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Data-supported timely management in cooperation with a physician-staffed centre for telemedicine in advanced cardiac failure[1]

Extract

[1] Translation of Chapters 1 to 8 and Appendix A of the rapid report N19-01 *Datengestütztes, zeitnahes Management in Zusammenarbeit mit einem ärztlichen telemedizinischen Zentrum bei fortgeschrittener Herzinsuffizienz* (Version 1.0; Status: 27 September 2019 [German original], 28 November 2019 [English translation]). Please note: This document is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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This rapid report was prepared in collaboration with external experts.

The responsibility for the contents of the report lies solely with IQWiG.

According to §139b (3) No. 2 of Social Code Book (SGB) V, Statutory Health Insurance, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received". The Institute received the completed *Form for disclosure of potential conflicts of interest* from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information on conflicts of interest provided by the external experts and external reviewers is presented in Appendix B of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

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IQWiG thanks the external expert for his collaboration in the project.

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
CI	confidence interval
CRS	clinical study report
CRT	cardiac resynchronization therapy
CRT-D	cardiac resynchronization therapy defibrillator
ECG	electrocardiogram
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
ICD	implantable cardioverter defibrillator
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
LVEF	left-ventricular ejection fraction
MCS	Mental Health Composite Scale
MLHFQ	Minnesota Living with Heart Failure Questionnaire
NYHA	New York Heart Association
OR	odds ratio
PCS	Physical Composite Scale
RCT	randomized controlled trial
SAE	serious adverse event
SF-36	Short Form (36) Health Survey
SGB	Sozialgesetzbuch (Social Code Book)
TM	telemedicine
VAS	visual analogue scale

Executive summary

On 28 March 2019, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) with the assessment of data-supported timely management in cooperation with a physician-staffed centre for telemedicine (hereinafter also referred to as "telemonitoring with defined minimum requirements") for patients with advanced cardiac failure.

Research question

The aim of the present report is the benefit assessment of telemonitoring with defined minimum requirements in addition to standard care and the resulting interventions as management strategy in comparison with standard care without telemonitoring in patients with advanced cardiac failure regarding patient-relevant outcomes.

Methods

The target population of the benefit assessment consisted of patients with advanced cardiac failure. The experimental intervention was telemonitoring with defined minimum requirements in addition to standard care and the resulting interventions as management strategy.

Telemonitoring had to have the following specifics: at least daily transmission of at least the following parameters to a telemonitoring centre: heart rate and rhythm, as well as information on the general state of health (e.g. from self-assessment questionnaires or data on physical activity); close analysis of the data by a telemonitoring centre under the responsibility of a physician in addition to the treating physician; defined maximum reaction times of the telemonitoring centre (up to 1 working day) or of the treating physician (within 24 hours after knowledge).

The comparator treatment was standard care without telemonitoring.

Patient-relevant outcomes were considered in the assessment.

Only randomized controlled trials (RCTs) were included in the benefit assessment. Studies with at least 6 months of follow-up observation were included.

A systematic literature search for studies was conducted in the following databases: MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials. In parallel, a search for relevant systematic reviews was conducted in the databases MEDLINE, Embase and the Cochrane Database of Systematic Reviews.

In addition, the following information sources and search techniques were considered: study registries, documents sent by the G-BA, the websites of G-BA and IQWiG, as well as the screening of reference lists and author queries.

In order to assess the qualitative certainty of the results, the criteria of the risk of bias across outcomes were evaluated, and the risk of bias was classified as low or high. If the studies were comparable regarding the research question and relevant characteristics and no relevant heterogeneity was observed, the individual results were pooled quantitatively by means of meta-analyses.

Results

The information retrieval identified 4 RCTs as relevant for the research question of the present benefit assessment. No planned or ongoing studies were identified. The last search was conducted on 9 May 2019.

In the included studies, the data were either measured automatically by the implanted device (implantable cardioverter defibrillator [ICD] or cardiac resynchronization therapy [CRT]) and transmitted daily without involvement of the patients, or the patients themselves performed measurements once a day using external, non-invasive devices, and assessed their state of health. The data were then transmitted automatically.

The risk of bias was high in all studies. The follow-up observation period was between 12 months and 24 months.

Conclusion

The 4 included studies investigated 2 different telemonitoring strategies with defined minimum requirements. In telemonitoring type 1, the data were automatically measured by the implanted device (ICD or CRT-defibrillator [CRT-D]), no involvement of the patient was necessary. In telemonitoring type 2, it was the patient's task to measure the data using external, non-invasive devices.

Including all studies, there was no hint of a benefit or harm of telemonitoring for the outcome "all-cause mortality". Data for the subgroups of patients with and without depressive symptoms were only available for telemonitoring type 2. For the outcome "all-cause mortality", there was an indication of a benefit for patients without depressive symptoms.

The joint consideration of telemonitoring type 1 and type 2 showed a hint of a benefit for the outcome "cardiovascular mortality".

There was no hint of a benefit or harm of telemonitoring with defined minimum requirements for the following outcomes: hospitalization overall, cardiovascular hospitalization, stroke, cardiac arrhythmia requiring treatment, thromboembolic events, shocks delivered by a cardiac device and morbidity due to cardiac failure. Due to the incomplete data, no conclusion on the benefit was drawn for the following outcomes: serious adverse events (SAEs), depressive symptoms, cardiac decompensation, health status and health-related quality of life.

1 Background

Cardiac failure is a complex clinical syndrome that results from any structural or functional impairment of ventricular filling or ejection of blood [1]. Chronic cardiac failure is the inability of the heart to supply the organism with sufficient oxygen to ensure metabolism under both resting and exercise conditions [2]. It is a common disease in the older population [1] and is one of the most common causes of death in Germany [3].

