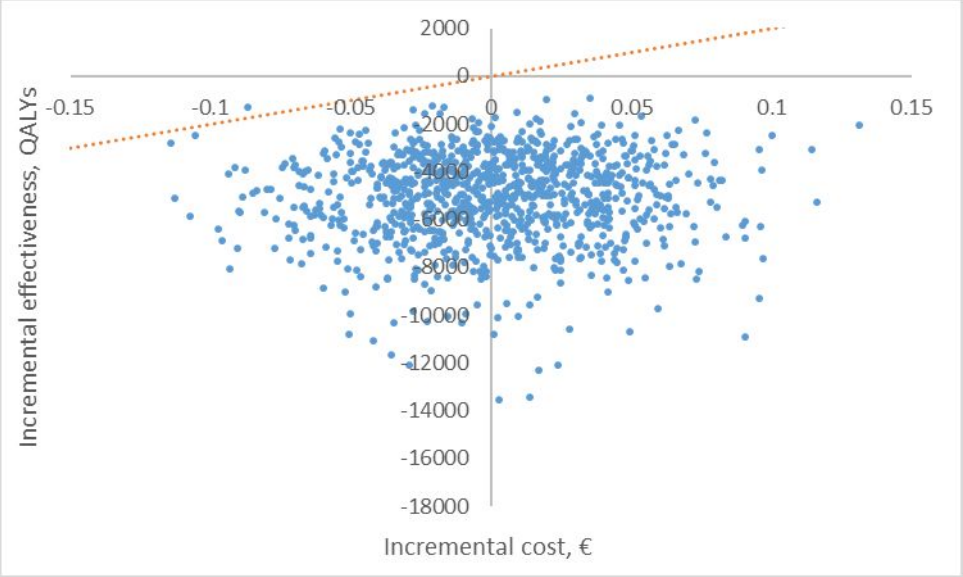


Figure 2. Incremental cost-effectiveness scatter plot based on the probabilistic sensitivity analysis. The dotted line indicates a cost-effectiveness threshold of £20,000 per quality-adjusted life year.



Appendix

Detailed information regarding the Danish TeleCare North Heart Failure Trial[25]. ACE: angiotensin-converting enzyme, HF: Heart failure, NYHA: New York Heart Association.

Trial characteristics	
Study characteristics	A multi-center, two-arm parallel group, unblinded, superiority study comparing a telehealthcare intervention to the usual practice in a Danish setting (the North Denmark Region). The study was executed in the period Jan 2016 to March 2018 with a follow-up of approximately 12 months; actual follow-up differed between participants due to continuous enrollment. The predetermined sample size was 316 participants under an expected loss to follow-up of 10 %, giving 284 participants. The estimate was based on an expected change equal to 5 for the SF-36 physical component summary score (effect measure applied in the effectiveness evaluation) indicating statistical significance with a two-sided *p*-value of <0.05, a power of 80%, equal-sized groups, and a standard deviation of 15%. Two hundred ninety-nine participants were enrolled; 35% were lost in follow-up (23 participants withdrew their consent, 15 died, and 67 did not respond).
Eligibility criteria	All patients were considered eligible who had a diagnosis of HF[7], a NYHA classification of II-IV, and who were expected to benefit from telehealthcare. In addition, patients should exhibit motivation for participating in the study and the use of telehealthcare, as evaluated by healthcare professionals. Furthermore, patients should have permanent residence, have a landline or mobile phone, and be able to speak Danish or live with a relative speaking Danish. Comorbidity was not considered a reason for

	exclusion. Clinical staff were responsible for identifying potential participants, and patient participation was voluntary.
Control group	
Usual care	Participants in the control group received usual care as provided in real-life practice to HF patients in the North Denmark Region, including monitoring, care, and, if necessary, treatment. As part of usual care, in the North Denmark Region, HF patients are offered rehabilitation consisting of screening for risk factors and dietary advice (if necessary) amongst other potential lifestyle changes that may be beneficial in relation to their disease, training, and medication review in response to patients' health (e.g. evaluation of prescriptions of ACE inhibitors, beta-blockers, spironolactone, etc.). The rehabilitation period usually lasts three to six months. Usual care is managed by general practitioners or outpatient clinics.
Intervention group	
Healthcare provision intervention	Before the start-up of the trial, several meetings were held to inform different staff groups of the trial and to provide general competency development on the management of HF. The trial administration office behind the TeleCare North HF was in charge of the meetings and educational seminars: - Project managers, key persons, and health care professionals expected to be involved in the implementation of the trial participated in kick-off information meetings - General practitioners received information on the trial and telehealthcare solution in after-work meetings

	- Regional and municipality nurses participated in an educational seminar and received initial and follow-up education on the use of the Telekit and the associated monitoring system (Open Tele) - Regional nurses participated in an educational seminar on rehabilitation - Specialist nursing professionals who worked with telemedicine from municipalities and HF outpatient clinics participated in educational seminars on palliation - Meetings were held, providing municipality nurses and health care assistants with general competency development on the management of HF, specifically on the monitoring responsibility in relation to the trial. The responsibility for the monitoring was shared between educated municipality nurses in the participants' residing municipality. The responsible parties were to incorporate the monitoring into their normal job duties. The monitoring included assessment and evaluation of measurements and was performed asynchronously on a weekly or biweekly basis. After the assessment, an acknowledgment of assessment was transmitted to the patient. If physical measurements were outside predefined thresholds (systolic blood pressure 100-170 mmHg, diastolic blood pressure 90-50 mmHg, pulse 80-55 beats per minute, and weight ±2 kg compared to baseline), the nurses had the option to 1) contact the patient to ensure the accuracy of the measurement or have the measurement replicated, if necessary, 2) contact the patient to assess his/her condition, 3) start a self-treatment plan for the patient, 4) ask the patient to contact his/her own general practitioner if considered suitable, and 5)

	establish rapport with the patient's general practitioner directly. Measurements were classified as being within or outside the normal ranges.
Patient-level intervention	After randomization, participants in the intervention group were contacted by phone by a nurse from their residing municipality, and an appointment was made on whether the patient would like to receive the Telekit in their home or a municipality health center. If the patient wanted to receive the Telekit at home, a 45-min appointment was made at which time an educated municipality nurse would demonstrate the use of the tablet and how to make the physical measurements using the associated equipment. If the participants wanted to participate in a group session of 3-4 persons at the municipality center to be introduced to the use of the equipment, the session would be 75 min long. Participants were asked to use the blood pressure monitor and scale daily in the two first weeks of the trial. 2-4 weeks after the first appointment, a follow-up appointment of 45 min was made with participants to ensure that they used the Telekit correctly. Instructions on the use of the Telekit were handled by municipality nurses.
Device characteristics; Telekit	In the trial, the Telekit consisted of a tablet (Samsung Galaxy Tab 2, incl. a target stylus) and associated equipment. The equipment consisted of a digital blood pressure monitor (UA-767 Plus BT-C, A&D Medical, Tokyo, Japan) and a scale with automatic Bluetooth connection to the tablet (UC-321 PBT-C, A&D Medical, Tokyo, Japan). The tablet automatically reminded the patients to take measurements and transmitted the information to enable asynchronous monitoring by healthcare professionals. In addition, the participants received an information package including a welcome letter, a user manual, and various patient information leaflets.

	Delivery and replacement of faulty equipment were performed by the supplier (Atea Denmark, Aalborg, Denmark), and support and maintenance were managed by a specialized support center.

Appendix

Detailed information on the cost estimates associated with the telehealthcare solution.

Assumptions		Elaboration	Reference
Number of heart failure patients in Denmark	66,000	Estimate from 2014 based on registrations in the Danish National Patient Registry.	[4]
Number of heart failure patients in the North Denmark Region	6700	Cross-country prevalence, expected to be equal, though the North Denmark Region is known to have a lower registered prevalence. Per 2017, approximately one-tenth of the Danish population resided in the North Denmark Region.	[4]
Number of heart failure patients and patients with chronic obstructive pulmonary disease in the North Denmark Region	10,500	Estimate applied in the TeleCare North COPD trial.	[24]
Overhead and development costs may be allocated to more patients			
One-time start-up costs are annuitized		Under the expectation that the intervention will be used over a more extended period, i.e., the lifetime of the equipment	
Technology lifetime	5	Used for annuitization	[38]
Discount rate	0.04	The socio-economic discount rate	[39]
Annuity factor given a lifetime of 5 years and a discount rate of 0.04	4.4518	Annual costs = K/annuity factor	[26]
Annuitized cost items		Software development costs + support in relation to heart failure, education of healthcare professionals, Telekit including instructions.	
Conversion rate DKKR to £	8.2718	DKKR8.2719 per £1 per 31 December 2018	[29]
Use of effective hourly wages		'præsteret time' in Statistics Denmark - the combined earnings in relation to the job: the basic earnings incl. holiday allowances, holiday and public holiday payments, pensions, benefits in kind, nuisance compensations, etc. but excluding holidays, free hours of public holidays, absence due to sickness, children's sickness, parental leave, etc. Used to estimate the payers' hourly expenses of having the employee.' Approximation of the effective hourly wage, in accordance with good practice in economic evaluation to use effective hours.	[26,35]

Costs of respite care, daily expense 2018	£156.74	Estimated from annual expenses assessed in 2002. Indexed to represent 2018 using the consumer price index.	

Wage estimate	£ (2018)	Assumption	Reference
Municipality nurse without managerial responsibility	£37.16	statistikbanken.dk - LONS20 // earnings per hour performed // 2221 nursing work without managerial responsibility in municipalities // salaried and hourly paid // 2017 (222110 in DISCO-08)	[35]
Municipality nurse with managerial responsibility	£46.39	statistikbanken.dk - LONS20 // earnings per hour performed // 2221 nursing work w managerial responsibility in municipalities // salaried and hourly paid // 2017 (222110 in DISCO-08)	[35]
Regional nurse without managerial responsibility	£37.03	statistikbanken.dk - LONS20 // earnings per hour performed // 2221 nursing work without managerial responsibility in regions // salaried and hourly paid // 2017 (222110 in DISCO-08)	[35]
Regional nurse with managerial responsibility	£46.57	statistikbanken.dk - LONS20 // earnings per hour performed // 2221 nursing work w managerial responsibility in regions // salaried and hourly paid // 2017 (222110 in DISCO-08)	[35]
Physician with managerial responsibility, the Regions	£82.64	statistikbanken.dk - LONS20 // earnings per hour performed // 2211 standard medical work w managerial responsibility in regions // salaried and hourly paid // 2017 (221100 in DISCO-08)	[35]
Physician without managerial responsibility, the Regions	£52.50	statistikbanken.dk - LONS20 // earnings per hour performed // 2211 standard medical work w/o managerial responsibility in regions // salaried and hourly paid // 2017 (221100 in DISCO-08)	[35]
Administrative manager within the public sector	£73.18	statistikbanken.dk - LONS20 // earnings per hour performed // 1213 management within public administration w managerial responsibility in regions // salaried and hourly paid // 2017 (121320 in DISCO-08)	[35]
Physiotherapist w/o managerial responsibility (the Regions and municipalities)	£34.98	statistikbanken.dk - LONS20 // earnings per hour performed // 2264 physiotherapist and relaxation therapists w/o managerial responsibility in municipalities and regions // salaried and hourly paid // 2017 (226410 in DISCO-08)	[35]

Software development costs + support in relation to HF	£	Assumption
2016 ATEA: planning and status meetings	£1878.35	Fixed cost, irrespective of the number of patients. Development of software and modification of hardware, support. It could be considered whether this should be allocated to all HF patients in DK and not the proportion in the North Denmark Region - cut to a tenth.
2016 OTH: new questionnaire	£1390.25	
2016 C-Innovation - info app	£2671.70	
2017 ATEA New MDM group comorbidity	£2130.71	
Total	£8071.00	
Total per patient given 6700 HF patients	**£1.20**	

Telekit incl. instructions	£	Assumption
Tablet Samsung Galaxy tab incl. charger	£197.78	Based on expected purchase price 2018. Original cost 2333
Cover	£18.13	
Digital blood pressure monitor, UA-767 Plus BTC w. 1 cuff Continua Certified	£139.02	
Scale	£15.71	Note: The expectation of having a normal non-Bluetooth connected scale in the future - precision is irrelevant. Original cost £184.36. Scale 200 kg UC-321 PBT-C, Continua Certificeret Blue Tooth. // New price estimate based on purchase price in stores.
Flightcase	£14.51	
Target stylus	£0.46	Original price £4.23. New offer, supplied to patients now.
User manual, welcome letter, patient leaflets	£2.42	
Instruction for use of the Telekit	£27.87	Performed by municipality nurses without managerial responsibility. Expectation of a 45 min session. Not included transport to and from the resident's home. Conservative estimate; otherwise in group sessions of 3-4 persons at the municipality health center of duration 75 minutes.

Follow-up appointment in use of the Telekit	£27.87	Performed by municipality nurses without managerial responsibility. Expectation of a 45-min session, not including transport to and from the resident's home.
Delivery by Atea	£100,94	Price paid
Total per patient	**£544,71**	

Education of health care professionals	**N, courses held**	**Duration, hours**	**Participants, N**	**Target group**	**Instructor**	**Valuation, participants**		**Valuation, instructor**		**Total cost**
						job function	**£**	**job function**	**£**	**£**
Kickoff meetings	4	1.5	88	Project managers, key persons, and health care professionals who will be affiliated with the TCN HF project	The steering committee and administrative office, TCN HF	Regional nurse w/managerial responsibility	46.57	Administrative manager within public sector	£73.18	£ 6220.54
Open Teleseminar	5	4.0	51	Regional and municipality nurses and other clinicians who are to use Open Tele and the Telekit in relation to TCN HF	Specialist nursing consultant (nurse)	Municipality nurse w/o managerial responsibility	37.16	Regional nurse w managerial responsibility	£46.57	£ 7626.62
Academic meeting	2	8.5	48	Municipal specialist nursing players with monitoring tasks in TCH HF	Regional ECG technician, staff physician, nurse	Municipality nurse w/o managerial responsibility	37.16	Physician w/managerial responsibility, regions	£82.64	£ 15242.74
Educational seminar	2	6.0	45	Regional and municipality nurses in TCN HF	2*Developmental consultant (nurse) spl. cand.mag. and spl. cand.cur.	Municipality nurse w/o managerial responsibility	37.16	Regional nurse w/managerial responsibility	£46.57	£10078.99
Project day about rehab.	1	3.0	41	Regional HF nurses	Municipality rehabilitation nurses	Regional nurse w/o managerial responsibility	37.03	Municipality nurse w/o managerial responsibility	£37.16	£4591.42

Project day about palliation	2	3.0	37	Specialist nursing players from HF ambulatories and municipalities	Nurse in the hospital (Cardiologic department, AAUH) and healthcare center, Aalborg	Municipality nurse w/o managerial responsibility	37.16	Regional nurse w/managerial responsibility	£46.57	£4171.01
After-work meetings, general practitioners	3	2.0	30	General practitioners and general practice workers	Staff physician, HF	Physician w/o managerial responsibility, regions	52.50	Physician w/managerial responsibility, regions	£82.64	£3232.38
Seminar on increasing competencies in HF	30	2.0	510	Municipality nurses working with HF	Municipality nurse	Municipality nurse w/o managerial responsibility	.37.16	Municipality nurse w/o managerial responsibility	£37.16	£37937.42
Follow-up education Open Tele	5	3.0	15	Regional and municipality nurses and other clinicians who are to use Open Tele and the Telekit in relation to TCH HF	Specialist nursing consultant (nurse)	Municipality nurse w/o managerial responsibility	37.16	Regional nurse w/managerial responsibility	£46.57	£1718.64

Basic operation, COPD + HF	**£**	**Assumption**
Server service in the North Denmark Region (hardware, licenses, surveillance, operation of shared services)	£45502.97	
Monitoring system, Open Tele Health, support and contingency arrangements, 2nd and 3rd level	£10154.86	
Support of health professionals performed by Frederikshavn municipality, 2nd level	£33245.08	Given 780 hours/year
Total	£88902.91	
Total, per patient given 10500 patients	**£8.47**	

Development costs and extra support	£	Assumption
ATEA: Development costs and extra support (RFCs, changes, apps, certificate expiration, etc)	£15727.40	Though not occurring each year, development costs, changes to IT systems, further requests for support, licenses, expiry of app useful life, etc., should be expected and are, therefore, included here. Related to 'extraordinary' operation that cannot be anticipated. If excluded, the costs related to running the system would be underestimated. // Running from August 2016 to November 2018 (28 months). Only annual costs are needed = (12/28 months) of total costs.
ATEA: Status meetings	£6392.12	
FRH: Extra support, first half of 2017	£9187.73	
OTH Development costs and extra support	£8846.21	
IT North Denmark Region, extra support hours, system update	£2961.83	
Total	£43115.31	
Total, per patient given 10500 patients	**£1.76**	

Operational costs	£	Assumption
ATEA: Substitution of faulty equipment	£0.56	£100.94 per 1 substitution per month in 180 users.
ATEA: Handling of assets, number in use + 30% (number of active units used)	£0.54	
ATEA: MDM License: number in use + 30% (number of active units used)	£2.82	
TCD: Simcard, data, number in use + 30% (number of active units in use)	£2.93	
Total per month	£6.85	
Total per patient per year	**£82.15**	

Appendix.

Description of imputation approach in accordance with the methods described by Faria et al. [20].

At baseline, there were 2.92% missing values in the EQ-5D summary score (seven patients in the intervention group and one in the control group). Twenty-three (8.39%) participants died during the trial (ten in the intervention group and 13 in the control group) and were assigned an EQ-5D summary score of zero at the date of their death, which was used for interpolation in the estimation of the QALY gain. Furthermore, 90 participants had missing data in the follow-up EQ-5D summary score, either due to non-response or because of missingness in single components of the EQ-5D-5L questionnaire (43 patients in the intervention group and 47 in the control group). 50% had missing values in municipality costs (66 patients in the intervention group and 71 in the control group), whereas complete information existed on all other cost parameters for all patients (see Table 2). For patients who withdrew their consent during the trial, data collected up to the withdrawal date were included for analysis, and data that were to be collected after the withdrawal date was included as missing.

Complete data for both total costs and EQ-5D summary scores at baseline and follow-up were available for 89 patients. A sensitivity analysis was performed on complete cases only.

Based on a visual inspection of the pattern of missingness and regression analysis to evaluate the correlation between missingness and baseline variables, missing data at follow-up were assumed to be missing at random (MAR)[20]. Multiple imputations were used to account for missing values at both baseline and follow-up. It was assumed that the multiple imputations of baseline variables would not augment covariate imbalance substantially due to low missingness in most of the variables (see Table 2)[20].

Missingness in the baseline EQ-5D-5L summary score was mainly caused by missingness in the individual components of the EQ-5D questionnaire. For this reason, the imputation was performed on the level of the individual components at baseline. At follow-up, missingness of the EQ-5D-5L summary score was mainly caused by missingness of the entire follow-up questionnaire, so the imputation was performed for the summary score.

A combined imputation model using chained equations was generated for both costs and outcomes and was performed using the *mi impute chained (pmm,knn(5))* command in STATA15.1[43,44]. Continuous variables such as municipality cost and multinomial variables such as the individual components of the EQ-5D questionnaire at baseline were imputed using predictive mean matching with the k=5 nearest neighbors. Sixty complete datasets were generated. The imputation model included the outcome variables

themselves, predictors for the outcome variables, and predictors for missingness in the outcome variables. The imputation models were estimated separately for the intervention group and control group and included patients' sociodemographic characteristics (age, gender, relationship status, and level of education), the individual components of the EQ-5D questionnaire at baseline, the summary score of the EQ-5D-3L questionnaire at follow-up, patients' self-reported length of HF diagnosis, NYHA classification at baseline, presence of self-reported comorbidity (diabetes mellitus, COPD, psychological disorder, musculoskeletal disorder, cancer, or 'other'), self-reported smoking status (yes/no), total costs excluding municipality costs in the year preceding the study start date, municipality costs in the year preceding the study start date, total costs excluding municipality costs at follow-up, and municipality costs at follow-up (see Table 1).

BMJ Open

Is telehealthcare for heart failure patients cost-effective? An economic evaluation alongside the Danish TeleCare North Heart Failure trial.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-031670.R1
Article Type:	Original research
Date Submitted by the Author:	17-Oct-2019
Complete List of Authors:	Vestergaard, Anne; Aalborg Universitet, Department of Business and Management Hansen, Louise; Aalborg Universitet, Department of Business and Management Sørensen, Sabrina; Aalborg Universitet, Department of Business and Management Jensen, Morten; Aarhus University, Aarhus Business School Ehlers, Lars; Aalborg University, Danish Center for Healthcare Improvements, Department of Business and Management
Primary Subject Heading:	Health economics
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	HEALTH ECONOMICS, Heart failure < CARDIOLOGY, Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title page

Title:

Is telehealthcare for heart failure patients cost-effective? An economic evaluation alongside the Danish TeleCare North Heart Failure trial.

Authors:

- Anne Sig Sørensen (Vestergaard)[1], Ph.d
- Louise Hansen[1], Ph.d
- Sabrina Storgaard Sørensen[1], Ph.d
- Morten Berg Jensen[1,2], Ph.d
- Lars Holger Ehlers[1], Ph.d

Total word count: 4.441

Brief title: Cost-effectiveness of telehealthcare in HF

Affiliations:

[1]Danish Center for Healthcare Improvements, Dept. of Business and Management, Faculty of Social Sciences, Aalborg University, Aalborg, Denmark

[2]Department of Economics and Business Economics, Aarhus Business School, Aarhus University, Denmark

Address for correspondence

Lars Holger Ehlers

Aalborg University

Fibigerstraede 11, room 73

9220 Aalborg East

Denmark

Telephone: 0045 9940 8257

Fax: -

e-mail: lehlers@id.aau.dk

Suggested Keywords
Health Economics, Telemedicine, Heart Failure.

Abstract

Objective. This study aimed to assess the cost-effectiveness of telehealthcare in heart failure patients as add on to usual care.

Design. A cost-utility analysis was conducted from a public payer perspective alongside the randomized controlled TeleCare North trial.

Setting: The North Denmark Region, Denmark.

Participants: The study included 275 heart failure patients with self-reported NYHA class II-IV.

Interventions: Patients in the intervention group were provided with a Telekit consisting of a tablet, a digital blood pressure monitor, and a scale and were instructed to perform measurements 1-2 times a week. The responsibility of the education, instructions and monitoring of the HF patients was placed on municipality nurses trained in HF and telemonitoring. Both groups received usual care.

Outcome measures. Cost-effectiveness was reported as incremental net monetary benefit (NMB). A micro-costing approach was applied to evaluate the derived savings in the first year in the public health sector. Quality-adjusted life-years (QALY) gained were estimated using the EQ-5D-3L questionnaire at baseline and at a one-year follow-up.

Results. Data for 274 patients were included in the main analysis. The telehealthcare solution provided a positive incremental NMB of £5164. The one-year adjusted QALY difference between the telehealthcare solution and the usual care group was 0.0034 [95% CI: -0.0711; 0.0780]. The adjusted difference in costs was -£5096 [95%CI: -8736;-1456] corresponding to a reduction in total healthcare costs by 35%. All sensitivity analyses showed the main results were robust.

Conclusions. The TeleCare North solution for monitoring HF was highly cost-effective. There were significant costs savings on hospitalizations, primary care contacts, and total costs.

Article summary

Strengths and limitations of this study

This study should be relevant for decision-makers at the national healthcare level as well as at the clinical level.

It is the first economic evaluation of telehealthcare in heart failure patients that strictly follows international guidelines for health economic evaluation alongside clinical trials.

Precise assessment of the economic costs was allowed through micro costing analyses based on patient specific data and detailed registration of operational as well as capital costs of telehealthcare.

No evidence was provided, however, on the long-term cost-effectiveness or on the explanation of what components of the intervention were actually effective or whether the effect was contingent on the intervention in its entirety.

1. Introduction

Heart failure (HF) is a common chronic disease with an estimated global prevalence of approximately two percent[1–3]. In Denmark, approximately 9000 patients are diagnosed with HF each year. The incidence increases with higher age, and it has been estimated that one in five individuals will develop HF during their lifetime[2–4]. In total, the condition is conservatively estimated to affect approximately 66,000 citizens in Denmark, and about five percent of all Danish citizens above the age of 75 have been diagnosed with HF[4,5]. The prevalence of HF is, however, expected to rise in the future due to, amongst others, a higher prevalence of predisposing factors, such as hypertension, diabetes, and obesity but also due to the increased longevity of patients with HF, which is likely the result of an improved treatment of the condition[1,2,6].

HF symptoms include dyspnea, fatigue, lethargy, and edema[3,4]. The severity of patients' HF is often described according to the New York Heart Association (NYHA) functional classification system, which may be used by patients to classify the severity of their HF according to their own experience of the condition. Class I indicates that the condition does not limit physical activity and that ordinary activity does not cause any symptoms. In higher classes, the symptoms reported are increasingly more severe; thus, in class IV, patients cannot perform physical activity without experiencing symptoms, or they experience symptoms even at rest[3,7]. HF is believed to impair patients' health-related quality of life (HRQoL) compared to individuals without the condition, and the condition entails a substantially increased mortality[2,8–10]. In addition to the personal burden that HF entails, the condition also causes a substantial burden on health care systems worldwide, accounting for approximately two percent of total health care expenditures[2,11]. Hospitalizations are recognized as the primary driver for the total costs related to HF, though outpatient visits also constitute a substantial part[2,12].

In 2016, the European Society of Cardiology published updated guidelines for the diagnosis and treatment of acute and chronic HF[13], emphasizing the beneficial impact of continuous monitoring of, amongst others, biomedical parameters to enable the detection of the development of complications and disease progression that may prompt changes to patients' disease management. In the guidelines, telehealthcare is mentioned as a possible means of monitoring patients[13]. Evidence suggests that telehealthcare in different forms may be beneficial in the management of HF, both for the improvement of patients' HRQoL but also in the prevention of, for example, hospitalizations and all-cause mortality[14–16]. Findings, however, are inconsistent[13,17], which might be ascribed to the fact that the components of the investigated telehealthcare solutions differ. Effectively, this heterogeneity makes the various telehealthcare solutions incomparable in terms of their design, effectiveness and, consequently, cost-effectiveness [15–

17]. A number of reviews [16–18] have requested more high-quality studies of the health economic consequences of telehealthcare interventions. To our knowledge, however, up until now, no cost-effectiveness analysis of telehealthcare in HF patients have been conducted according to international good practice guidelines for the economic evaluation alongside clinical trials[19,20].

In Denmark, a national strategy has been formulated for the introduction of telehealthcare as a means of reducing healthcare costs while also providing patients with greater HRQoL and the feeling of improved control of their disease [21,22]. In this respect, the North Denmark Region has played a major role in the formulation of the national strategy by performing pre-launch, large-scale randomized controlled trials and health economic evaluations and national business cases as decision-support for the nationwide implementation[23,24]. In the wake of the first TeleCare North trial directed at patients suffering from chronic obstructive pulmonary disease (COPD), which was executed in 2014-2015[23,24], the TeleCare North Heart Failure (HF) trial was launched in 2016 with the purpose of evaluating the effectiveness and cost-effectiveness of a telehealthcare solution directed at patients with HF[25]. The purpose of this economic evaluation is to evaluate the cost-effectiveness of the TeleCare North HF solution, comparing the impact on costs and effects (i.e. quality-adjusted life years (QALYs)) with that of the usual practice for the treatment of HF in Denmark.

2. Methods

The cost-utility analysis was conducted in accordance with international guidelines for health economic evaluations alongside clinical trials[19,20,26]. All clinical and costs data for the analysis were collected alongside the TeleCare North HF trial, and the time horizon for the analysis was restricted to a one-year period. A Danish public healthcare sector perspective was applied, including costs accumulating under the auspices of the regional healthcare (i.e. pre-hospital services and inpatient and outpatient services in somatic and psychiatric healthcare), municipality-based health and social care (e.g. home care services and rehabilitation), and primary healthcare (e.g. general practice and physiotherapy) and costs associated with purchases of prescription medicine at Danish pharmacies. Costs associated with patient- or relative-paid transportation and productivity costs were not included.

The trial protocol presenting the design of the TeleCare North HF Trial and associated economic evaluation has previously been published[25]. The participants in the intervention group received patient education and telehealthcare equipment for continuous monitoring of physiological measurements. Patients in the intervention group were provided with a Telekit consisting of a tablet, a digital blood pressure monitor, and

a scale, and were instructed to perform measurements 1-2 times a week. The responsibility of the education, instructions and monitoring of the HF patients was placed on municipality nurses trained in HF and telemonitoring. The nurses were given the authority to intervene and change medication if, for instance, measurements indicated a deterioration in the patient's health. The specialized nurses could contact the heart failure clinic at the central university hospital for guidance regarding specific patient issues. Patients in the control group received the usual care, where general practitioners were responsible for the monitoring of the patients (see the appendix A for elaboration).

The result of the economic evaluation is expressed as the incremental net monetary benefit (NMB) = ($\Delta QALY \times Rt - \Delta Cost$)[27], where ΔQALY is the incremental quality of life, and ΔCost is the incremental costs. Under the assumption of a cost-effectiveness threshold (Rt) of £20,000 per QALY gained, an incremental NMB > 0 indicates that the telehealthcare solution is cost-effective compared to the usual care [26].

The cost-effectiveness of the telehealthcare solution is estimated for a 12-month period starting 30 days after participant enrollment in the study. This 30-day 'blanking period' for both groups was introduced from the day of referral to accommodate that participants in the intervention group would only receive the telehealthcare solution belatedly compared to the referral date and therefore effectively did not receive any intervention in this period. The difference in follow-up length was accommodated for in the estimation of cost and effect accumulation by weighting the accumulation by the lengths of the follow-up of individual participants to represent a 12-month follow-up. The enrollment period started on September 1, 2016, and the follow-up period ended on March 4, 2018.

a. Cost accumulation

All costs are presented in 2018 values in British Pounds Sterling (£). The Danish consumer price index for health care products and services[28] was used to adjust the cost data from 2016 and 2017 to the price level in 2018. Costs were estimated in Danish Krone (DKK) and subsequently converted, based on a conversion rate of Danish Kroner (DKK) 827.19 per £100 from December 31, 2018[29].

i. Healthcare service use and healthcare costs

Patient-specific costs related to health care service use were estimated based on register data. In Denmark, all citizens are provided with a unique personal identification number at birth or immigration, which

enables the linkage of information from various registers at the individual level. Information on patients' gender, birthday, migration status, and vital status was retrieved from the Danish Civil Registration System[30].

Information on patients' use of prescription medicine was retrieved from the Danish National Prescription Registry. The costs related to prescription medicine were valued at pharmacy selling prices excluding VAT.

Patients' contacts with general practice were identified through the National Health Insurance Service Register[31,32]. The costs associated with the contacts to general practice are registered in the registry and based on fees quoted in a collective agreement negotiated with the Danish Medical Association[33].

Information on patient hospitalizations was retrieved from the Danish National Patient Registry, which holds information on all inpatient, outpatient, and emergency hospitalizations in somatic and psychiatric wards in Denmark[34]. In the registry, each contact is valued according to the designated diagnosis-related group used for reimbursement, the actual procedures performed, and the length of stay in relation to the contact.

Estimates of the resource consumption of community care services in the municipalities were based on detailed registrations from four of the 11 contributory municipalities (the administrative units for tax-financed local health and social care). For patients in both groups, registrations included all local care activities, such as personal care, practical help, home nursing, rehabilitation, and telehealthcare activities. To increase generalizability to other settings in Denmark, the registered time consumption for standard care activities was valued using the national average effective hourly wage of the municipality nurses without managerial responsibility[35]. Time consumption in relation to rehabilitation consisting of physiotherapy was valued using the national average effective hourly wage of the municipality and regional physiotherapists without managerial responsibility[35]. Days of respite care in relation to rehabilitation were valued according to the estimated expenses of a day in care homes (see appendix B) [36,37].

Information on trial participants' health care service use and health care costs was retrieved for 12 months following their individual study startup date (30 days after the date of their enrollment). Information on health service use and health care costs was retrieved for the participants from 12 months before the study start date for each participant to control for differences in health care utilization before the start of the intervention.

i. Telehealthcare intervention costs

The administrative office for TeleCare North provided a detailed registration of all intervention costs (see appendix B). Capital costs included the development of software and hardware modifications for the Telekit, the delivery of and the Telekit itself, and one-time start-up costs related to the education of patients and healthcare professionals. In the analysis, capital costs were annuitized over a period of five years with a discount rate of four per cent per annum and included as equivalent annual costs. The useful equipment lifetime and applied discount rate are in accordance with what applies for 'other IT equipment' in Danish capital accounting[38,39]. Operational costs included, among other things, maintenance, support, and licenses. The daily work with continuous monitoring of the patients was included in the municipalities' registrations of healthcare service use and healthcare costs described above.

Software development and hardware configuration were valued as prices paid to an external supplier, reflecting actual tenders. The Telekit was valued based on the expected purchase price if the intervention were to be implemented and used in real-life practice following the results of the TeleCare North HF trial. The delivery of hardware, running costs related to licenses, handling of assets, data charges, and substitution of malfunctioning equipment were valued as the price negotiated and paid to the external supplier.

Before the trial, various meetings and educational seminars were held to train healthcare professionals in the use of the telehealthcare solution and monitoring duties and to increase their general knowledge on the management of HF, rehabilitation, and palliation. Participants in these meetings and seminars included general practitioners and regional and municipality nurses. In addition, meetings were held informing project managers, key persons, and healthcare professionals on the telehealthcare solution and the implementation of the intervention. The per-patient costs of educating health care professionals and others were estimated based on the planned time spent in the meetings, the number of participants at the meetings, and the average effective hourly wage of the participants. The applied average effective hourly wages were estimated based on national average wages to increase generalizability to the other Regions in Denmark[35].

Costs of modifications of the hardware, software development, and education for healthcare professionals and management staff were allocated to all HF patients who would be offered the telehealthcare solution in the North Denmark Region. The number of HF patients in the North Denmark Region was estimated to be 6700, given an estimated prevalence of 66,000 HF patients in Denmark[4] and that approximately 10% of the Danish population resides in the North Denmark Region.

The annual operational costs of telehealthcare were allocated to the estimated number of HF patients andother patients using the regional telehealth system in the North Denmark Region (10,500 patients[24]). The operational costs were valued as prices paid.

b. Measure of effectiveness

Information on patients' HRQoL was collected from questionnaires at baseline and at the end of the follow-up. Index scores for participants' HRQoL were estimated based on the EuroQol-5Dimensions-5Levels (EQ-5D-5L) questionnaire. Currently, however, there are no Danish societal weights estimated for the EQ-5D-5L questionnaire for which reason the responses in the EQ-5D-5L questionnaire were used to predict responses in the EuroQol-5Dimensions-3Levels (EQ-5D-3L) questionnaire by applying a response mapping approach[40,41]. Danish societal weights for the EQ-5D-3L questionnaire were subsequently applied[42]. Information on mortality was retrieved from the Danish Registry of Causes of Death, which holds information on all causes of death in Denmark. Information on participants' HRQoL and relevant demographic characteristics were collected at baseline at participant enrollment in the outpatient clinics or after the participant returned home, if preferred by the patient[25]. Irrespective of where the data were collected, the time of collection was dated to be 30 days after the date of their enrollment. At the end of the follow-up, the EQ-5D-5L questionnaire was sent in paper form to patients' home addresses from the trial administration office. A prepaid return envelope was included. The response was dated to the end of follow-up (March 4, 2018). [43].

Linear interpolation of the utility scores from baseline to follow-up was performed to estimate the QALY gain and was scaled to represent the QALY gain within one year. The utility score for patients who died during follow-up was set to zero at the time of death.

3. Analysis

a. Missing data management

In accordance with good research practice guidelines within effectiveness and cost-effectiveness studies, the primary analysis was performed according to the intention-to-treat principle and imputation was performed to account for missing data [19,20,44,45]. Imputations of missing data for the primary analysis was performed in accordance with the methods for multiple imputations described by Faria et al. [20]. A full description of the imputation approach is provided in the appendix C.

In total, 299 participants were enrolled in the trial (intervention group n=145, control group n=154) (see Figure 1). One patient was enrolled but was never randomized to any treatment group and, therefore, not included in the study. Four patients did not return questionnaires at either baseline or follow-up due to withdrawal shortly after enrollment for which reason no data were available on them except basic registry information. As no effectiveness data were available for these patients and they did, de facto, not participate in the study, they were excluded from analyses in accordance with guidelines on post-randomization exclusion[46]. Furthermore, 21 patients with a self-reported NYHA I classification were wrongfully included in the randomization. Given the eligibility criteria of the trial, these patients were excluded from the primary analysis. For the primary analysis, the intervention group included 134 patients, and the control group included 140 patients.

b. Cost-utility analysis

For descriptive statistics, all data are reported as means and standard errors, and differences in means between the intervention and the control group are presented as raw, unadjusted differences. *P* values for between-group differences have been evaluated by a Student's t-test for continuous variables and a Pearson's Chi-square test for binary and multinomial variables. Statistical significance was assumed for *P* values < 0.05, and all significance tests were two-tailed.

The estimates of incremental costs and QALYs between the intervention group and the control group were based on a seemingly unrelated regression analysis. This regression method is recommended and widely used in economic evaluation because cost and HRQoL is normally correlated[47]. In the primary analysis, both total costs and QALYs were adjusted for group allocation, age, gender, baseline EQ-5D-3L summary score, total costs in the year preceding the study start date, self-reported NYHA classification at baseline, the self-reported length of HF diagnosis at study start, education level, relationship status, and the presence of self-reported smoking, diabetes mellitus, psychological disorder, COPD, cancer, and musculoskeletal disorder. The estimations were performed using the *mi estimate, cmdok: sureg* command in STATA.

The deterministic incremental NMB was estimated using the treatment beta coefficients from the seemingly unrelated regressions, and a probabilistic sensitivity analysis was performed to evaluate the decision uncertainty. A scatter plot of incremental cost-effectiveness was generated based on 10,000 simulations. The simulations were based on random draws from the estimated treatment effect on cost

and QALY accumulation and their associated standard errors. The incremental costs were expected to assume a gamma distribution and the QALYs were expected to assume a Gaussian distribution.

All statistical analyses were performed in STATA, version 15.1.

c. Sensitivity analyses

Both the primary analysis and sensitivity analyses were performed with and without adjustment. For deterministic sensitivity analyses, three different scenarios were investigated;

Scenario I: A complete case analysis, that is, an analysis in which information on all outcome variables and variables used for adjustment were available.

Scenario II: An analysis including all patients that were enrolled in the study, including patients with a self-reported NYHA classification of I.

Scenario III: To evaluate whether results were driven by a minority of patients with very high resource consumption, a sensitivity analysis was performed in which the upper ten percent of patients with the highest resource consumption before imputation were excluded before imputation.

Scenario analysis II and III were both based on imputed data sets.

d. Patient and public involvement

Patient and public involvement in the project was organized by the TeleCare North project organization placed within the regional healthcare administration. This included open seminars/meetings with patients, relatives, health care providers, and others. A special homepage was designed with relevant information for patients and relatives, hospitals, municipalities, and general practitioners, respectively. The TeleCare North project organization also organized the development of the educational programs for patients and healthcare providers in all sectors. The research-based evaluation of the project was presented in public for all interested citizens free of charge. At the local political and public administrative levels, the project was followed and discussed in relevant fora with participation from all municipalities and the region.

4. Results

There were no statistically significant differences in baseline characteristics between the two groups, and missingness in variables was also fairly distributed between them (Table 1).

Within the one-year follow-up, the group receiving the telehealthcare solution had a consistently lower resource consumption across all health care cost categories compared to the group receiving usual care, leading to a total raw difference of -£5,668 (Table 2). Thus, the usage of telemedicine reduces total healthcare costs by 35% (5,668 off a base of 16,241 British pounds). This lower mean cost per patient was primarily driven by lower costs associated with hospitalizations (intervention group £5,055 vs. control group £9,064, *p*-value=0.01).

In the primary analysis, the one-year adjusted QALY difference between the telehealthcare solution and the usual care group was 0.0034 [95% CI: -0.0711; 0.0780], indicating an insignificant gain in HRQoL for patients receiving the telehealthcare solution (Table 3). The adjusted baseline utility score was similar across the two groups (0.7079 for control and 0.7075 for intervention). The mortality was similar between both groups, with 5 deaths in the control group and 7 deaths in the intervention group.

The adjusted difference in costs was -£5096 [95%CI: -8736; -1456], indicating a significantly lower total mean cost per patient in the telehealthcare solution group. Based on the incremental cost and QALY estimates and an assumed cost-effectiveness threshold of £20,000 per QALY[27], the telehealthcare solution provides a positive incremental NMB of £5164, indicating that the telehealthcare solution is cost-effective. The unadjusted analysis also indicates that the telehealthcare solution provides a significant cost saving (-£5539 [95% CI: -9483; -1595]) and an insignificant impact on patients' QALY gain (-0.0005 [95% CI: -0.0723; 0.0714]) and therefore is cost-effective (NMB = £5530). The result of the probabilistic sensitivity analysis is shown in the incremental cost-effectiveness scatter plot in Figure 2. The incremental cost-effectiveness distribution disperses across the southwest and southeast quadrant of the incremental cost-effectiveness plane in agreement with the QALY gain associated with the telehealthcare solution being insignificant but the incremental negative cost being significant.