Severity of cardiac failure is usually classified according to the New York Heart Association criteria (NYHA) [4]. However, the NYHA stage is not stable, i.e. it can change in one and the same person [4] and also relies heavily on the physician's subjective assessment [5]. Therefore, the NYHA classification is not clear. However, no other classification system has yet been established as the standard [4].

Telemonitoring refers to the use of communication technologies to transmit and monitor physiological data describing health status [6].

Benefit assessment N16-02 assessed telemonitoring using active cardiac implantable devices in ventricular tachyarrhythmia and heart failure [7]. However, close remote monitoring in cardiac failure patients can also be performed using non-invasive telemetric devices (e.g. scales or electrocardiogram [ECG]) or implantable haemodynamic monitors [4,6,8]. In the oral hearing on the preliminary report N16-02, a significant role was attributed to telemonitoring intensity [9]. The telemonitoring intensity can be determined, for example, by the closeness of the data query and the data review, by the rapid reaction to changes and by the monitoring by a second entity (telemonitoring centre). Telemonitoring in addition to the treating physician by a centre for telemedicine can be implemented in different ways [10-12]. In 2019, the telemonitoring working group of the German Cardiac Society published proposals on basic structural features of a centre for telemedicine for patients with cardiac failure [8]. Many of the proposals are in line with the specifications from the concretization for this benefit assessment regarding the minimum requirements for a telemonitoring centre [13].

2 Research question

The aim of the present report is

- the benefit assessment of telemonitoring with defined minimum requirements in addition to standard care and the resulting interventions as management strategy in comparison with standard care without telemonitoring

in patients with advanced cardiac failure regarding patient-relevant outcomes.

3 Course of the project

On 28 March 2019, the G-BA commissioned IQWiG with the assessment of data-supported timely management in cooperation with a physician-staffed centre for telemedicine for patients with advanced cardiac failure.

External experts were involved in the project.

A rapid report was prepared on the basis of the project outline. This report was sent to the G-BA and published on the IQWiG website 4 weeks later.

4 Methods

The assessment was based on the *General Methods 5.0* [14].

4.1 Criteria for the inclusion of studies in the investigation

4.1.1 Population

Studies with patients with advanced cardiac failure were included in the assessment.

4.1.2 Experimental and comparator intervention

The experimental intervention was telemonitoring with defined minimum requirements and the resulting interventions in addition to standard care as management strategy.

Telemonitoring had to have the following specifics:

- at least daily transmission of at least the following parameters to a telemonitoring centre:
  - heart rate and rhythm, as well as
  - information on the general state of health (e.g. from self-assessment questionnaires or data on physical activity)
- close analysis of the data by a telemonitoring centre under the responsibility of a physician in addition to the treating physician
- defined maximum reaction times of the telemonitoring centre (up to 1 working day) or of the treating physician (within 24 hours after knowledge)

The comparator treatment was standard care without telemonitoring. If telemonitoring in the intervention group was carried out using an active cardiac device, such a device also had to be used in the comparator group.

4.1.3 Patient-relevant outcomes

The following patient-relevant outcomes were considered in the assessment:

- all-cause mortality
- cardiovascular mortality
- stroke
- cardiac decompensation
- cardiac arrhythmia requiring treatment
- venous and/or arterial thromboembolic events
- hospitalization overall
- cardiovascular hospitalization

- for implanted implantable cardioverter defibrillator (ICD)/cardiac resynchronization therapy defibrillator (CRT-D): shocks delivered by implant/device
- adverse effects and complications of the diagnostic-therapeutic strategy used
- health-related quality of life including activities of daily living, dependence on the help of others and participation in professional and social life

If data on other patient-relevant morbidity outcomes were available, these were also included.

4.1.4 Types of study

Randomized controlled trials (RCTs) are associated with the least uncertainty of results if they have been conducted methodically adequate and appropriate to the respective research question. They therefore provide the most reliable results for assessing the benefit of a medical intervention.

For all interventions mentioned under 4.1.2 and all outcomes mentioned under 4.1.3, an evaluation within the framework of RCTs is possible and practicable.

For the report to be prepared, only RCTs were therefore included as relevant scientific literature in the benefit assessment.

4.1.5 Study duration

Studies with at least 6 months of follow-up observation were included.

4.1.6 Publication language

The publication had to be in German or English.

4.1.7 Tabular presentation of the criteria for study inclusion

The following table lists the criteria that studies had to meet in order to be included in the assessment.

Table 1: Overview of the criteria for study inclusion

Inclusion criteria	
E1	Patients with advanced cardiac failure (see also Section 4.1.1)
E2	Experimental intervention: telemonitoring with defined minimum requirements and the resulting interventions in addition to standard care as management strategy (see also Section 4.1.2)
E3	Comparator intervention: standard care without telemonitoring (see also Section 4.1.2)
E4	Patient-relevant outcomes as formulated in Section 4.1.3
E5	Randomized controlled trials as formulated in Section 4.1.4
E6	Minimum duration of follow-up observation of at least 6 months (see also Section 4.1.5)
E7	Language of publication: German or English
E8	Full publication available[a]

a: In this context, "full publication" also refers to a clinical study report in accordance with ICH E3 [15] or a report on the study fulfilling the criteria of the CONSORT Statement [16] and allowing an assessment of the study, provided the information on the study methods and study results contained in these documents are not confidential.

CONSORT: Consolidated Standards of Reporting Trials; ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

4.1.8 Inclusion of studies that do not fully meet the above criteria

For the inclusion criteria E1 (population), E