All scenario analyses showed the same result with telehealthcare associated with lower costs and an insignificant impact on patients' health-related quality of life (Table 3). Across the adjusted and unadjusted sensitivity analyses, the cost-effectiveness result is relatively robust, with all analyses indicating a positive incremental NMB of the telehealthcare solution compared to usual practice.

5. Discussion

The principal finding of this study is that the investigated telehealthcare solution is highly cost-effective for the treatment of HF patients in the Danish setting. High-quality economic evaluations of telehealthcare solutions in the management of HF have been requested[16–18] and, to our knowledge, the present study is the first economic evaluation of telehealthcare in HF patients that strictly follows international guidelines for health economic evaluation alongside clinical trials[19]. Thus, a particular strength of this study was the micro-costing approach, including the availability of information on patient-specific resource usage from the Danish registers. The majority of information on patients' resource consumption was retrieved from well-validated Danish registers, ensuring the validity of the registrations with no missing data in these parameters. For the resource consumption in the municipalities, data from four out of the 11 participatory municipalities were applicable. The four municipalities were relatively large (making for approximately 50% of the total participant sample), and thus, the representativeness of their organization and consequently costs for smaller municipalities is debatable. However, municipality costs only constitute a minor share of the total costs (cf. Table 3); for which reason it could be suspected that even if the estimate of municipality costs is not representative for all participatory municipalities, the cost-effectiveness conclusion would not be markedly affected.

In the present cost-utility analysis, the impact on patients' QALY gain was insignificant across all analyses. The increased sensitivity, which could have been achieved by using the 5L questionnaire[19], may effectively have been watered down when predicting the 3L responses from the 5L responses and applying the 3L weights. This might provide an explanation of why it was not possible to observe any substantial differences in QALY accumulation between the two intervention groups, which could otherwise have been expected given findings in previous studies[16].

In general, telehealthcare interventions and the studies of them are relatively heterogeneous, making a comparison of them difficult[15,16]. In a Cochrane review from 2015[16], structured telephone support and telemonitoring for HF patients were found to reduce all-cause mortality and HF-related hospitalizations. In addition, the impact on patients HRQoL and cost accumulation was inconsistent, emphasizing the difficulties of evaluating and comparing the cost-effectiveness of telehealthcare interventions aggregately.[16]

Only a few papers report on cost savings in relation to telehealthcare within this field. These studies do not have economic evaluation as their primary aim and do not strictly follow proper practice guidelines for economic evaluations[19,26]. Nevertheless, they all point in the same direction of potentially huge savings

[16–18]. Frederix et al.[48] reported insignificant long-term savings of approximately 27% from an initial 6-month telehealthcare intervention. Jiménez-Morrero et al.[49] report savings of approximately 38% for a subgroup of HF patients with a left ventricular ejection fraction >40. Comín-Colet et al. [50] report savings of approximately 45%, mainly driven by a significant reduction in hospitalizations between the telehealthcare group and control group. An economic modeling study by Liu et al. [51] also points in the same direction of possible savings from telehealthcare interventions directed at intermediate- and high-risk patients over a 1- to 5-year window. Their results suggest the economic viability of telehealthcare programs for the management of chronic HF, but emphasized the importance of risk stratification in such programs[51]. In our study, however, the severity of HF did not seem to be important, as there appeared to be only minor differences in cost savings depending on whether patients reporting being in NYHA class I were included or not. A particular difference between our study and other studies may also have been the level of organizational learning and knowledge management, as the TeleCare North trial builds upon many years of experience with telehealthcare solutions from previous trials[23,24] as well as the national implementation of telehealth program for COPD in Denmark decided in 2015[22].

As the design of the TeleCare North HF trial and the components of the telehealthcare intervention was somewhat similar to that of the TeleCare North COPD trial[23,25], the present study anticipated that the economic evaluation would essentially produce results similar to that of Udsen et al.[24]. In agreement with the economic evaluation by Udsen et al.[24], no significant difference in QALY accumulation between the intervention groups was observed in this study. In contrast, the present study found telehealthcare to produce substantial cost savings, which contrasts with the added costs associated with telehealthcare found by Udsen et al.[24]. The difference is that telehealthcare is cost-effective for HF patients but not all COPD patients. This discrepancy indicates that the cost-effectiveness of telehealthcare interventions, to a large degree, depends on the recipient patient group, making it difficult to comment on the cost-effectiveness of telehealthcare interventions as a whole. The characteristics of specific patient groups ought, therefore, to be incorporated when telehealthcare interventions are designed and implemented.

The impact of the TeleCare North solution of patients Qol measured with the Short-Form 36 (SF-36) questionnaire's physical and mental component summary scores and the Kansas City Cardiomyopathy Questionnaire 12 score are published elsewhere[52]. It was only possible to detect a small but significant positive change in the SF-36 mental component summary score. Thus, with respect to the impact on patients' HRQoL, the telehealthcare solution cannot be characterized as an unqualified success. It could, however, be hypothesized that the currently applied methods of measurement of effect are too insensitive to detect any beneficial impact especially on patients' mental well-being, as suggested by the positive

impact on the SF-36 mental component summary score but none of the other measures. It is possible that the positive impact of telehealthcare does not manifest itself as an impact on patients' HRQoL but rather their opinions and beliefs, which subsequently affects their healthcare-seeking behavior.

Given the complexity and multiple purposes of the intervention under investigation[25], it is possible that conventional measures of effectiveness, such as HRQol and QALY, do not sufficiently capture all potential effects. It is possible that impacts on other parameters could have been observed, such as patients' satisfaction, self-perceived risk of dying, comfort, ability to reduce anxiety through telephone contact with a well-known local nurse, and an increased sense of capability among others. It could be considered whether the slightly narrow focus on patients' HRQoL and QALY in the present analysis represent an appropriate evaluation approach to this particular kind of complex intervention.

Though the present economic evaluation found the telehealthcare solution to be highly cost-effective, questions remain as to why this result was achieved. Thus, it remains unclear what components of the intervention were actually effective or whether the effect is contingent on the intervention in its entirety. In the design phase of future trials on the effectiveness and cost-effectiveness of complex interventions such as telehealthcare, early consideration of mechanisms of action and programme theory [53] ought to be introduced to improve our understanding of why some interventions may prove effective and cost-effective and others not. This may increase the cost-effectiveness of future telehealth solutions.

Acknowledgments: The authors would like to thank all of the participants in TeleCare North Heart Failure for their time and effort when filling out questionnaires and reporting physical measurements. Likewise, a thank you goes out to all healthcare professionals involved in the execution of the trial, the North Denmark Region, and the municipalities for their goodwill in making this trial possible. A special thank you to Kuno Strand Kudajewski, project manager for the TeleCare North Heart Failure Trial at the North Denmark Region for helping with information on cost data and for proof-reading the manuscript, and to Simon Lebech Cichosz for the lengthy keying of the EQ-5D questionnaire data.

Author contributions: LHE is the primary investigator for economic evaluation in the TeleCare North Heart Failure Trial; LHE planned the design of the economic evaluation and stands as a guarantor of the statistical quality for the evaluation as a whole. LHE, LH, MBJ, SSS and ASV contributed equally to the detailed planning and design of the analyses in the economic evaluation. LH was mainly responsible for data management. All analyses were performed by collaboration by all authors, and ASV drafted the paper in collaboration with the other authors. All authors had full access to the data and accept responsibility for the integrity of the data and the data analyses. All authors met regularly during the data analysis period and contributed equally to the interpretation and presentation of data. All authors reviewed and approved the manuscript prior to submission.

Ethics: The trial has been authorized by the Danish Data Protection Agency. The study is being conducted in accordance with the Helsinki declaration. The trial has been presented to the Ethical Committee for Medical Research in the North Denmark Region; this committee decided that no ethical approval was necessary.

Trial registration number: ClinicalTrials.gov: NCT02860013

Competing interests: None

Funding: The study was funded by the Danish Agency for Digitalisation under the Danish Ministry of Finance the North Denmark Region.

Patient content: not required

Data statement: no additional data available

Figures legends:

Figure 1. Flowchart of exclusion of patients for the economic evaluation.

Figure 2. Incremental cost-effectiveness scatter plot based on the probabilistic sensitivity analysis. The dotted line indicates a cost-effectiveness threshold of £20,000 per quality-adjusted life year.

References

[1] Savarese G, Lund LH. Global Public Health Burden of Heart Failure. *Card Fail* Rev 2017;03:7. doi:10.15420/cfr.2016:25:2.

[2] Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. *Nat Rev Cardiol* 2011;8:30–41. doi:10.1038/nrcardio.2010.165.

[3] Inamdar A, Inamdar A. Heart Failure: Diagnosis, Management and Utilization. *J Clin Med* 2016;5:62. doi:10.3390/jcm5070062.

[4] Madelaire C, Gislason G. Hjertesvigt i Danmark 2017 - socioøkonomiske forskelle i forekomst, dødelighed og behandling [Heart Failure in Denmark 2017 - socioeconomic differences in prevalence, mortality, and treatment]. 2017.

[5] Dansk Selskab for Almen Medicin. Kronisk hjertesvigt/kronisk systolisk hjerteinsufficiens [Chronic heart failure/chronic systolic heart failure]. *DSAM Guidel* 2013. https://vejledninger.dsam.dk/hjerteinsufficiens/?mode=visKapitel&cid=597&gotoChapter=597 (accessed November 7, 2018).

[6] Roger VL. Epidemiology of Heart Failure. *Circ Res* 2013;113:646–59. doi:10.1161/CIRCRESAHA.113.300268.

[7] Dansk Cardiologisk Selskab. Behandlingsvejledning, 5. Kronisk hjertesvigt [Treatment Guidelines, Chronic Heart Failure] 2017. https://www.cardio.dk/chf#55-behandling (accessed November 16, 2018).

[8] Polikandrioti M. Health Failure and Health Related Quality of Life. *Heal Sci J* 2008;3:119–20.

[9] Juenger J, Schellberg D, Kraemer S, Haunstetter A, Zugck C, Herzog W, et al. Health related quality of life in patients with congestive heart failure: comparison with other chronic diseases and relation to functional variables. *Heart* 2002;87:235–41. doi:10.1136/heart.87.3.235.

[10] Comín-Colet J, Anguita M, Formiga F, Almenar L, Crespo-Leiro MG, Manzano L, et al. Health-related Quality of Life of Patients With Chronic Systolic Heart Failure in Spain: Results of the VIDA-IC Study. *Rev Española Cardiol* (English Ed 2016;69:256–71. doi:10.1016/j.rec.2015.07.030.

[11] Shafie AA, Tan YP, Ng CH. Systematic review of economic burden of heart failure. *Heart Fail Rev* 2018;23:131–45. doi:10.1007/s10741-017-9661-0.

[12] Brorholt G, Jakobsen M, Hauge AM, Kjellberg Med Bidrag Fra J, Grønbaek M, Terkelsen CJ, et al. En helhjertet indsats – En artikelbaseret klinisk, patientnær og sundhedsøkonomisk kortlægning af hjerte-kar-området [A whole-hearted effort - a paper-based clinical, patient-relevant and health economic survey of the cardiovascular area]. København K: 2018.

[13] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2016;37:2129–200. doi:10.1093/eurheartj/ehw128.

[14] Bashi N, Karunanithi M, Fatehi F, Ding H, Walters D. Remote Monitoring of Patients With Heart Failure: An Overview of Systematic Reviews. *J Med Internet Res* 2017;19:e18. doi:10.2196/jmir.6571.

[15] Dierckx R, Inglis SC, Clark RA, Prieto-Merino D, Cleland JGF. Telemedicine in heart failure: new insights from the Cochrane meta-analyses. *Eur J Heart Fail* 2017;19:304–6. doi:10.1002/ejhf.759.

[16] Inglis SC, Clark RA, Dierckx R, Prieto-Merino D, Cleland JG. Structured telephone support or non-invasive telemonitoring for patients with heart failure. Cochrane Database Syst Rev 2015. doi:10.1002/14651858.CD007228.pub3.

[17] Gensini GF, Alderighi C, Rasoini R, Mazzanti M, Casolo G. Value of Telemonitoring and Telemedicine in Heart Failure Management. *Card Fail Rev* 2017;3:1. doi:10.15420/cfr.2017:6:2.

[18] Grustam AS, Severens JL, van Nijnatten J, Koymans R, Vrijhoef HJM. Cost-effectiveness of telehealth interventions for chronic heart failure patients: A literature review. *Int J Technol Assess Health Care* 2014;30:59–68. doi:10.1017/S0266462313000779.

[19] Ramsey SD, Willke RJ, Glick H, Reed SD, Augustovski F, Jonsson B, et al. Cost-effectiveness analysis alongside clinical trials II - An ISPOR good research practices task force report. *Value Heal* 2015;18:161–72. doi:10.1016/j.jval.2015.02.001.

[20] Faria R, Gomes M, Epstein D, White IR. A Guide to Handling Missing Data in Cost-Effectiveness Analysis Conducted Within Randomised Controlled Trials. *Pharmacoeconomics* 2014;32:1157–70. doi:10.1007/s40273-014-0193-3.

[21] Digitaliseringsstyrelsen. Telemedicin - en nøgle til fremtidens sundhedsydelser. National handlingsplan for udbredelse af telemedicin - kort fortalt [Telehealthcare - a key to future healthcare services. A national action plan for the introduction of telehealthcare - in brief]. København K: 2012.

[22] Sundhedsdatastyrelsen. Telemedicin og telesundhed [Telemedicine and telehealth] 2018. https://sundhedsdatastyrelsen.dk/da/rammer-og-retningslinjer/telemedicin-og-telesundhed (accessed December 21, 2018).

[23] Udsen FW, Lilholt PH, Hejlesen O, Ehlers LH. Effectiveness and cost-effectiveness of telehealthcare for chronic obstructive pulmonary disease: Study protocol for a cluster randomized controlled trial. *Trials* 2014;15:1–7. doi:10.1186/1745-6215-15-178.

[24] Witt Udsen F, Lilholt PH, Hejlesen O, Ehlers L. Cost-effectiveness of telehealthcare to patients with chronic obstructive pulmonary disease: results from the Danish 'TeleCare North' cluster-randomised trial. *BMJ* Open 2017;7:e014616. doi:10.1136/bmjopen-2016-014616.

[25] Cichosz SL, Ehlers LH, Hejlesen O. Health effectiveness and cost-effectiveness of telehealthcare for heart failure: Study protocol for a randomized controlled trial. *Trials* 2016;17:4–9. doi:10.1186/s13063-016-1722-5.

[26] Drummond MF, Schulpher M, Claxton K, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. 4th ed. Oxford: Oxford University Press; 2015.

[27] Devlin N, Parkin D. Does NICE have a cost-effectiveness threshold and what other factors influence its decisions? A binary choice analysis. *Health Econ* 2004;13:437–52. doi:10.1002/hec.864.

[28] Statistics Denmark. Pris111: Consumer price index ((2015=100) by commodity group and unit 2018. http://www.statistikbanken.dk/PRIS8 (accessed December 5, 2018).

[29] EUROinvestor. Valutakurser [Exchange rates] 2018. https://www.valutakurser.dk/ (accessed February 15, 2019).

[30] Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014:541–9. doi:10.1007/s10654-014-9930-3.

[31] Sundhedsdatastyrelsen. Sygesikringsregisteret (SSR) [National Health Insurance Service Register] 2017. https://sundhedsdatastyrelsen.dk/da/registre-og-services/om-de-nationale-sundhedsregistre/sundhedsoekonomi-og-finansiering/sygesikringsregisteret (accessed November 20, 2018).

[32] Sahl Andersen J, De Fine Olivarius N, Krasnik A. The Danish national health service register. *Scand J Public Health* 2011;39:34–7. doi:10.1177/1403494810394718.

[33] Danish Medical Association. Honorartabel 01-10-2018 [Fee table 2018-10-01] 2018.

https://www.laeger.dk/sites/default/files/honorartabel_2018_oktober_web.pdf.

[34] Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: A review of content, data quality, and research potential. *Clin Epidemiol* 2015;7:449–90. doi:10.2147/CLEP.S91125.

[35] Statistics Denmark. Statistikbanken - LONS20: Løn efter arbejdsfunktion, sektor, aflønningsform, lønmodtagergruppe, lønkomponenter og køn [Statistikbanken - LONS20: Wages estimated based on job function, sector, payment form, employment group, wage component and gender]○ 2018. http://statistikbanken.dk/statbank5a/default.asp?w=1920 (accessed November 19, 2018).

[36] Ministry of Finance. Frit valg og kvalitet - afregningsmodeller på de kommunale serviceområder [Liberty of choice and quality - models of settlements in the municipal service areas]. Ministry of Finance; 2003.

[37] Jakobsen M, Klausen E, Kolodziejczyk C. Omkostninger ved blodprop i hjernen og blødninger blandt patienter med atrieflimren i Danmark - en registerbaseret 'cost of illness'-analyse [The costs of stroke and hemorrhages amongst patients with atrial fibrillation - a register-based cost of illness. Copenhagen: KORA; 2014.

[38] Agency for Modernisation - Ministry of Finance. Levetider [Service lives]. Den Økonomiske Adm Vejl [Economic Adm Instr 2018. https://modst.dk/oekonomi/oeav/regnskabsregler/generelle-bogfoeringsbestemmelser/levetider/ (accessed November 7, 2018).

[39] Ministry of Finance. Den samfundsøkonomiske diskonteringsrente [The economic discount rate] 2018:1–19.

[40] Van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Heal* 2012;15:708–15. doi:10.1016/j.jval.2012.02.008.

[41] The EuroQol Group. EQ-5D-5L Crosswalk Index Value Calculator for Windows 2018.

[42] Wittrup-Jensen KU, Lauridsen J, Pedersen KM, Gudex C. Generation of a Danish TTO value set for EQ-5D health states. *Scand J Public Health* 2009;37:459–66. doi:10.1177/1403494809105287.

[43] Sundhedsdatastyrelsen. Dødsårsagsregisteret (DAR) [Danish Registry of Causes of Death] n.d. https://sundhedsdatastyrelsen.dk/dar (accessed November 12, 2018).

[44] Gupta SK. Intention-to-treat concept: A review. *Perspect Clin Res* 2011;2:109. doi:10.4103/2229-

3485.83221.

[45] Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;338:b2393–b2393. doi:10.1136/bmj.b2393.

[46] Fergusson D. Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. *BMJ* 2002;325:652–4. doi:10.1136/bmj.325.7365.652.

[47] Nixon RM, Thompson SG. Methods for incorporating covariate adjustment, subgroup analysis and between-centre differences into cost-effectiveness evaluations. *Health Econ* 2005;14:1217–29. doi:10.1002/hec.1008.

[48] Frederix I, Vanderlinden L, Verboven A-S, Welten M, Wouters D, De Keulenaer G, et al. Long-term impact of a six-month telemedical care programme on mortality, heart failure readmissions and healthcare costs in patients with chronic heart failure. *J Telemed Telecare* 2018;0:1357633X1877463. doi:10.1177/1357633x18774632.

[49] Jiménez-Marrero S, Yun S, Cainzos-Achirica M, Enjuanes C, Garay A, Farre N, et al. Impact of telemedicine on the clinical outcomes and healthcare costs of patients with chronic heart failure and mid-range or preserved ejection fraction managed in a multidisciplinary chronic heart failure programme: A sub-analysis of the iCOR randomized trial. *J Telemed Telecare* 2018. doi:10.1177/1357633X18796439.

[50] Comín-Colet J, Enjuanes C, Verdú-Rotellar JM, Linas A, Ruiz-Rodriguez P, González-Robledo G, et al. Impact on clinical events and healthcare costs of adding telemedicine to multidisciplinary disease management programmes for heart failure: Results of a randomized controlled trial. *J Telemed Telecare* 2016;22:282–95. doi:10.1177/1357633X15600583.

[51] Liu SX, Xiang R, Lagor C, Liu N, Sullivan K. Economic Modeling of Heart Failure Telehealth Programs: When Do They Become Cost Saving? *Int J Telemed Appl* 2016;2016:1–9. doi:10.1155/2016/3289628.

[52] Cichosz SL, Udsen FW. Hejlesen OK. The impact of telehealth care on health-related quality of life of patients with heart failure: Results from the Danish TeleCare North heart failure trial. *J Telemed Telecare* [accepted April 2019].

[53] Pawson R, Tilley N. Realistic Evaluation. London: Sage; 1997.

Table 1. Participant baseline characteristics. P-values for differences have been evaluated by Student's t-test for continuous variables and Pearson's Chi-square test for binary and multinomial variables. *Variable has no missing values. COPD: Chronic Obstructive Pulmonary Disease, HF: Heart failure, NYHA: New York Heart Association.

Study population	Telehealthcare solution	Control group	Raw between-group difference	P-value for difference
No of patients, n (%)	134 (49 %)	140 (51 %)		
Age, mean (SD), y*	67.21 (11.51)	67.30 (11.78)	-0.09	0.95
Sex, female, %*	18.91 (n=24)	20.71 (n=29)	-1.8	0.56
Relationship status				0.14
- *Missing, %*	1.49 (n=2)	0.71 (n=1)		
- Living with somebody, %	75.76 (n=100)	67.63 (n=94)	8.13	
- Living alone, %	24.24 (n=32)	32.37 (n=45)	-8.13	
Education				0.67
- *Missing, %*	2.23 (n=3)	1.43 (n=2)		
- Primary (<3 years), %	65.65 (n=86)	68.12 (n=94)	-2.47	
- Secondary (>3 years), %	34.35 (n=45)	31.88 (n=44)	2.47	
Smoking, (yes)* %	23.31 (n=31)	17.14 (n=24)	6.17	0.20
Self-reported duration of HF				
- *Missing, %*	5.97 (n=8)	6.43 (n=9)		
- Mean (SD), y	5.27 (7.45)	5.47 (7.13)	-0.20	0.82
- Median, y	2	2	0	
NYHA score at baseline, mean (SD)	2.55 (0.69)	2.50 (0.61)	0.05	0.53
- *Missing, %*	4.48 (n=6)	5.00 (n=7)		
- NYHA class II, %	56.25 (n=72)	56.39 (n=75)	-0.14	
- NYHA class III, %	32.81 (n=42)	37.59 (n=50)	-5.41	
- NYHA class IV, %	10.94 (n=14)	6.02 (n=8)	4.92	
Self-reported comorbidity, %*	41.04 (n=55)	41.43 (n=58)	-0.39	0.95
- Diabetes, %	13.43 (n=18)	19.29 (n=27)	-5.86	0.19
- COPD, %	16.42 (n=22)	15.71 (n=22)	0.71	0.87

- Psychological disorder, %	2.24 (n=3)	2.14 (n=3)	0.10	0.96
- Musculoskeletal disorder, %	16.42 (n=22)	15.71 (n=22)	0.71	0.87
- Cancer, %	6.72 (n=9)	7.14 (n=10)	-0.42	0.89
Baseline EQ-5D-3L index score, mean (SD)	0.7073 (0.1514)	0.7078 (0.1465)	0	0.98
- *Missing, %*	5.22 (n=7)	0.7 (n=1)		
Baseline historical costs excl. municipality costs (£), mean (SD)*	18,587.52 (21,605.38)	19,560.00 (23,491.52)	-972.48	0.72
Baseline historical municipality costs (£), mean (SD)	122.24 (303.18)	479.88 (1585.97)	-357.64	0.07
- *Missing, %*	49. 25 (n=66)	50.71 (n=71)		

Table 2. Unadjusted mean costs per patient in the intervention group and the control group, respectively, partitioned into cost categories over the 12-month follow-up (2018 £). For all cost categories, data are complete except for the municipality costs of which 50% missing (N=137). The costs associated with the telehealthcare solution is based on deterministic estimates. SE: Standard error of the mean.

*Annuitized over a 5-year period with a discount rate of 4 per cent,

**Costs divided amongst the expected number of HF patients in the North Denmark Region (6700 patients).

***Costs divided amongst the expected number of HF and COPD patients in the North Denmark Region (10,500 patients[24]). See appendix B for further information.

	Mean costs (SE), £			
Cost category	Telehealthcare solution (n=134)	Control group (n=140)	Raw between-group difference (£)	P-value for difference
Hospital contacts				
- Hospitalizations	5055.13 (1027.31)	9063.65 (1217.95)	-4008.52	0.01
- Outpatient contacts	3163.53 (264.85)	4191.29 (644.82)	-1027.76	0.15
- Psychiatric outpatient contacts	13.72 (5.95)	62.46 (39.20)	-48.74	0.23
Primary care contacts	469.26 (44.37)	600.36 (40.43)	-131.10	0.03
Pharmacy purchases	972.25 (94.01)	1076.57 (81.31)	-104.32	0.40
Municipality costs (home care, rehabilitation, monitoring in relation to the telehealthcare solution, etc.)	681.61 (137.16)	1246.88 (461.78)	-565.27	0.25
Healthcare costs, excl. costs of the telehealthcare solution	10,355.50	16,241.21	-5,885.71	0.01
Costs of the telehealthcare solution, excl. costs of monitoring:				
Software development and support*/**	0.27	0	0.27	

Basic operation: surveillance, support of health professionals, server licenses, etc***	8.47	0	8.47	
Running development of apps, system updates, etc. ***	1.76	0	1.76	
Education of health care professionals*/**	3.04	0	3.04	
Telekit, including initial delivery and patient education*	122.36	0	122.36	
Annual operational costs: licenses, sim card data, substitution of faulty equipment, etc.	82.15	0	82.15	
Total costs (incl. costs of the telehealthcare solution)	10,573.55	16,241.21	-5,667.66	0.01

Table 3. Incremental costs (£) and quality-adjusted life years after 12-month follow-up. CI: confidence interval, QALYs: Quality-adjusted life-years.

*Estimated based on an expected cost-effectiveness threshold of £20,000 per QALY.

**Seemingly unrelated regression, adjustment for group allocation, age, gender, baseline EQ-5D-3L summary score, total costs in the year preceding the study start date, self-reported NYHA classification at baseline, the self-reported length of HF diagnosis, education level, relationship status, and the presence of self-reported smoking, diabetes mellitus, psychological disorder, COPD, cancer, and musculoskeletal disorder.

***Seemingly unrelated regression with intervention group as the only predictor.

Scenario	N	Incremental costs, £ (95% CI)	Incremental QALYs (95% CI)	Net monetary benefit, £*
Primary analysis, adjusted**	274	-5095.92 [-8736.33; -1455.51]	0.0034 [-0.0712; 0.0780]	5163.98
Primary analysis, unadjusted***	274	-5539.10 [-9483.26; -1594.95]	-0.0005 [-0.0723; 0.0714]	5530.04
Scenario I:				
Complete case analysis, adjusted**	89	-1609.85 [-7036.27; 3816.57]	-0.0239 [-0.0605; 0.0127]	1131.62
Complete case analysis, unadjusted***	94	-2752.84 [-8438.59; 2932.91]	-0.0157 [-0.0536; 0.0221]	3570.69
Scenario II:				
Incl. NYHA class I patients, adjusted**	295	-4572.69 [-8030.66; -1114.73]	-0.0037 [-0.0736; 0.0663]	4498.88
Incl. NYHA class I patients, unadjusted***	295	-4857.43 [-8587.98; -1126.88]	-0.0061 [-0.0730; 0.0609]	4736.20
Scenario III:				
Excl. top 10th percentile resource-heavy patients, leaving out municipality costs, adjusted**	247	-3060.50 [-4836.08; -1284.93]	-0.0096 [-0.0949; 0.0756]	2867.62

Excl. top 10th percentile resource-heavy patients, leaving out municipality costs, unadjusted***	247	-3181.34 [-5103.28; -1259.40]	-0.0130 [-0.0944; 0.0683]	2921.12

Figure 1. Flowchart of exclusion of patients for the economic evaluation.

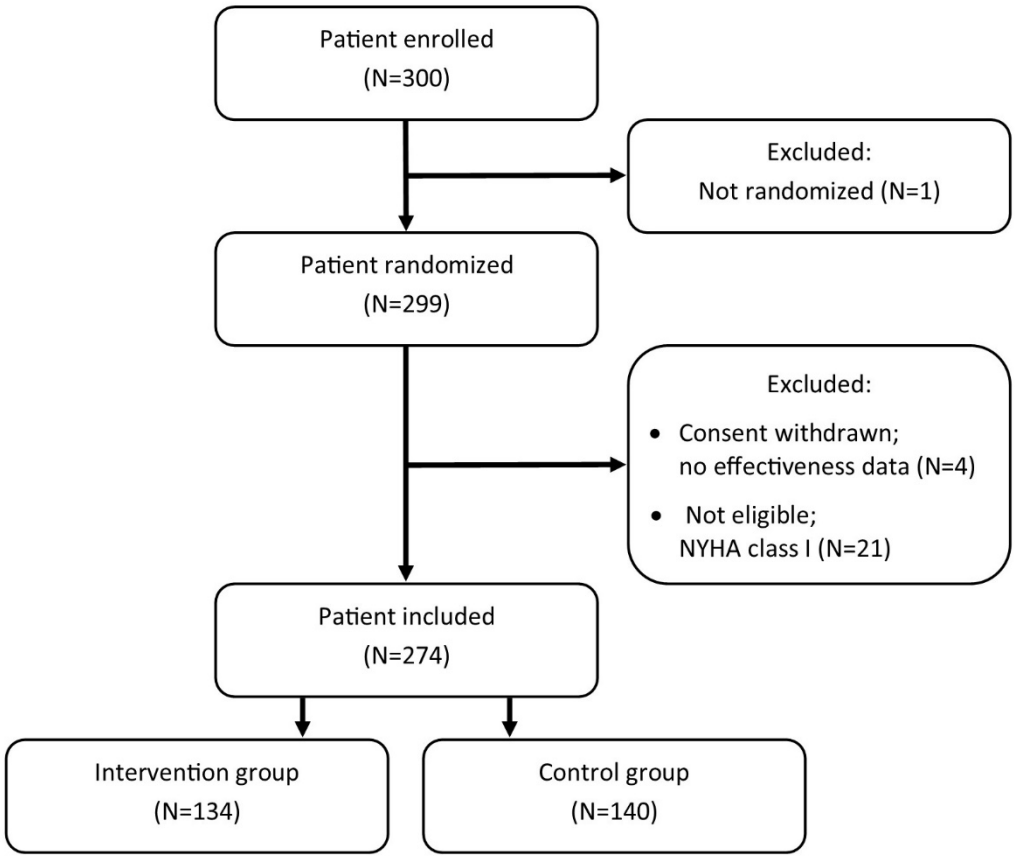
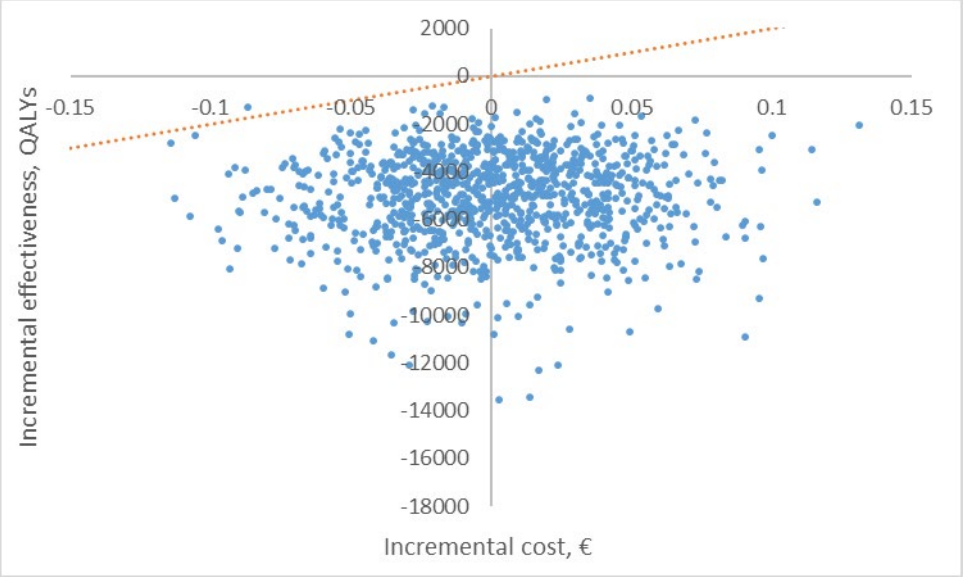


Figure 2. Incremental cost-effectiveness scatter plot based on the probabilistic sensitivity analysis. The dotted line indicates a cost-effectiveness threshold of £20,000 per quality-adjusted life year.



Appendix A.

Detailed information regarding the Danish TeleCare North Heart Failure Trial[25]. ACE: angiotensin-converting enzyme, HF: Heart failure, NYHA: New York Heart Association.

Trial characteristics	
Study characteristics	A multi-center, two-arm parallel group, unblinded, superiority study comparing a telehealthcare intervention to the usual practice in a Danish setting (the North Denmark Region). The study was executed in the period Jan 2016 to March 2018 with a follow-up of approximately 12 months; actual follow-up differed between participants due to continuous enrollment. The predetermined sample size was 316 participants under an expected loss to follow-up of 10 %, giving 284 participants. The estimate was based on an expected change equal to 5 for the SF-36 physical component summary score (effect measure applied in the effectiveness evaluation) indicating statistical significance with a two-sided *p*-value of <0.05, a power of 80%, equal-sized groups, and a standard deviation of 15%. Two hundred ninety-nine participants were enrolled; 35% were lost in follow-up (23 participants withdrew their consent, 15 died, and 67 did not respond).
Eligibility criteria	All patients were considered eligible who had a diagnosis of HF[7], a NYHA classification of II-IV, and who were expected to benefit from telehealthcare. In addition, patients should exhibit motivation for participating in the study and the use of telehealthcare, as evaluated by healthcare professionals. Furthermore, patients should have permanent residence, have a landline or mobile phone, and be able to speak Danish or live with a relative speaking Danish. Comorbidity was not considered a reason for

	exclusion. Clinical staff were responsible for identifying potential participants, and patient participation was voluntary.
Control group	
Usual care	Participants in the control group received usual care as provided in real-life practice to HF patients in the North Denmark Region, including monitoring, care, and, if necessary, treatment. As part of usual care, in the North Denmark Region, HF patients are offered rehabilitation consisting of screening for risk factors and dietary advice (if necessary) amongst other potential lifestyle changes that may be beneficial in relation to their disease, training, and medication review in response to patients' health (e.g. evaluation of prescriptions of ACE inhibitors, beta-blockers, spironolactone, etc.). The rehabilitation period usually lasts three to six months. Usual care is managed by general practitioners or outpatient clinics.
Intervention group	
Healthcare provision intervention	Before the start-up of the trial, several meetings were held to inform different staff groups of the trial and to provide general competency development on the management of HF. The trial administration office behind the TeleCare North HF was in charge of the meetings and educational seminars: - Project managers, key persons, and health care professionals expected to be involved in the implementation of the trial participated in kick-off information meetings - General practitioners received information on the trial and telehealthcare solution in after-work meetings

	- Regional and municipality nurses participated in an educational seminar and received initial and follow-up education on the use of the Telekit and the associated monitoring system (Open Tele) - Regional nurses participated in an educational seminar on rehabilitation - Specialist nursing professionals who worked with telemedicine from municipalities and HF outpatient clinics participated in educational seminars on palliation - Meetings were held, providing municipality nurses and health care assistants with general competency development on the management of HF, specifically on the monitoring responsibility in relation to the trial. The responsibility for the monitoring was shared between educated municipality nurses in the participants' residing municipality. The responsible parties were to incorporate the monitoring into their normal job duties. The monitoring included assessment and evaluation of measurements and was performed asynchronously on a weekly or biweekly basis. After the assessment, an acknowledgment of assessment was transmitted to the patient. If physical measurements were outside predefined thresholds (systolic blood pressure 100-170 mmHg, diastolic blood pressure 90-50 mmHg, pulse 80-55 beats per minute, and weight ±2 kg compared to baseline), the nurses had the option to 1) contact the patient to ensure the accuracy of the measurement or have the measurement replicated, if necessary, 2) contact the patient to assess his/her condition, 3) start a self-treatment plan for the patient, 4) ask the patient to contact his/her own general practitioner if considered suitable, and 5)

	establish rapport with the patient's general practitioner directly. Measurements were classified as being within or outside the normal ranges.
Patient-level intervention	After randomization, participants in the intervention group were contacted by phone by a nurse from their residing municipality, and an appointment was made on whether the patient would like to receive the Telekit in their home or a municipality health center. If the patient wanted to receive the Telekit at home, a 45-min appointment was made at which time an educated municipality nurse would demonstrate the use of the tablet and how to make the physical measurements using the associated equipment. If the participants wanted to participate in a group session of 3-4 persons at the municipality center to be introduced to the use of the equipment, the session would be 75 min long. Participants were asked to use the blood pressure monitor and scale daily in the two first weeks of the trial. 2-4 weeks after the first appointment, a follow-up appointment of 45 min was made with participants to ensure that they used the Telekit correctly. Instructions on the use of the Telekit were handled by municipality nurses.
Device characteristics; Telekit	In the trial, the Telekit consisted of a tablet (Samsung Galaxy Tab 2, incl. a target stylus) and associated equipment. The equipment consisted of a digital blood pressure monitor (UA-767 Plus BT-C, A&D Medical, Tokyo, Japan) and a scale with automatic Bluetooth connection to the tablet (UC-321 PBT-C, A&D Medical, Tokyo, Japan). The tablet automatically reminded the patients to take measurements and transmitted the information to enable asynchronous monitoring by healthcare professionals. In addition, the participants received an information package including a welcome letter, a user manual, and various patient information leaflets.

	Delivery and replacement of faulty equipment were performed by the supplier (Atea Denmark, Aalborg, Denmark), and support and maintenance were managed by a specialized support center.

Appendix B.

Detailed information on the cost estimates associated with the telehealthcare solution.

Assumptions		**Elaboration**	**Reference**
Number of heart failure patients in Denmark	66,000	Estimate from 2014 based on registrations in the Danish National Patient Registry.	[4]
Number of heart failure patients in the North Denmark Region	6700	Cross-country prevalence, expected to be equal, though the North Denmark Region is known to have a lower registered prevalence. Per 2017, approximately one-tenth of the Danish population resided in the North Denmark Region.	[4]
Number of heart failure patients and patients with chronic obstructive pulmonary disease in the North Denmark Region	10,500	Estimate applied in the TeleCare North COPD trial.	[24]
Overhead and development costs may be allocated to more patients			
One-time start-up costs are annuitized		Under the expectation that the intervention will be used over a more extended period, i.e., the lifetime of the equipment	
Technology lifetime	5	Used for annuitization	[38]
Discount rate	0.04	The socio-economic discount rate	[39]
Annuity factor given a lifetime of 5 years and a discount rate of 0.04	4.4518	Annual costs = K/annuity factor	[26]
Annuitized cost items		Software development costs + support in relation to heart failure, education of healthcare professionals, Telekit including instructions.	
Conversion rate DKKR to £	8.2718	DKKR8.2719 per £1 per 31 December 2018	[29]
Use of effective hourly wages		'præsteret time' in Statistics Denmark - the combined earnings in relation to the job: the basic earnings incl. holiday allowances, holiday and public holiday payments, pensions, benefits in kind, nuisance compensations, etc. but excluding holidays, free hours of public holidays, absence due to sickness, children's sickness, parental leave, etc. Used to estimate the payers' hourly expenses of having the employee.' Approximation of the effective hourly wage, in accordance with good practice in economic evaluation to use effective hours.	[26,35]
Costs of respite care, daily expense 2018	£156.74	Estimated from annual expenses assessed in 2002. Indexed to represent 2018 using the consumer price index.	

Wage estimate	£ (2018)	Assumption	Reference
Municipality nurse without managerial responsibility	£37.16	statistikbanken.dk - LONS20 // earnings per hour performed // 2221 nursing work without managerial responsibility in municipalities // salaried and hourly paid // 2017 (222110 in DISCO-08)	[35]
Municipality nurse with managerial responsibility	£46.39	statistikbanken.dk - LONS20 // earnings per hour performed // 2221 nursing work w managerial responsibility in municipalities // salaried and hourly paid // 2017 (222110 in DISCO-08)	[35]
Regional nurse without managerial responsibility	£37.03	statistikbanken.dk - LONS20 // earnings per hour performed // 2221 nursing work without managerial responsibility in regions // salaried and hourly paid // 2017 (222110 in DISCO-08)	[35]
Regional nurse with managerial responsibility	£46.57	statistikbanken.dk - LONS20 // earnings per hour performed // 2221 nursing work w managerial responsibility in regions // salaried and hourly paid // 2017 (222110 in DISCO-08)	[35]
Physician with managerial responsibility, the Regions	£82.64	statistikbanken.dk - LONS20 // earnings per hour performed // 2211 standard medical work w managerial responsibility in regions // salaried and hourly paid // 2017 (221100 in DISCO-08)	[35]
Physician without managerial responsibility, the Regions	£52.50	statistikbanken.dk - LONS20 // earnings per hour performed // 2211 standard medical work w/o managerial responsibility in regions // salaried and hourly paid // 2017 (221100 in DISCO-08)	[35]
Administrative manager within the public sector	£73.18	statistikbanken.dk - LONS20 // earnings per hour performed // 1213 management within public administration w managerial responsibility in regions // salaried and hourly paid // 2017 (121320 in DISCO-08)	[35]
Physiotherapist w/o managerial responsibility (the Regions and municipalities)	£34.98	statistikbanken.dk - LONS20 // earnings per hour performed // 2264 physiotherapist and relaxation therapists w/o managerial responsibility in municipalities and regions // salaried and hourly paid // 2017 (226410 in DISCO-08)	[35]

Software development costs + support in relation to HF	**£**	**Assumption**
2016 ATEA: planning and status meetings	£1878.35	Fixed cost, irrespective of the number of patients. Development of software and modification of hardware, support. It could be considered whether this should be allocated to all HF patients in DK and not the proportion in the North Denmark Region - cut to a tenth.
2016 OTH: new questionnaire	£1390.25	
2016 C-Innovation - info app	£2671.70	
2017 ATEA New MDM group comorbidity	£2130.71	
Total	£8071.00	
Total per patient given 6700 HF patients	**£1.20**	

Telekit incl. instructions	£	**Assumption**
Tablet Samsung Galaxy tab incl. charger	£197.78	Based on expected purchase price 2018. Original cost 2333
Cover	£18.13	
Digital blood pressure monitor, UA-767 Plus BTC w. 1 cuff Continua Certified	£139.02	
Scale	£15.71	Note: The expectation of having a normal non-Bluetooth connected scale in the future - precision is irrelevant. Original cost £184.36. Scale 200 kg UC-321 PBT-C, Continua Certificeret Blue Tooth. // New price estimate based on purchase price in stores.
Flightcase	£14.51	
Target stylus	£0.46	Original price £4.23. New offer, supplied to patients now.
User manual, welcome letter, patient leaflets	£2.42	
Instruction for use of the Telekit	£27.87	Performed by municipality nurses without managerial responsibility. Expectation of a 45 min session. Not included transport to and from the resident's home. Conservative estimate; otherwise in group sessions of 3-4 persons at the municipality health center of duration 75 minutes.

Follow-up appointment in use of the Telekit	£27.87	Performed by municipality nurses without managerial responsibility. Expectation of a 45-min session, not including transport to and from the resident's home.
Delivery by Atea	£100,94	Price paid
Total per patient	**£544,71**	

Education of health care professionals	**N, courses held**	**Duration, hours**	**Participants, N**	**Target group**	**Instructor**	**Valuation, participants**		**Valuation, instructor**		**Total cost**
						job function	**£**	**job function**	**£**	**£**
Kickoff meetings	4	1.5	88	Project managers, key persons, and health care professionals who will be affiliated with the TCN HF project	The steering committee and administrative office, TCN HF	Regional nurse w/managerial responsibility	46.57	Administrative manager within public sector	£73.18	£ 6220.54
Open Teleseminar	5	4.0	51	Regional and municipality nurses and other clinicians who are to use Open Tele and the Telekit in relation to TCN HF	Specialist nursing consultant (nurse)	Municipality nurse w/o managerial responsibility	37.16	Regional nurse w managerial responsibility	£46.57	£ 7626.62
Academic meeting	2	8.5	48	Municipal specialist nursing players with monitoring tasks in TCH HF	Regional ECG technician, staff physician, nurse	Municipality nurse w/o managerial responsibility	37.16	Physician w/managerial responsibility, regions	£82.64	£ 15242.74
Educational seminar	2	6.0	45	Regional and municipality nurses in TCN HF	2*Developmental consultant (nurse) spl. cand.mag. and spl. cand.cur.	Municipality nurse w/o managerial responsibility	37.16	Regional nurse w/managerial responsibility	£46.57	£10078.99
Project day about rehab.	1	3.0	41	Regional HF nurses	Municipality rehabilitation nurses	Regional nurse w/o managerial responsibility	37.03	Municipality nurse w/o managerial responsibility	£37.16	£4591.42

Project day about palliation	2	3.0	37	Specialist nursing players from HF ambulatories and municipalities	Nurse in the hospital (Cardiologic department, AAUH) and healthcare center, Aalborg	Municipality nurse w/o managerial responsibility	37.16	Regional nurse w/managerial responsibility	£46.57	£4171.01
After-work meetings, general practitioners	3	2.0	30	General practitioners and general practice workers	Staff physician, HF	Physician w/o managerial responsibility, regions	52.50	Physician w/managerial responsibility, regions	£82.64	£3232.38
Seminar on increasing competencies in HF	30	2.0	510	Municipality nurses working with HF	Municipality nurse	Municipality nurse w/o managerial responsibility	.37.16	Municipality nurse w/o managerial responsibility	£37.16	£37937.42
Follow-up education Open Tele	5	3.0	15	Regional and municipality nurses and other clinicians who are to use Open Tele and the Telekit in relation to TCH HF	Specialist nursing consultant (nurse)	Municipality nurse w/o managerial responsibility	37.16	Regional nurse w/managerial responsibility	£46.57	£1718.64

Basic operation, COPD + HF	**£**	**Assumption**
Server service in the North Denmark Region (hardware, licenses, surveillance, operation of shared services)	£45502.97	
Monitoring system, Open Tele Health, support and contingency arrangements, 2nd and 3rd level	£10154.86	
Support of health professionals performed by Frederikshavn municipality, 2nd level	£33245.08	Given 780 hours/year
Total	£88902.91	
Total, per patient given 10500 patients	**£8.47**	

Development costs and extra support	£	Assumption
ATEA: Development costs and extra support (RFCs, changes, apps, certificate expiration, etc)	£15727.40	Though not occurring each year, development costs, changes to IT systems, further requests for support, licenses, expiry of app useful life, etc., should be expected and are, therefore, included here. Related to 'extraordinary' operation that cannot be anticipated. If excluded, the costs related to running the system would be underestimated. // Running from August 2016 to November 2018 (28 months). Only annual costs are needed = (12/28 months) of total costs.
ATEA: Status meetings	£6392.12	
FRH: Extra support, first half of 2017	£9187.73	
OTH Development costs and extra support	£8846.21	
IT North Denmark Region, extra support hours, system update	£2961.83	
Total	£43115.31	
Total, per patient given 10500 patients	**£1.76**	

Operational costs	£	Assumption
ATEA: Substitution of faulty equipment	£0.56	£100.94 per 1 substitution per month in 180 users.
ATEA: Handling of assets, number in use + 30% (number of active units used)	£0.54	
ATEA: MDM License: number in use + 30% (number of active units used)	£2.82	
TCD: Simcard, data, number in use + 30% (number of active units in use)	£2.93	
Total per month	£6.85	
Total per patient per year	**£82.15**	

Appendix C.

Description of imputation approach in accordance with the methods described by Faria et al. [20].

At baseline, there were 2.92% missing values in the EQ-5D summary score (seven patients in the intervention group and one in the control group). Twenty-three (8.39%) participants died during the trial (ten in the intervention group and 13 in the control group) and were assigned an EQ-5D summary score of zero at the date of their death, which was used for interpolation in the estimation of the QALY gain. Furthermore, 90 participants had missing data in the follow-up EQ-5D summary score, either due to non-response or because of missingness in single components of the EQ-5D-5L questionnaire (43 patients in the intervention group and 47 in the control group). 50% had missing values in municipality costs (66 patients in the intervention group and 71 in the control group), whereas complete information existed on all other cost parameters for all patients (see Table 2). For patients who withdrew their consent during the trial, data collected up to the withdrawal date were included for analysis, and data that were to be collected after the withdrawal date was included as missing.

Complete data for both total costs and EQ-5D summary scores at baseline and follow-up were available for 89 patients. A sensitivity analysis was performed on complete cases only.

Based on a visual inspection of the pattern of missingness and regression analysis to evaluate the correlation between missingness and baseline variables, missing data at follow-up were assumed to be missing at random (MAR)[20]. Multiple imputations were used to account for missing values at both baseline and follow-up. It was assumed that the multiple imputations of baseline variables would not augment covariate imbalance substantially due to low missingness in most of the variables (see Table 2)[20].

Missingness in the baseline EQ-5D-5L summary score was mainly caused by missingness in the individual components of the EQ-5D questionnaire. For this reason, the imputation was performed on the level of the individual components at baseline. At follow-up, missingness of the EQ-5D-5L summary score was mainly caused by missingness of the entire follow-up questionnaire, so the imputation was performed for the summary score.

A combined imputation model using chained equations was generated for both costs and outcomes and was performed using the *mi impute chained (pmm,knn(5))* command in STATA15.1[43,44]. Continuous variables such as municipality cost and multinomial variables such as the individual components of the EQ-5D questionnaire at baseline were imputed using predictive mean matching with the k=5 nearest neighbors. Sixty complete datasets were generated. The imputation model included the outcome variables

themselves, predictors for the outcome variables, and predictors for missingness in the outcome variables. The imputation models were estimated separately for the intervention group and control group and included patients' sociodemographic characteristics (age, gender, relationship status, and level of education), the individual components of the EQ-5D questionnaire at baseline, the summary score of the EQ-5D-3L questionnaire at follow-up, patients' self-reported length of HF diagnosis, NYHA classification at baseline, presence of self-reported comorbidity (diabetes mellitus, COPD, psychological disorder, musculoskeletal disorder, cancer, or 'other'), self-reported smoking status (yes/no), total costs excluding municipality costs in the year preceding the study start date, municipality costs in the year preceding the study start date, total costs excluding municipality costs at follow-up, and municipality costs at follow-up (see Table 1).

Table

Table 1| **CHEERS checklist—Items to include when reporting economic evaluations of health interventions**

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	3
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	5
		Present the study question and its relevance for health policy or practice decisions.	6
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	6
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	6
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	6
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	6-7
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	7
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	9
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	10
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	6, 11
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	N.A.
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	10
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	8-10
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	N.A.
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	7,
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	11
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	N.A
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	10-12
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	12
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	12
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	12

BMJ 2013;346:f1049 doi: 10.1136/bmj.f1049 (Published 25 March 2013)

(continued)

Section/item	Item No	Recommendation	Reported on page No/ line No
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	N.A.
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	12
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	12-16
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	17
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	17

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist

BMJ Open

Is telehealthcare for heart failure patients cost-effective? An economic evaluation alongside the Danish TeleCare North Heart Failure trial.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-031670.R2
Article Type:	Original research
Date Submitted by the Author:	20-Nov-2019
Complete List of Authors:	Vestergaard, Anne; Aalborg Universitet, Department of Business and Management Hansen, Louise; Aalborg Universitet, Department of Business and Management Sørensen, Sabrina; Aalborg Universitet, Department of Business and Management Jensen, Morten; Aarhus University, Aarhus Business School Ehlers, Lars; Aalborg University, Danish Center for Healthcare Improvements, Department of Business and Management
Primary Subject Heading:	Health economics
Secondary Subject Heading:	Cardiovascular medicine
Keywords:	HEALTH ECONOMICS, Heart failure < CARDIOLOGY, Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS, Health informatics < BIOTECHNOLOGY & BIOINFORMATICS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Title page

Title:

Is telehealthcare for heart failure patients cost-effective? An economic evaluation alongside the Danish TeleCare North Heart Failure trial.

Authors:

- Anne Sig Sørensen (Vestergaard)[1], Ph.d
- Louise Hansen[1], Ph.d
- Sabrina Storgaard Sørensen[1], Ph.d
- Morten Berg Jensen[1,2], Ph.d
- Lars Holger Ehlers[1], Ph.d

Total word count: 4.441

Brief title: Cost-effectiveness of telehealthcare in HF

Affiliations:

[1]Danish Center for Healthcare Improvements, Dept. of Business and Management, Faculty of Social Sciences, Aalborg University, Aalborg, Denmark

[2]Department of Economics and Business Economics, Aarhus Business School, Aarhus University, Denmark

Address for correspondence

Lars Holger Ehlers

Aalborg University

Fibigerstraede 11, room 73

9220 Aalborg East

Denmark

Telephone: 0045 9940 8257

Fax: -

e-mail: lehlers@id.aau.dk

Suggested Keywords
Health Economics, Telemedicine, Heart Failure.

Abstract

Objective. This study aimed to assess the cost-effectiveness of telehealthcare in heart failure patients as add on to usual care.

Design. A cost-utility analysis was conducted from a public payer perspective alongside the randomized controlled TeleCare North trial.

Setting: The North Denmark Region, Denmark.

Participants: The study included 275 heart failure patients with self-reported NYHA class II-IV.

Interventions: Patients in the intervention group were provided with a Telekit consisting of a tablet, a digital blood pressure monitor, and a scale and were instructed to perform measurements 1-2 times a week. The responsibility of the education, instructions and monitoring of the HF patients was placed on municipality nurses trained in HF and telemonitoring. Both groups received usual care.

Outcome measures. Cost-effectiveness was reported as incremental net monetary benefit (NMB). A micro-costing approach was applied to evaluate the derived savings in the first year in the public health sector. Quality-adjusted life-years (QALY) gained were estimated using the EQ-5D-3L questionnaire at baseline and at a one-year follow-up.

Results. Data for 274 patients were included in the main analysis. The telehealthcare solution provided a positive incremental NMB of £5164. The one-year adjusted QALY difference between the telehealthcare solution and the usual care group was 0.0034 [95% CI: -0.0711; 0.0780]. The adjusted difference in costs was -£5096 [95%CI: -8736;-1456] corresponding to a reduction in total healthcare costs by 35%. All sensitivity analyses showed the main results were robust.

Conclusions. The TeleCare North solution for monitoring HF was highly cost-effective. There were significant costs savings on hospitalizations, primary care contacts, and total costs.

Article summary

Strengths and limitations of this study

This study should be relevant for decision-makers at the national healthcare level as well as at the clinical level.

It is the first economic evaluation of telehealthcare in heart failure patients that strictly follows international guidelines for health economic evaluation alongside clinical trials.

Precise assessment of the economic costs was allowed through patient specific data and detailed registration of operational as well as capital costs of telehealthcare.

No evidence was provided, however, on the long-term cost-effectiveness or on the explanation of what components of the intervention were actually effective or whether the effect was contingent on the intervention in its entirety.

Trial-based economic evaluations are limited by truncated time horizons, difficulty in generalizing to other settings, and failure to incorporate evidence from other trials or observational studies.

1. Introduction

Heart failure (HF) is a common chronic disease with an estimated global prevalence of approximately two percent[1–3]. In Denmark, approximately 9000 patients are diagnosed with HF each year. The incidence increases with higher age, and it has been estimated that one in five individuals will develop HF during their lifetime[2–4]. In total, the condition is conservatively estimated to affect approximately 66,000 citizens in Denmark, and about five percent of all Danish citizens above the age of 75 have been diagnosed with HF[4,5]. The prevalence of HF is, however, expected to rise in the future due to, amongst others, a higher prevalence of predisposing factors, such as hypertension, diabetes, and obesity but also due to the increased longevity of patients with HF, which is likely the result of an improved treatment of the condition[1,2,6].

HF symptoms include dyspnea, fatigue, lethargy, and edema[3,4]. The severity of patients' HF is often described according to the New York Heart Association (NYHA) functional classification system, which may be used by patients to classify the severity of their HF according to their own experience of the condition. Class I indicates that the condition does not limit physical activity and that ordinary activity does not cause any symptoms. In higher classes, the symptoms reported are increasingly more severe; thus, in class IV, patients cannot perform physical activity without experiencing symptoms, or they experience symptoms even at rest[3,7]. HF is believed to impair patients' health-related quality of life (HRQoL) compared to individuals without the condition, and the condition entails a substantially increased mortality[2,8–10]. In addition to the personal burden that HF entails, the condition also causes a substantial burden on health care systems worldwide, accounting for approximately two percent of total health care expenditures[2,11]. Hospitalizations are recognized as the primary driver for the total costs related to HF, though outpatient visits also constitute a substantial part[2,12].

In 2016, the European Society of Cardiology published updated guidelines for the diagnosis and treatment of acute and chronic HF[13], emphasizing the beneficial impact of continuous monitoring of, amongst others, biomedical parameters to enable the detection of the development of complications and disease progression that may prompt changes to patients' disease management. In the guidelines, telehealthcare is mentioned as a possible means of monitoring patients[13]. Evidence suggests that telehealthcare in different forms may be beneficial in the management of HF, both for the improvement of patients' HRQoL but also in the prevention of, for example, hospitalizations and all-cause mortality[14–16]. Findings, however, are inconsistent[13,17], which might be ascribed to the fact that the components of the investigated telehealthcare solutions differ. Effectively, this heterogeneity makes the various telehealthcare solutions incomparable in terms of their design, effectiveness and, consequently, cost-effectiveness [15–

17]. A number of reviews [16–18] have requested more high-quality studies of the health economic consequences of telehealthcare interventions. To our knowledge, however, up until now, no cost-effectiveness analysis of telehealthcare in HF patients have been conducted according to international good practice guidelines for the economic evaluation alongside clinical trials[19,20].

In Denmark, a national strategy has been formulated for the introduction of telehealthcare as a means of reducing healthcare costs while also providing patients with greater HRQoL and the feeling of improved control of their disease [21,22]. In this respect, the North Denmark Region has played a major role in the formulation of the national strategy by performing pre-launch, large-scale randomized controlled trials and health economic evaluations and national business cases as decision-support for the nationwide implementation[23,24]. In the wake of the first TeleCare North trial directed at patients suffering from chronic obstructive pulmonary disease (COPD), which was executed in 2014-2015[23,24], the TeleCare North Heart Failure (HF) trial was launched in 2016 with the purpose of evaluating the effectiveness and cost-effectiveness of a telehealthcare solution directed at patients with HF[25]. The purpose of this economic evaluation is to evaluate the cost-effectiveness of the TeleCare North HF solution, comparing the impact on costs and effects (i.e. quality-adjusted life years (QALYs)) with that of the usual practice for the treatment of HF in Denmark.

2. Methods

The cost-utility analysis was conducted in accordance with international guidelines for health economic evaluations alongside clinical trials[19,20,26]. All clinical and costs data for the analysis were collected alongside the TeleCare North HF trial, and the time horizon for the analysis was restricted to a one-year period. A Danish public healthcare sector perspective was applied, including costs accumulating under the auspices of the regional healthcare (i.e. pre-hospital services and inpatient and outpatient services in somatic and psychiatric healthcare), municipality-based health and social care (e.g. home care services and rehabilitation), and primary healthcare (e.g. general practice and physiotherapy) and costs associated with purchases of prescription medicine at Danish pharmacies. Costs associated with patient- or relative-paid transportation and productivity costs were not included.

The trial protocol presenting the design of the TeleCare North HF Trial and associated economic evaluation has previously been published[25]. The participants in the intervention group received patient education and telehealthcare equipment for continuous monitoring of physiological measurements. Patients in the intervention group were provided with a Telekit consisting of a tablet, a digital blood pressure monitor, and

a scale, and were instructed to perform measurements 1-2 times a week. The responsibility of the education, instructions and monitoring of the HF patients was placed on municipality nurses trained in HF and telemonitoring. The nurses were given the authority to intervene and change medication if, for instance, measurements indicated a deterioration in the patient's health. The specialized nurses could contact the heart failure clinic at the central university hospital for guidance regarding specific patient issues. Patients in the control group received the usual care, where general practitioners were responsible for the monitoring of the patients (see the appendix A for elaboration).

The result of the economic evaluation is expressed as the incremental net monetary benefit (NMB) = ($\Delta QALY \times Rt - \Delta Cost$)[27], where ΔQALY is the incremental quality of life, and ΔCost is the incremental costs. Under the assumption of a cost-effectiveness threshold (Rt) of £20,000 per QALY gained, an incremental NMB > 0 indicates that the telehealthcare solution is cost-effective compared to the usual care [26].

The cost-effectiveness of the telehealthcare solution is estimated for a 12-month period starting 30 days after participant enrollment in the study. This 30-day 'blanking period' for both groups was introduced from the day of referral to accommodate that participants in the intervention group would only receive the telehealthcare solution belatedly compared to the referral date and therefore effectively did not receive any intervention in this period. The difference in follow-up length was accommodated for in the estimation of cost and effect accumulation by weighting the accumulation by the lengths of the follow-up of individual participants to represent a 12-month follow-up. The enrollment period started on September 1, 2016, and the follow-up period ended on March 4, 2018.

a. Cost accumulation

All costs are presented in 2018 values in British Pounds Sterling (£). The Danish consumer price index for health care products and services[28] was used to adjust the cost data from 2016 and 2017 to the price level in 2018. Costs were estimated in Danish Krone (DKK) and subsequently converted, based on a conversion rate of Danish Kroner (DKK) 827.19 per £100 from December 31, 2018[29].

i. Healthcare service use and healthcare costs

Patient-specific costs related to health care service use were estimated based on register data. In Denmark, all citizens are provided with a unique personal identification number at birth or immigration, which

enables the linkage of information from various registers at the individual level. Information on patients' gender, birthday, migration status, and vital status was retrieved from the Danish Civil Registration System[30].

Information on patients' use of prescription medicine was retrieved from the Danish National Prescription Registry. The costs related to prescription medicine were valued at pharmacy selling prices excluding VAT.

Patients' contacts with general practice were identified through the National Health Insurance Service Register[31,32]. The costs associated with the contacts to general practice are registered in the registry and based on fees quoted in a collective agreement negotiated with the Danish Medical Association[33].

Information on patient hospitalizations was retrieved from the Danish National Patient Registry, which holds information on all inpatient, outpatient, and emergency hospitalizations in somatic and psychiatric wards in Denmark[34]. In the registry, each contact is valued according to the designated diagnosis-related group used for reimbursement, the actual procedures performed, and the length of stay in relation to the contact.

Estimates of the resource consumption of community care services in the municipalities were based on detailed registrations from four of the 11 contributory municipalities (the administrative units for tax-financed local health and social care). For patients in both groups, registrations included all local care activities, such as personal care, practical help, home nursing, rehabilitation, and telehealthcare activities. To increase generalizability to other settings in Denmark, the registered time consumption for standard care activities was valued using the national average effective hourly wage of the municipality nurses without managerial responsibility[35]. Time consumption in relation to rehabilitation consisting of physiotherapy was valued using the national average effective hourly wage of the municipality and regional physiotherapists without managerial responsibility[35]. Days of respite care in relation to rehabilitation were valued according to the estimated expenses of a day in care homes (see appendix B) [36,37].

Information on trial participants' health care service use and health care costs was retrieved for 12 months following their individual study startup date (30 days after the date of their enrollment). Information on health service use and health care costs was retrieved for the participants from 12 months before the study start date for each participant to control for differences in health care utilization before the start of the intervention.

i. Telehealthcare intervention costs

The administrative office for TeleCare North provided a detailed registration of all intervention costs (see appendix B). Capital costs included the development of software and hardware modifications for the Telekit, the delivery of and the Telekit itself, and one-time start-up costs related to the education of patients and healthcare professionals. In the analysis, capital costs were annuitized over a period of five years with a discount rate of four per cent per annum and included as equivalent annual costs. The useful equipment lifetime and applied discount rate are in accordance with what applies for 'other IT equipment' in Danish capital accounting[38,39]. Operational costs included, among other things, maintenance, support, and licenses. The daily work with continuous monitoring of the patients was included in the municipalities' registrations of healthcare service use and healthcare costs described above.

Software development and hardware configuration were valued as prices paid to an external supplier, reflecting actual tenders. The Telekit was valued based on the expected purchase price if the intervention were to be implemented and used in real-life practice following the results of the TeleCare North HF trial. The delivery of hardware, running costs related to licenses, handling of assets, data charges, and substitution of malfunctioning equipment were valued as the price negotiated and paid to the external supplier.

Before the trial, various meetings and educational seminars were held to train healthcare professionals in the use of the telehealthcare solution and monitoring duties and to increase their general knowledge on the management of HF, rehabilitation, and palliation. Participants in these meetings and seminars included general practitioners and regional and municipality nurses. In addition, meetings were held informing project managers, key persons, and healthcare professionals on the telehealthcare solution and the implementation of the intervention. The per-patient costs of educating health care professionals and others were estimated based on the planned time spent in the meetings, the number of participants at the meetings, and the average effective hourly wage of the participants. The applied average effective hourly wages were estimated based on national average wages to increase generalizability to the other Regions in Denmark[35].

Costs of modifications of the hardware, software development, and education for healthcare professionals and management staff were allocated to all HF patients who would be offered the telehealthcare solution in the North Denmark Region. The number of HF patients in the North Denmark Region was estimated to be 6700, given an estimated prevalence of 66,000 HF patients in Denmark[4] and that approximately 10% of the Danish population resides in the North Denmark Region.

The annual operational costs of telehealthcare were allocated to the estimated number of HF patients andother patients using the regional telehealth system in the North Denmark Region (10,500 patients[24]). The operational costs were valued as prices paid.

b. Measure of effectiveness

Information on patients' HRQoL was collected from questionnaires at baseline and at the end of the follow-up. Index scores for participants' HRQoL were estimated based on the EuroQol-5Dimensions-5Levels (EQ-5D-5L) questionnaire. Currently, however, there are no Danish societal weights estimated for the EQ-5D-5L questionnaire for which reason the responses in the EQ-5D-5L questionnaire were used to predict responses in the EuroQol-5Dimensions-3Levels (EQ-5D-3L) questionnaire by applying a response mapping approach[40,41]. Danish societal weights for the EQ-5D-3L questionnaire were subsequently applied[42]. Information on mortality was retrieved from the Danish Registry of Causes of Death, which holds information on all causes of death in Denmark. Information on participants' HRQoL and relevant demographic characteristics were collected at baseline at participant enrollment in the outpatient clinics or after the participant returned home, if preferred by the patient[25]. Irrespective of where the data were collected, the time of collection was dated to be 30 days after the date of their enrollment. At the end of the follow-up, the EQ-5D-5L questionnaire was sent in paper form to patients' home addresses from the trial administration office. A prepaid return envelope was included. The response was dated to the end of follow-up (March 4, 2018). [43].

Linear interpolation of the utility scores from baseline to follow-up was performed to estimate the QALY gain and was scaled to represent the QALY gain within one year. The utility score for patients who died during follow-up was set to zero at the time of death.

3. Analysis

a. Missing data management

In accordance with good research practice guidelines within effectiveness and cost-effectiveness studies, the primary analysis was performed according to the intention-to-treat principle and imputation was performed to account for missing data [19,20,44,45]. Imputations of missing data for the primary analysis was performed in accordance with the methods for multiple imputations described by Faria et al. [20]. A full description of the imputation approach is provided in the appendix C.

In total, 299 participants were enrolled in the trial (intervention group n=145, control group n=154) (see Figure 1). One patient was enrolled but was never randomized to any treatment group and, therefore, not included in the study. Four patients did not return questionnaires at either baseline or follow-up due to withdrawal shortly after enrollment for which reason no data were available on them except basic registry information. As no effectiveness data were available for these patients and they did, de facto, not participate in the study, they were excluded from analyses in accordance with guidelines on post-randomization exclusion[46]. Furthermore, 21 patients with a self-reported NYHA I classification were wrongfully included in the randomization. Given the eligibility criteria of the trial, these patients were excluded from the primary analysis. For the primary analysis, the intervention group included 134 patients, and the control group included 140 patients.

b. Cost-utility analysis

For descriptive statistics, all data are reported as means and standard errors, and differences in means between the intervention and the control group are presented as raw, unadjusted differences. *P* values for between-group differences have been evaluated by a Student's t-test for continuous variables and a Pearson's Chi-square test for binary and multinomial variables. Statistical significance was assumed for *P* values < 0.05, and all significance tests were two-tailed.

The estimates of incremental costs and QALYs between the intervention group and the control group were based on a seemingly unrelated regression analysis. This regression method is recommended and widely used in economic evaluation because cost and HRQoL is normally correlated[47]. In the primary analysis, both total costs and QALYs were adjusted for group allocation, age, gender, baseline EQ-5D-3L summary score, total costs in the year preceding the study start date, self-reported NYHA classification at baseline, the self-reported length of HF diagnosis at study start, education level, relationship status, and the presence of self-reported smoking, diabetes mellitus, psychological disorder, COPD, cancer, and musculoskeletal disorder. The estimations were performed using the *mi estimate, cmdok: sureg* command in STATA.

The deterministic incremental NMB was estimated using the treatment beta coefficients from the seemingly unrelated regressions, and a probabilistic sensitivity analysis was performed to evaluate the decision uncertainty. A scatter plot of incremental cost-effectiveness was generated based on 10,000 simulations. The simulations were based on random draws from the estimated treatment effect on cost

and QALY accumulation and their associated standard errors. The incremental costs were expected to assume a gamma distribution and the QALYs were expected to assume a Gaussian distribution.

All statistical analyses were performed in STATA, version 15.1.

c. Sensitivity analyses

Both the primary analysis and sensitivity analyses were performed with and without adjustment. For deterministic sensitivity analyses, three different scenarios were investigated;

Scenario I: A complete case analysis, that is, an analysis in which information on all outcome variables and variables used for adjustment were available.

Scenario II: An analysis including all patients that were enrolled in the study, including patients with a self-reported NYHA classification of I.

Scenario III: To evaluate whether results were driven by a minority of patients with very high resource consumption, a sensitivity analysis was performed in which the upper ten percent of patients with the highest resource consumption before imputation were excluded before imputation.

Scenario analysis II and III were both based on imputed data sets.

d. Patient and public involvement

Patient and public involvement in the project was organized by the TeleCare North project organization placed within the regional healthcare administration. This included open seminars/meetings with patients, relatives, health care providers, and others. A special homepage was designed with relevant information for patients and relatives, hospitals, municipalities, and general practitioners, respectively. The TeleCare North project organization also organized the development of the educational programs for patients and healthcare providers in all sectors. The research-based evaluation of the project was presented in public for all interested citizens free of charge. At the local political and public administrative levels, the project was followed and discussed in relevant fora with participation from all municipalities and the region.

4. Results

There were no statistically significant differences in baseline characteristics between the two groups, and missingness in variables was also fairly distributed between them (Table 1).

Within the one-year follow-up, the group receiving the telehealthcare solution had a consistently lower resource consumption across all health care cost categories compared to the group receiving usual care, leading to a total raw difference of -£5,668 (Table 2). Thus, the usage of telemedicine reduces total healthcare costs by 35% (5,668 off a base of 16,241 British pounds). This lower mean cost per patient was primarily driven by lower costs associated with hospitalizations (intervention group £5,055 vs. control group £9,064, *p*-value=0.01).

In the primary analysis, the one-year adjusted QALY difference between the telehealthcare solution and the usual care group was 0.0034 [95% CI: -0.0711; 0.0780], indicating an insignificant gain in HRQoL for patients receiving the telehealthcare solution (Table 3). The adjusted baseline utility score was similar across the two groups (0.7079 for control and 0.7075 for intervention). The mortality was similar between both groups, with 5 deaths in the control group and 7 deaths in the intervention group.

The adjusted difference in costs was -£5096 [95%CI: -8736; -1456], indicating a significantly lower total mean cost per patient in the telehealthcare solution group. Based on the incremental cost and QALY estimates and an assumed cost-effectiveness threshold of £20,000 per QALY[27], the telehealthcare solution provides a positive incremental NMB of £5164, indicating that the telehealthcare solution is cost-effective. The unadjusted analysis also indicates that the telehealthcare solution provides a significant cost saving (-£5539 [95% CI: -9483; -1595]) and an insignificant impact on patients' QALY gain (-0.0005 [95% CI: -0.0723; 0.0714]) and therefore is cost-effective (NMB = £5530). The result of the probabilistic sensitivity analysis is shown in the incremental cost-effectiveness scatter plot in Figure 2. The incremental cost-effectiveness distribution disperses across the southwest and southeast quadrant of the incremental cost-effectiveness plane in agreement with the QALY gain associated with the telehealthcare solution being insignificant but the incremental negative cost being significant.

All scenario analyses showed the same result with telehealthcare associated with lower costs and an insignificant impact on patients' health-related quality of life (Table 3). Across the adjusted and unadjusted sensitivity analyses, the cost-effectiveness result is relatively robust, with all analyses indicating a positive incremental NMB of the telehealthcare solution compared to usual practice.

5. Discussion

The principal finding of this study is that the investigated telehealthcare solution is highly cost-effective for the treatment of HF patients in the Danish setting. High-quality economic evaluations of telehealthcare solutions in the management of HF have been requested[16–18] and, to our knowledge, the present study is the first economic evaluation of telehealthcare in HF patients that strictly follows international guidelines for health economic evaluation alongside clinical trials[19]. Thus, a particular strength of this study was the micro-costing approach, including the availability of information on patient-specific resource usage from the Danish registers. The majority of information on patients' resource consumption was retrieved from well-validated Danish registers, ensuring the validity of the registrations with no missing data in these parameters. For the resource consumption in the municipalities, data from four out of the 11 participatory municipalities were applicable. The four municipalities were relatively large (making for approximately 50% of the total participant sample), and thus, the representativeness of their organization and consequently costs for smaller municipalities is debatable. However, municipality costs only constitute a minor share of the total costs (cf. Table 3); for which reason it could be suspected that even if the estimate of municipality costs is not representative for all participatory municipalities, the cost-effectiveness conclusion would not be markedly affected.

In the present cost-utility analysis, the impact on patients' QALY gain was insignificant across all analyses. The increased sensitivity, which could have been achieved by using the 5L questionnaire[19], may effectively have been watered down when predicting the 3L responses from the 5L responses and applying the 3L weights. This might provide an explanation of why it was not possible to observe any substantial differences in QALY accumulation between the two intervention groups, which could otherwise have been expected given findings in previous studies[16].

In general, telehealthcare interventions and the studies of them are relatively heterogeneous, making a comparison of them difficult[15,16]. In a Cochrane review from 2015[16], structured telephone support and telemonitoring for HF patients were found to reduce all-cause mortality and HF-related hospitalizations. In addition, the impact on patients HRQoL and cost accumulation was inconsistent, emphasizing the difficulties of evaluating and comparing the cost-effectiveness of telehealthcare interventions aggregately.[16]

Only a few papers report on cost savings in relation to telehealthcare within this field. These studies do not have economic evaluation as their primary aim and do not strictly follow proper practice guidelines for economic evaluations[19,26]. Nevertheless, they all point in the same direction of potentially huge savings

[16–18]. Frederix et al.[48] reported insignificant long-term savings of approximately 27% from an initial 6-month telehealthcare intervention. Jiménez-Morrero et al.[49] report savings of approximately 38% for a subgroup of HF patients with a left ventricular ejection fraction >40. Comín-Colet et al. [50] report savings of approximately 45%, mainly driven by a significant reduction in hospitalizations between the telehealthcare group and control group. An economic modeling study by Liu et al. [51] also points in the same direction of possible savings from telehealthcare interventions directed at intermediate- and high-risk patients over a 1- to 5-year window. Their results suggest the economic viability of telehealthcare programs for the management of chronic HF, but emphasized the importance of risk stratification in such programs[51]. In our study, however, the severity of HF did not seem to be important, as there appeared to be only minor differences in cost savings depending on whether patients reporting being in NYHA class I were included or not. A particular difference between our study and other studies may also have been the level of organizational learning and knowledge management, as the TeleCare North trial builds upon many years of experience with telehealthcare solutions from previous trials[23,24] as well as the national implementation of telehealth program for COPD in Denmark decided in 2015[22].

As the design of the TeleCare North HF trial and the components of the telehealthcare intervention was somewhat similar to that of the TeleCare North COPD trial[23,25], the present study anticipated that the economic evaluation would essentially produce results similar to that of Udsen et al.[24]. In agreement with the economic evaluation by Udsen et al.[24], no significant difference in QALY accumulation between the intervention groups was observed in this study. In contrast, the present study found telehealthcare to produce substantial cost savings, which contrasts with the added costs associated with telehealthcare found by Udsen et al.[24]. The difference is that telehealthcare is cost-effective for HF patients but not all COPD patients. This discrepancy indicates that the cost-effectiveness of telehealthcare interventions, to a large degree, depends on the recipient patient group, making it difficult to comment on the cost-effectiveness of telehealthcare interventions as a whole. The characteristics of specific patient groups ought, therefore, to be incorporated when telehealthcare interventions are designed and implemented.

The impact of the TeleCare North solution of patients Qol measured with the Short-Form 36 (SF-36) questionnaire's physical and mental component summary scores and the Kansas City Cardiomyopathy Questionnaire 12 score are published elsewhere[52]. It was only possible to detect a small but significant positive change in the SF-36 mental component summary score. Thus, with respect to the impact on patients' HRQoL, the telehealthcare solution cannot be characterized as an unqualified success. It could, however, be hypothesized that the currently applied methods of measurement of effect are too insensitive to detect any beneficial impact especially on patients' mental well-being, as suggested by the positive

impact on the SF-36 mental component summary score but none of the other measures. It is possible that the positive impact of telehealthcare does not manifest itself as an impact on patients' HRQoL but rather their opinions and beliefs, which subsequently affects their healthcare-seeking behavior.

Given the complexity and multiple purposes of the intervention under investigation[25], it is possible that conventional measures of effectiveness, such as HRQol and QALY, do not sufficiently capture all potential effects. It is possible that impacts on other parameters could have been observed, such as patients' satisfaction, self-perceived risk of dying, comfort, ability to reduce anxiety through telephone contact with a well-known local nurse, and an increased sense of capability among others. It could be considered whether the slightly narrow focus on patients' HRQoL and QALY in the present analysis represent an appropriate evaluation approach to this particular kind of complex intervention.

Though the present economic evaluation found the telehealthcare solution to be highly cost-effective, questions remain as to why this result was achieved. Thus, it remains unclear what components of the intervention were actually effective or whether the effect is contingent on the intervention in its entirety. In the design phase of future trials on the effectiveness and cost-effectiveness of complex interventions such as telehealthcare, early consideration of mechanisms of action and programme theory [53] ought to be introduced to improve our understanding of why some interventions may prove effective and cost-effective and others not. This may increase the cost-effectiveness of future telehealth solutions.

Acknowledgments: The authors would like to thank all of the participants in TeleCare North Heart Failure for their time and effort when filling out questionnaires and reporting physical measurements. Likewise, a thank you goes out to all healthcare professionals involved in the execution of the trial, the North Denmark Region, and the municipalities for their goodwill in making this trial possible. A special thank you to Kuno Strand Kudajewski, project manager for the TeleCare North Heart Failure Trial at the North Denmark Region for helping with information on cost data and for proof-reading the manuscript, and to Simon Lebech Cichosz for the lengthy keying of the EQ-5D questionnaire data.

Author contributions: LHE is the primary investigator for economic evaluation in the TeleCare North Heart Failure Trial; LHE planned the design of the economic evaluation and stands as a guarantor of the statistical quality for the evaluation as a whole. LHE, LH, MBJ, SSS and ASV contributed equally to the detailed planning and design of the analyses in the economic evaluation. LH was mainly responsible for data management. All analyses were performed by collaboration by all authors, and ASV drafted the paper in collaboration with the other authors. All authors had full access to the data and accept responsibility for the integrity of the data and the data analyses. All authors met regularly during the data analysis period and contributed equally to the interpretation and presentation of data. All authors reviewed and approved the manuscript prior to submission.

Ethics: The trial has been authorized by the Danish Data Protection Agency. The study is being conducted in accordance with the Helsinki declaration. The trial has been presented to the Ethical Committee for Medical Research in the North Denmark Region; this committee decided that no ethical approval was necessary.

Trial registration number: ClinicalTrials.gov: NCT02860013

Competing interests: None

Funding: The study was funded by the Danish Agency for Digitalisation under the Danish Ministry of Finance the North Denmark Region.

Patient content: not required

Data statement: no additional data available

Figures legends:

Figure 1. Flowchart of exclusion of patients for the economic evaluation.

Figure 2. Incremental cost-effectiveness scatter plot based on the probabilistic sensitivity analysis. The dotted line indicates a cost-effectiveness threshold of £20,000 per quality-adjusted life year.

References

[1] Savarese G, Lund LH. Global Public Health Burden of Heart Failure. *Card Fail* Rev 2017;03:7. doi:10.15420/cfr.2016:25:2.

[2] Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. *Nat Rev Cardiol* 2011;8:30–41. doi:10.1038/nrcardio.2010.165.

[3] Inamdar A, Inamdar A. Heart Failure: Diagnosis, Management and Utilization. *J Clin Med* 2016;5:62. doi:10.3390/jcm5070062.

[4] Madelaire C, Gislason G. Hjertesvigt i Danmark 2017 - socioøkonomiske forskelle i forekomst, dødelighed og behandling [Heart Failure in Denmark 2017 - socioeconomic differences in prevalence, mortality, and treatment]. 2017.

[5] Dansk Selskab for Almen Medicin. Kronisk hjertesvigt/kronisk systolisk hjerteinsufficiens [Chronic heart failure/chronic systolic heart failure]. *DSAM Guidel* 2013. https://vejledninger.dsam.dk/hjerteinsufficiens/?mode=visKapitel&cid=597&gotoChapter=597 (accessed November 7, 2018).

[6] Roger VL. Epidemiology of Heart Failure. *Circ Res* 2013;113:646–59. doi:10.1161/CIRCRESAHA.113.300268.

[7] Dansk Cardiologisk Selskab. Behandlingsvejledning, 5. Kronisk hjertesvigt [Treatment Guidelines, Chronic Heart Failure] 2017. https://www.cardio.dk/chf#55-behandling (accessed November 16, 2018).

[8] Polikandrioti M. Health Failure and Health Related Quality of Life. *Heal Sci J* 2008;3:119–20.

[9] Juenger J, Schellberg D, Kraemer S, Haunstetter A, Zugck C, Herzog W, et al. Health related quality of life in patients with congestive heart failure: comparison with other chronic diseases and relation to functional variables. *Heart* 2002;87:235–41. doi:10.1136/heart.87.3.235.

[10] Comín-Colet J, Anguita M, Formiga F, Almenar L, Crespo-Leiro MG, Manzano L, et al. Health-related Quality of Life of Patients With Chronic Systolic Heart Failure in Spain: Results of the VIDA-IC Study. *Rev Española Cardiol* (English Ed 2016;69:256–71. doi:10.1016/j.rec.2015.07.030.

[11] Shafie AA, Tan YP, Ng CH. Systematic review of economic burden of heart failure. *Heart Fail Rev* 2018;23:131–45. doi:10.1007/s10741-017-9661-0.

[12] Brorholt G, Jakobsen M, Hauge AM, Kjellberg Med Bidrag Fra J, Grønbaek M, Terkelsen CJ, et al. En helhjertet indsats – En artikelbaseret klinisk, patientnær og sundhedsøkonomisk kortlægning af hjerte-kar-området [A whole-hearted effort - a paper-based clinical, patient-relevant and health economic survey of the cardiovascular area]. København K: 2018.

[13] Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2016;37:2129–200. doi:10.1093/eurheartj/ehw128.

[14] Bashi N, Karunanithi M, Fatehi F, Ding H, Walters D. Remote Monitoring of Patients With Heart Failure: An Overview of Systematic Reviews. *J Med Internet Res* 2017;19:e18. doi:10.2196/jmir.6571.

[15] Dierckx R, Inglis SC, Clark RA, Prieto-Merino D, Cleland JGF. Telemedicine in heart failure: new insights from the Cochrane meta-analyses. *Eur J Heart Fail* 2017;19:304–6. doi:10.1002/ejhf.759.

[16] Inglis SC, Clark RA, Dierckx R, Prieto-Merino D, Cleland JG. Structured telephone support or non-invasive telemonitoring for patients with heart failure. Cochrane Database Syst Rev 2015. doi:10.1002/14651858.CD007228.pub3.

[17] Gensini GF, Alderighi C, Rasoini R, Mazzanti M, Casolo G. Value of Telemonitoring and Telemedicine in Heart Failure Management. *Card Fail Rev* 2017;3:1. doi:10.15420/cfr.2017:6:2.

[18] Grustam AS, Severens JL, van Nijnatten J, Koymans R, Vrijhoef HJM. Cost-effectiveness of telehealth interventions for chronic heart failure patients: A literature review. *Int J Technol Assess Health Care* 2014;30:59–68. doi:10.1017/S0266462313000779.

[19] Ramsey SD, Willke RJ, Glick H, Reed SD, Augustovski F, Jonsson B, et al. Cost-effectiveness analysis alongside clinical trials II - An ISPOR good research practices task force report. *Value Heal* 2015;18:161–72. doi:10.1016/j.jval.2015.02.001.

[20] Faria R, Gomes M, Epstein D, White IR. A Guide to Handling Missing Data in Cost-Effectiveness Analysis Conducted Within Randomised Controlled Trials. *Pharmacoeconomics* 2014;32:1157–70. doi:10.1007/s40273-014-0193-3.

[21] Digitaliseringsstyrelsen. Telemedicin - en nøgle til fremtidens sundhedsydelser. National handlingsplan for udbredelse af telemedicin - kort fortalt [Telehealthcare - a key to future healthcare services. A national action plan for the introduction of telehealthcare - in brief]. København K: 2012.

[22] Sundhedsdatastyrelsen. Telemedicin og telesundhed [Telemedicine and telehealth] 2018. https://sundhedsdatastyrelsen.dk/da/rammer-og-retningslinjer/telemedicin-og-telesundhed (accessed December 21, 2018).

[23] Udsen FW, Lilholt PH, Hejlesen O, Ehlers LH. Effectiveness and cost-effectiveness of telehealthcare for chronic obstructive pulmonary disease: Study protocol for a cluster randomized controlled trial. *Trials* 2014;15:1–7. doi:10.1186/1745-6215-15-178.

[24] Witt Udsen F, Lilholt PH, Hejlesen O, Ehlers L. Cost-effectiveness of telehealthcare to patients with chronic obstructive pulmonary disease: results from the Danish 'TeleCare North' cluster-randomised trial. *BMJ* Open 2017;7:e014616. doi:10.1136/bmjopen-2016-014616.

[25] Cichosz SL, Ehlers LH, Hejlesen O. Health effectiveness and cost-effectiveness of telehealthcare for heart failure: Study protocol for a randomized controlled trial. *Trials* 2016;17:4–9. doi:10.1186/s13063-016-1722-5.

[26] Drummond MF, Schulpher M, Claxton K, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. 4th ed. Oxford: Oxford University Press; 2015.

[27] Devlin N, Parkin D. Does NICE have a cost-effectiveness threshold and what other factors influence its decisions? A binary choice analysis. *Health Econ* 2004;13:437–52. doi:10.1002/hec.864.

[28] Statistics Denmark. Pris111: Consumer price index ((2015=100) by commodity group and unit 2018. http://www.statistikbanken.dk/PRIS8 (accessed December 5, 2018).

[29] EUROinvestor. Valutakurser [Exchange rates] 2018. https://www.valutakurser.dk/ (accessed February 15, 2019).

[30] Schmidt M, Pedersen L, Sørensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014:541–9. doi:10.1007/s10654-014-9930-3.

[31] Sundhedsdatastyrelsen. Sygesikringsregisteret (SSR) [National Health Insurance Service Register] 2017. https://sundhedsdatastyrelsen.dk/da/registre-og-services/om-de-nationale-sundhedsregistre/sundhedsoekonomi-og-finansiering/sygesikringsregisteret (accessed November 20, 2018).

[32] Sahl Andersen J, De Fine Olivarius N, Krasnik A. The Danish national health service register. *Scand J Public Health* 2011;39:34–7. doi:10.1177/1403494810394718.

[33] Danish Medical Association. Honorartabel 01-10-2018 [Fee table 2018-10-01] 2018.

https://www.laeger.dk/sites/default/files/honorartabel_2018_oktober_web.pdf.

[34] Schmidt M, Schmidt SAJ, Sandegaard JL, Ehrenstein V, Pedersen L, Sørensen HT. The Danish National Patient Registry: A review of content, data quality, and research potential. *Clin Epidemiol* 2015;7:449–90. doi:10.2147/CLEP.S91125.

[35] Statistics Denmark. Statistikbanken - LONS20: Løn efter arbejdsfunktion, sektor, aflønningsform, lønmodtagergruppe, lønkomponenter og køn [Statistikbanken - LONS20: Wages estimated based on job function, sector, payment form, employment group, wage component and gender]○ 2018. http://statistikbanken.dk/statbank5a/default.asp?w=1920 (accessed November 19, 2018).

[36] Ministry of Finance. Frit valg og kvalitet - afregningsmodeller på de kommunale serviceområder [Liberty of choice and quality - models of settlements in the municipal service areas]. Ministry of Finance; 2003.

[37] Jakobsen M, Klausen E, Kolodziejczyk C. Omkostninger ved blodprop i hjernen og blødninger blandt patienter med atrieflimren i Danmark - en registerbaseret 'cost of illness'-analyse [The costs of stroke and hemorrhages amongst patients with atrial fibrillation - a register-based cost of illness. Copenhagen: KORA; 2014.

[38] Agency for Modernisation - Ministry of Finance. Levetider [Service lives]. Den Økonomiske Adm Vejl [Economic Adm Instr 2018. https://modst.dk/oekonomi/oeav/regnskabsregler/generelle-bogfoeringsbestemmelser/levetider/ (accessed November 7, 2018).

[39] Ministry of Finance. Den samfundsøkonomiske diskonteringsrente [The economic discount rate] 2018:1–19.

[40] Van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: Mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Heal* 2012;15:708–15. doi:10.1016/j.jval.2012.02.008.

[41] The EuroQol Group. EQ-5D-5L Crosswalk Index Value Calculator for Windows 2018.

[42] Wittrup-Jensen KU, Lauridsen J, Pedersen KM, Gudex C. Generation of a Danish TTO value set for EQ-5D health states. *Scand J Public Health* 2009;37:459–66. doi:10.1177/1403494809105287.

[43] Sundhedsdatastyrelsen. Dødsårsagsregisteret (DAR) [Danish Registry of Causes of Death] n.d. https://sundhedsdatastyrelsen.dk/dar (accessed November 12, 2018).

[44] Gupta SK. Intention-to-treat concept: A review. *Perspect Clin Res* 2011;2:109. doi:10.4103/2229-

3485.83221.

[45] Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;338:b2393–b2393. doi:10.1136/bmj.b2393.

[46] Fergusson D. Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. *BMJ* 2002;325:652–4. doi:10.1136/bmj.325.7365.652.

[47] Nixon RM, Thompson SG. Methods for incorporating covariate adjustment, subgroup analysis and between-centre differences into cost-effectiveness evaluations. *Health Econ* 2005;14:1217–29. doi:10.1002/hec.1008.

[48] Frederix I, Vanderlinden L, Verboven A-S, Welten M, Wouters D, De Keulenaer G, et al. Long-term impact of a six-month telemedical care programme on mortality, heart failure readmissions and healthcare costs in patients with chronic heart failure. *J Telemed Telecare* 2018;0:1357633X1877463. doi:10.1177/1357633x18774632.

[49] Jiménez-Marrero S, Yun S, Cainzos-Achirica M, Enjuanes C, Garay A, Farre N, et al. Impact of telemedicine on the clinical outcomes and healthcare costs of patients with chronic heart failure and mid-range or preserved ejection fraction managed in a multidisciplinary chronic heart failure programme: A sub-analysis of the iCOR randomized trial. *J Telemed Telecare* 2018. doi:10.1177/1357633X18796439.

[50] Comín-Colet J, Enjuanes C, Verdú-Rotellar JM, Linas A, Ruiz-Rodriguez P, González-Robledo G, et al. Impact on clinical events and healthcare costs of adding telemedicine to multidisciplinary disease management programmes for heart failure: Results of a randomized controlled trial. *J Telemed Telecare* 2016;22:282–95. doi:10.1177/1357633X15600583.

[51] Liu SX, Xiang R, Lagor C, Liu N, Sullivan K. Economic Modeling of Heart Failure Telehealth Programs: When Do They Become Cost Saving? *Int J Telemed Appl* 2016;2016:1–9. doi:10.1155/2016/3289628.

[52] Cichosz SL, Udsen FW. Hejlesen OK. The impact of telehealth care on health-related quality of life of patients with heart failure: Results from the Danish TeleCare North heart failure trial. *J Telemed Telecare* [accepted April 2019].

[53] Pawson R, Tilley N. Realistic Evaluation. London: Sage; 1997.

Table 1. Participant baseline characteristics. P-values for differences have been evaluated by Student's t-test for continuous variables and Pearson's Chi-square test for binary and multinomial variables. *Variable has no missing values. COPD: Chronic Obstructive Pulmonary Disease, HF: Heart failure, NYHA: New York Heart Association.

Study population	Telehealthcare solution	Control group	Raw between-group difference	P-value for difference
No of patients, n (%)	134 (49 %)	140 (51 %)		
Age, mean (SD), y*	67.21 (11.51)	67.30 (11.78)	-0.09	0.95
Sex, female, %*	18.91 (n=24)	20.71 (n=29)	-1.8	0.56
Relationship status				0.14
- *Missing, %*	1.49 (n=2)	0.71 (n=1)		
- Living with somebody, %	75.76 (n=100)	67.63 (n=94)	8.13	
- Living alone, %	24.24 (n=32)	32.37 (n=45)	-8.13	
Education				0.67
- *Missing, %*	2.23 (n=3)	1.43 (n=2)		
- Primary (<3 years), %	65.65 (n=86)	68.12 (n=94)	-2.47	
- Secondary (>3 years), %	34.35 (n=45)	31.88 (n=44)	2.47	
Smoking, (yes)* %	23.31 (n=31)	17.14 (n=24)	6.17	0.20
Self-reported duration of HF				
- *Missing, %*	5.97 (n=8)	6.43 (n=9)		
- Mean (SD), y	5.27 (7.45)	5.47 (7.13)	-0.20	0.82
- Median, y	2	2	0	
NYHA score at baseline, mean (SD)	2.55 (0.69)	2.50 (0.61)	0.05	0.53
- *Missing, %*	4.48 (n=6)	5.00 (n=7)		
- NYHA class II, %	56.25 (n=72)	56.39 (n=75)	-0.14	
- NYHA class III, %	32.81 (n=42)	37.59 (n=50)	-5.41	
- NYHA class IV, %	10.94 (n=14)	6.02 (n=8)	4.92	
Self-reported comorbidity, %*	41.04 (n=55)	41.43 (n=58)	-0.39	0.95
- Diabetes, %	13.43 (n=18)	19.29 (n=27)	-5.86	0.19
- COPD, %	16.42 (n=22)	15.71 (n=22)	0.71	0.87

- Psychological disorder, %	2.24 (n=3)	2.14 (n=3)	0.10	0.96
- Musculoskeletal disorder, %	16.42 (n=22)	15.71 (n=22)	0.71	0.87
- Cancer, %	6.72 (n=9)	7.14 (n=10)	-0.42	0.89
Baseline EQ-5D-3L index score, mean (SD)	0.7073 (0.1514)	0.7078 (0.1465)	0	0.98
- *Missing, %*	5.22 (n=7)	0.7 (n=1)		
Baseline historical costs excl. municipality costs (£), mean (SD)*	18,587.52 (21,605.38)	19,560.00 (23,491.52)	-972.48	0.72
Baseline historical municipality costs (£), mean (SD)	122.24 (303.18)	479.88 (1585.97)	-357.64	0.07
- *Missing, %*	49. 25 (n=66)	50.71 (n=71)		

Table 2. Unadjusted mean costs per patient in the intervention group and the control group, respectively, partitioned into cost categories over the 12-month follow-up (2018 £). For all cost categories, data are complete except for the municipality costs of which 50% missing (N=137). The costs associated with the telehealthcare solution is based on deterministic estimates. SE: Standard error of the mean.

*Annuitized over a 5-year period with a discount rate of 4 per cent,

**Costs divided amongst the expected number of HF patients in the North Denmark Region (6700 patients).

***Costs divided amongst the expected number of HF and COPD patients in the North Denmark Region (10,500 patients[24]). See appendix B for further information.

	Mean costs (SE), £			
Cost category	Telehealthcare solution (n=134)	Control group (n=140)	Raw between-group difference (£)	P-value for difference
Hospital contacts				
- Hospitalizations	5055.13 (1027.31)	9063.65 (1217.95)	-4008.52	0.01
- Outpatient contacts	3163.53 (264.85)	4191.29 (644.82)	-1027.76	0.15
- Psychiatric outpatient contacts	13.72 (5.95)	62.46 (39.20)	-48.74	0.23
Primary care contacts	469.26 (44.37)	600.36 (40.43)	-131.10	0.03
Pharmacy purchases	972.25 (94.01)	1076.57 (81.31)	-104.32	0.40
Municipality costs (home care, rehabilitation, monitoring in relation to the telehealthcare solution, etc.)	681.61 (137.16)	1246.88 (461.78)	-565.27	0.25
Healthcare costs, excl. costs of the telehealthcare solution	10,355.50	16,241.21	-5,885.71	0.01
Costs of the telehealthcare solution, excl. costs of monitoring:				
Software development and support*/**	0.27	0	0.27	

Basic operation: surveillance, support of health professionals, server licenses, etc***	8.47	0	8.47	
Running development of apps, system updates, etc. ***	1.76	0	1.76	
Education of health care professionals*/**	3.04	0	3.04	
Telekit, including initial delivery and patient education*	122.36	0	122.36	
Annual operational costs: licenses, sim card data, substitution of faulty equipment, etc.	82.15	0	82.15	
Total costs (incl. costs of the telehealthcare solution)	10,573.55	16,241.21	-5,667.66	0.01

Table 3. Incremental costs (£) and quality-adjusted life years after 12-month follow-up. CI: confidence interval, QALYs: Quality-adjusted life-years.

*Estimated based on an expected cost-effectiveness threshold of £20,000 per QALY.

**Seemingly unrelated regression, adjustment for group allocation, age, gender, baseline EQ-5D-3L summary score, total costs in the year preceding the study start date, self-reported NYHA classification at baseline, the self-reported length of HF diagnosis, education level, relationship status, and the presence of self-reported smoking, diabetes mellitus, psychological disorder, COPD, cancer, and musculoskeletal disorder.

***Seemingly unrelated regression with intervention group as the only predictor.

Scenario	N	Incremental costs, £ (95% CI)	Incremental QALYs (95% CI)	Net monetary benefit, £*
Primary analysis, adjusted**	274	-5095.92 [-8736.33; -1455.51]	0.0034 [-0.0712; 0.0780]	5163.98
Primary analysis, unadjusted***	274	-5539.10 [-9483.26; -1594.95]	-0.0005 [-0.0723; 0.0714]	5530.04
Scenario I:				
Complete case analysis, adjusted**	89	-1609.85 [-7036.27; 3816.57]	-0.0239 [-0.0605; 0.0127]	1131.62
Complete case analysis, unadjusted***	94	-2752.84 [-8438.59; 2932.91]	-0.0157 [-0.0536; 0.0221]	3570.69
Scenario II:				
Incl. NYHA class I patients, adjusted**	295	-4572.69 [-8030.66; -1114.73]	-0.0037 [-0.0736; 0.0663]	4498.88
Incl. NYHA class I patients, unadjusted***	295	-4857.43 [-8587.98; -1126.88]	-0.0061 [-0.0730; 0.0609]	4736.20
Scenario III:				
Excl. top 10th percentile resource-heavy patients, leaving out municipality costs, adjusted**	247	-3060.50 [-4836.08; -1284.93]	-0.0096 [-0.0949; 0.0756]	2867.62

Excl. top 10th percentile resource-heavy patients, leaving out municipality costs, unadjusted***	247	-3181.34 [-5103.28; -1259.40]	-0.0130 [-0.0944; 0.0683]	2921.12

Figure 1. Flowchart of exclusion of patients for the economic evaluation.

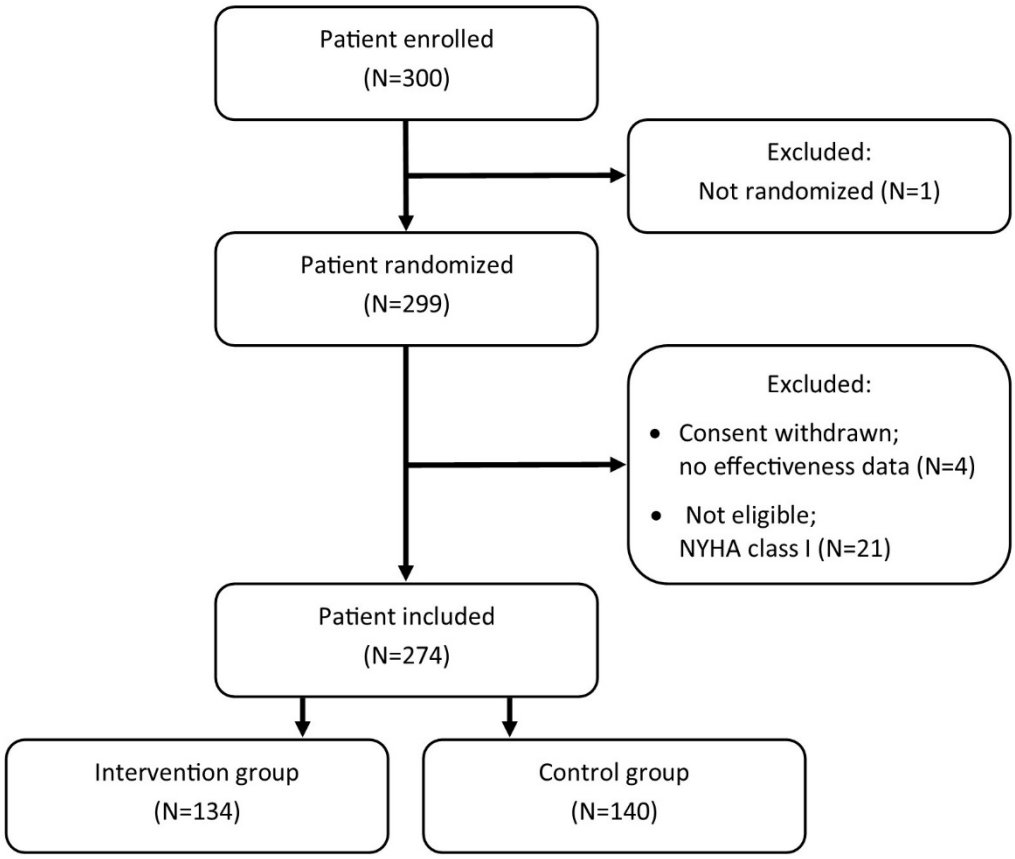
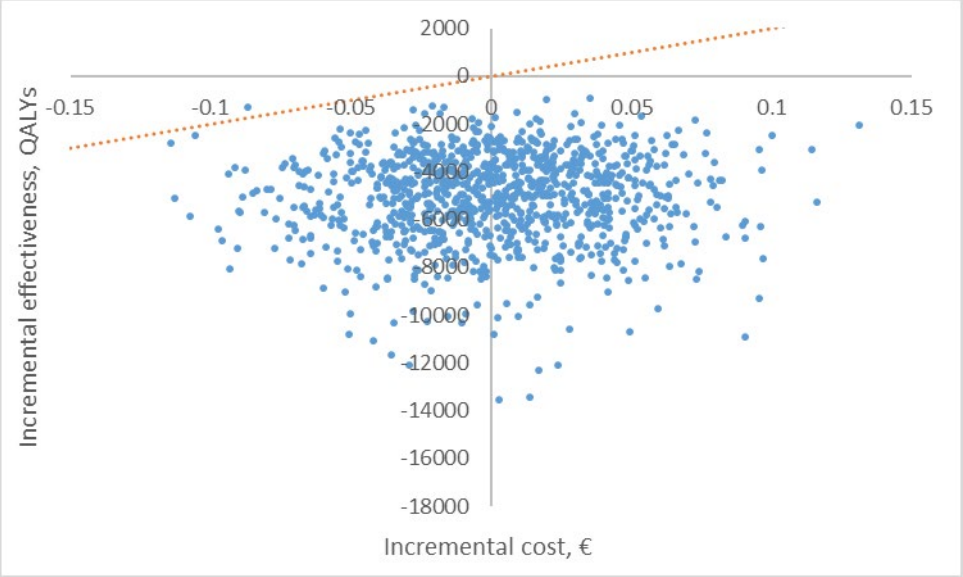


Figure 2. Incremental cost-effectiveness scatter plot based on the probabilistic sensitivity analysis. The dotted line indicates a cost-effectiveness threshold of £20,000 per quality-adjusted life year.



Appendix A.

Detailed information regarding the Danish TeleCare North Heart Failure Trial[25]. ACE: angiotensin-converting enzyme, HF: Heart failure, NYHA: New York Heart Association.

Trial characteristics	
Study characteristics	A multi-center, two-arm parallel group, unblinded, superiority study comparing a telehealthcare intervention to the usual practice in a Danish setting (the North Denmark Region). The study was executed in the period Jan 2016 to March 2018 with a follow-up of approximately 12 months; actual follow-up differed between participants due to continuous enrollment. The predetermined sample size was 316 participants under an expected loss to follow-up of 10 %, giving 284 participants. The estimate was based on an expected change equal to 5 for the SF-36 physical component summary score (effect measure applied in the effectiveness evaluation) indicating statistical significance with a two-sided *p*-value of <0.05, a power of 80%, equal-sized groups, and a standard deviation of 15%. Two hundred ninety-nine participants were enrolled; 35% were lost in follow-up (23 participants withdrew their consent, 15 died, and 67 did not respond).
Eligibility criteria	All patients were considered eligible who had a diagnosis of HF[7], a NYHA classification of II-IV, and who were expected to benefit from telehealthcare. In addition, patients should exhibit motivation for participating in the study and the use of telehealthcare, as evaluated by healthcare professionals. Furthermore, patients should have permanent residence, have a landline or mobile phone, and be able to speak Danish or live with a relative speaking Danish. Comorbidity was not considered a reason for

	exclusion. Clinical staff were responsible for identifying potential participants, and patient participation was voluntary.
Control group	
Usual care	Participants in the control group received usual care as provided in real-life practice to HF patients in the North Denmark Region, including monitoring, care, and, if necessary, treatment. As part of usual care, in the North Denmark Region, HF patients are offered rehabilitation consisting of screening for risk factors and dietary advice (if necessary) amongst other potential lifestyle changes that may be beneficial in relation to their disease, training, and medication review in response to patients' health (e.g. evaluation of prescriptions of ACE inhibitors, beta-blockers, spironolactone, etc.). The rehabilitation period usually lasts three to six months. Usual care is managed by general practitioners or outpatient clinics.
Intervention group	
Healthcare provision intervention	Before the start-up of the trial, several meetings were held to inform different staff groups of the trial and to provide general competency development on the management of HF. The trial administration office behind the TeleCare North HF was in charge of the meetings and educational seminars: - Project managers, key persons, and health care professionals expected to be involved in the implementation of the trial participated in kick-off information meetings - General practitioners received information on the trial and telehealthcare solution in after-work meetings

	- Regional and municipality nurses participated in an educational seminar and received initial and follow-up education on the use of the Telekit and the associated monitoring system (Open Tele) - Regional nurses participated in an educational seminar on rehabilitation - Specialist nursing professionals who worked with telemedicine from municipalities and HF outpatient clinics participated in educational seminars on palliation - Meetings were held, providing municipality nurses and health care assistants with general competency development on the management of HF, specifically on the monitoring responsibility in relation to the trial. The responsibility for the monitoring was shared between educated municipality nurses in the participants' residing municipality. The responsible parties were to incorporate the monitoring into their normal job duties. The monitoring included assessment and evaluation of measurements and was performed asynchronously on a weekly or biweekly basis. After the assessment, an acknowledgment of assessment was transmitted to the patient. If physical measurements were outside predefined thresholds (systolic blood pressure 100-170 mmHg, diastolic blood pressure 90-50 mmHg, pulse 80-55 beats per minute, and weight ±2 kg compared to baseline), the nurses had the option to 1) contact the patient to ensure the accuracy of the measurement or have the measurement replicated, if necessary, 2) contact the patient to assess his/her condition, 3) start a self-treatment plan for the patient, 4) ask the patient to contact his/her own general practitioner if considered suitable, and 5)

	establish rapport with the patient's general practitioner directly. Measurements were classified as being within or outside the normal ranges.
Patient-level intervention	After randomization, participants in the intervention group were contacted by phone by a nurse from their residing municipality, and an appointment was made on whether the patient would like to receive the Telekit in their home or a municipality health center. If the patient wanted to receive the Telekit at home, a 45-min appointment was made at which time an educated municipality nurse would demonstrate the use of the tablet and how to make the physical measurements using the associated equipment. If the participants wanted to participate in a group session of 3-4 persons at the municipality center to be introduced to the use of the equipment, the session would be 75 min long. Participants were asked to use the blood pressure monitor and scale daily in the two first weeks of the trial. 2-4 weeks after the first appointment, a follow-up appointment of 45 min was made with participants to ensure that they used the Telekit correctly. Instructions on the use of the Telekit were handled by municipality nurses.
Device characteristics; Telekit	In the trial, the Telekit consisted of a tablet (Samsung Galaxy Tab 2, incl. a target stylus) and associated equipment. The equipment consisted of a digital blood pressure monitor (UA-767 Plus BT-C, A&D Medical, Tokyo, Japan) and a scale with automatic Bluetooth connection to the tablet (UC-321 PBT-C, A&D Medical, Tokyo, Japan). The tablet automatically reminded the patients to take measurements and transmitted the information to enable asynchronous monitoring by healthcare professionals. In addition, the participants received an information package including a welcome letter, a user manual, and various patient information leaflets.

	Delivery and replacement of faulty equipment were performed by the supplier (Atea Denmark, Aalborg, Denmark), and support and maintenance were managed by a specialized support center.

Appendix B.

Detailed information on the cost estimates associated with the telehealthcare solution.

Assumptions		**Elaboration**	**Reference**
Number of heart failure patients in Denmark	66,000	Estimate from 2014 based on registrations in the Danish National Patient Registry.	[4]
Number of heart failure patients in the North Denmark Region	6700	Cross-country prevalence, expected to be equal, though the North Denmark Region is known to have a lower registered prevalence. Per 2017, approximately one-tenth of the Danish population resided in the North Denmark Region.	[4]
Number of heart failure patients and patients with chronic obstructive pulmonary disease in the North Denmark Region	10,500	Estimate applied in the TeleCare North COPD trial.	[24]
Overhead and development costs may be allocated to more patients			
One-time start-up costs are annuitized		Under the expectation that the intervention will be used over a more extended period, i.e., the lifetime of the equipment	
Technology lifetime	5	Used for annuitization	[38]
Discount rate	0.04	The socio-economic discount rate	[39]
Annuity factor given a lifetime of 5 years and a discount rate of 0.04	4.4518	Annual costs = K/annuity factor	[26]
Annuitized cost items		Software development costs + support in relation to heart failure, education of healthcare professionals, Telekit including instructions.	
Conversion rate DKKR to £	8.2718	DKKR8.2719 per £1 per 31 December 2018	[29]
Use of effective hourly wages		'præsteret time' in Statistics Denmark - the combined earnings in relation to the job: the basic earnings incl. holiday allowances, holiday and public holiday payments, pensions, benefits in kind, nuisance compensations, etc. but excluding holidays, free hours of public holidays, absence due to sickness, children's sickness, parental leave, etc. Used to estimate the payers' hourly expenses of having the employee.' Approximation of the effective hourly wage, in accordance with good practice in economic evaluation to use effective hours.	[26,35]
Costs of respite care, daily expense 2018	£156.74	Estimated from annual expenses assessed in 2002. Indexed to represent 2018 using the consumer price index.	

Wage estimate	£ (2018)	Assumption	Reference
Municipality nurse without managerial responsibility	£37.16	statistikbanken.dk - LONS20 // earnings per hour performed // 2221 nursing work without managerial responsibility in municipalities // salaried and hourly paid // 2017 (222110 in DISCO-08)	[35]
Municipality nurse with managerial responsibility	£46.39	statistikbanken.dk - LONS20 // earnings per hour performed // 2221 nursing work w managerial responsibility in municipalities // salaried and hourly paid // 2017 (222110 in DISCO-08)	[35]
Regional nurse without managerial responsibility	£37.03	statistikbanken.dk - LONS20 // earnings per hour performed // 2221 nursing work without managerial responsibility in regions // salaried and hourly paid // 2017 (222110 in DISCO-08)	[35]
Regional nurse with managerial responsibility	£46.57	statistikbanken.dk - LONS20 // earnings per hour performed // 2221 nursing work w managerial responsibility in regions // salaried and hourly paid // 2017 (222110 in DISCO-08)	[35]
Physician with managerial responsibility, the Regions	£82.64	statistikbanken.dk - LONS20 // earnings per hour performed // 2211 standard medical work w managerial responsibility in regions // salaried and hourly paid // 2017 (221100 in DISCO-08)	[35]
Physician without managerial responsibility, the Regions	£52.50	statistikbanken.dk - LONS20 // earnings per hour performed // 2211 standard medical work w/o managerial responsibility in regions // salaried and hourly paid // 2017 (221100 in DISCO-08)	[35]
Administrative manager within the public sector	£73.18	statistikbanken.dk - LONS20 // earnings per hour performed // 1213 management within public administration w managerial responsibility in regions // salaried and hourly paid // 2017 (121320 in DISCO-08)	[35]
Physiotherapist w/o managerial responsibility (the Regions and municipalities)	£34.98	statistikbanken.dk - LONS20 // earnings per hour performed // 2264 physiotherapist and relaxation therapists w/o managerial responsibility in municipalities and regions // salaried and hourly paid // 2017 (226410 in DISCO-08)	[35]

Software development costs + support in relation to HF	**£**	**Assumption**
2016 ATEA: planning and status meetings	£1878.35	Fixed cost, irrespective of the number of patients. Development of software and modification of hardware, support. It could be considered whether this should be allocated to all HF patients in DK and not the proportion in the North Denmark Region - cut to a tenth.
2016 OTH: new questionnaire	£1390.25	
2016 C-Innovation - info app	£2671.70	
2017 ATEA New MDM group comorbidity	£2130.71	
Total	£8071.00	
Total per patient given 6700 HF patients	**£1.20**	

Telekit incl. instructions	£	**Assumption**
Tablet Samsung Galaxy tab incl. charger	£197.78	Based on expected purchase price 2018. Original cost 2333
Cover	£18.13	
Digital blood pressure monitor, UA-767 Plus BTC w. 1 cuff Continua Certified	£139.02	
Scale	£15.71	Note: The expectation of having a normal non-Bluetooth connected scale in the future - precision is irrelevant. Original cost £184.36. Scale 200 kg UC-321 PBT-C, Continua Certificeret Blue Tooth. // New price estimate based on purchase price in stores.
Flightcase	£14.51	
Target stylus	£0.46	Original price £4.23. New offer, supplied to patients now.
User manual, welcome letter, patient leaflets	£2.42	
Instruction for use of the Telekit	£27.87	Performed by municipality nurses without managerial responsibility. Expectation of a 45 min session. Not included transport to and from the resident's home. Conservative estimate; otherwise in group sessions of 3-4 persons at the municipality health center of duration 75 minutes.

Follow-up appointment in use of the Telekit	£27.87	Performed by municipality nurses without managerial responsibility. Expectation of a 45-min session, not including transport to and from the resident's home.
Delivery by Atea	£100,94	Price paid
Total per patient	**£544,71**	

Education of health care professionals	**N, courses held**	**Duration, hours**	**Participants, N**	**Target group**	**Instructor**	**Valuation, participants**		**Valuation, instructor**		**Total cost**
						job function	**£**	**job function**	**£**	**£**
Kickoff meetings	4	1.5	88	Project managers, key persons, and health care professionals who will be affiliated with the TCN HF project	The steering committee and administrative office, TCN HF	Regional nurse w/managerial responsibility	46.57	Administrative manager within public sector	£73.18	£ 6220.54
Open Teleseminar	5	4.0	51	Regional and municipality nurses and other clinicians who are to use Open Tele and the Telekit in relation to TCN HF	Specialist nursing consultant (nurse)	Municipality nurse w/o managerial responsibility	37.16	Regional nurse w managerial responsibility	£46.57	£ 7626.62
Academic meeting	2	8.5	48	Municipal specialist nursing players with monitoring tasks in TCH HF	Regional ECG technician, staff physician, nurse	Municipality nurse w/o managerial responsibility	37.16	Physician w/managerial responsibility, regions	£82.64	£ 15242.74
Educational seminar	2	6.0	45	Regional and municipality nurses in TCN HF	2*Developmental consultant (nurse) spl. cand.mag. and spl. cand.cur.	Municipality nurse w/o managerial responsibility	37.16	Regional nurse w/managerial responsibility	£46.57	£10078.99
Project day about rehab.	1	3.0	41	Regional HF nurses	Municipality rehabilitation nurses	Regional nurse w/o managerial responsibility	37.03	Municipality nurse w/o managerial responsibility	£37.16	£4591.42

Project day about palliation	2	3.0	37	Specialist nursing players from HF ambulatories and municipalities	Nurse in the hospital (Cardiologic department, AAUH) and healthcare center, Aalborg	Municipality nurse w/o managerial responsibility	37.16	Regional nurse w/managerial responsibility	£46.57	£4171.01
After-work meetings, general practitioners	3	2.0	30	General practitioners and general practice workers	Staff physician, HF	Physician w/o managerial responsibility, regions	52.50	Physician w/managerial responsibility, regions	£82.64	£3232.38
Seminar on increasing competencies in HF	30	2.0	510	Municipality nurses working with HF	Municipality nurse	Municipality nurse w/o managerial responsibility	.37.16	Municipality nurse w/o managerial responsibility	£37.16	£37937.42
Follow-up education Open Tele	5	3.0	15	Regional and municipality nurses and other clinicians who are to use Open Tele and the Telekit in relation to TCH HF	Specialist nursing consultant (nurse)	Municipality nurse w/o managerial responsibility	37.16	Regional nurse w/managerial responsibility	£46.57	£1718.64

Basic operation, COPD + HF	**£**	**Assumption**
Server service in the North Denmark Region (hardware, licenses, surveillance, operation of shared services)	£45502.97	
Monitoring system, Open Tele Health, support and contingency arrangements, 2nd and 3rd level	£10154.86	
Support of health professionals performed by Frederikshavn municipality, 2nd level	£33245.08	Given 780 hours/year
Total	£88902.91	
Total, per patient given 10500 patients	**£8.47**	

Development costs and extra support	£	Assumption
ATEA: Development costs and extra support (RFCs, changes, apps, certificate expiration, etc)	£15727.40	Though not occurring each year, development costs, changes to IT systems, further requests for support, licenses, expiry of app useful life, etc., should be expected and are, therefore, included here. Related to 'extraordinary' operation that cannot be anticipated. If excluded, the costs related to running the system would be underestimated. // Running from August 2016 to November 2018 (28 months). Only annual costs are needed = (12/28 months) of total costs.
ATEA: Status meetings	£6392.12	
FRH: Extra support, first half of 2017	£9187.73	
OTH Development costs and extra support	£8846.21	
IT North Denmark Region, extra support hours, system update	£2961.83	
Total	£43115.31	
Total, per patient given 10500 patients	**£1.76**	

Operational costs	£	Assumption
ATEA: Substitution of faulty equipment	£0.56	£100.94 per 1 substitution per month in 180 users.
ATEA: Handling of assets, number in use + 30% (number of active units used)	£0.54	
ATEA: MDM License: number in use + 30% (number of active units used)	£2.82	
TCD: Simcard, data, number in use + 30% (number of active units in use)	£2.93	
Total per month	£6.85	
Total per patient per year	**£82.15**	

Appendix C.

Description of imputation approach in accordance with the methods described by Faria et al. [20].

At baseline, there were 2.92% missing values in the EQ-5D summary score (seven patients in the intervention group and one in the control group). Twenty-three (8.39%) participants died during the trial (ten in the intervention group and 13 in the control group) and were assigned an EQ-5D summary score of zero at the date of their death, which was used for interpolation in the estimation of the QALY gain. Furthermore, 90 participants had missing data in the follow-up EQ-5D summary score, either due to non-response or because of missingness in single components of the EQ-5D-5L questionnaire (43 patients in the intervention group and 47 in the control group). 50% had missing values in municipality costs (66 patients in the intervention group and 71 in the control group), whereas complete information existed on all other cost parameters for all patients (see Table 2). For patients who withdrew their consent during the trial, data collected up to the withdrawal date were included for analysis, and data that were to be collected after the withdrawal date was included as missing.

Complete data for both total costs and EQ-5D summary scores at baseline and follow-up were available for 89 patients. A sensitivity analysis was performed on complete cases only.

Based on a visual inspection of the pattern of missingness and regression analysis to evaluate the correlation between missingness and baseline variables, missing data at follow-up were assumed to be missing at random (MAR)[20]. Multiple imputations were used to account for missing values at both baseline and follow-up. It was assumed that the multiple imputations of baseline variables would not augment covariate imbalance substantially due to low missingness in most of the variables (see Table 2)[20].

Missingness in the baseline EQ-5D-5L summary score was mainly caused by missingness in the individual components of the EQ-5D questionnaire. For this reason, the imputation was performed on the level of the individual components at baseline. At follow-up, missingness of the EQ-5D-5L summary score was mainly caused by missingness of the entire follow-up questionnaire, so the imputation was performed for the summary score.

A combined imputation model using chained equations was generated for both costs and outcomes and was performed using the *mi impute chained (pmm,knn(5))* command in STATA15.1[43,44]. Continuous variables such as municipality cost and multinomial variables such as the individual components of the EQ-5D questionnaire at baseline were imputed using predictive mean matching with the k=5 nearest neighbors. Sixty complete datasets were generated. The imputation model included the outcome variables

themselves, predictors for the outcome variables, and predictors for missingness in the outcome variables. The imputation models were estimated separately for the intervention group and control group and included patients' sociodemographic characteristics (age, gender, relationship status, and level of education), the individual components of the EQ-5D questionnaire at baseline, the summary score of the EQ-5D-3L questionnaire at follow-up, patients' self-reported length of HF diagnosis, NYHA classification at baseline, presence of self-reported comorbidity (diabetes mellitus, COPD, psychological disorder, musculoskeletal disorder, cancer, or 'other'), self-reported smoking status (yes/no), total costs excluding municipality costs in the year preceding the study start date, municipality costs in the year preceding the study start date, total costs excluding municipality costs at follow-up, and municipality costs at follow-up (see Table 1).

Table

Table 1| **CHEERS checklist—Items to include when reporting economic evaluations of health interventions**

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	3
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	5
		Present the study question and its relevance for health policy or practice decisions.	6
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	6
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	6
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	6
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	6-7
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	7
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	9
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	10
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	6, 11
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	N.A.
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	10
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	8-10
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	N.A.
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	7,
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	11
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	N.A
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	10-12
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	12
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	12
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	12

BMJ 2013;346:f1049 doi: 10.1136/bmj.f1049 (Published 25 March 2013)

(continued)

Section/item	Item No	Recommendation	Reported on page No/ line No
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	N.A.
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	12
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	12-16
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	17
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	17

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist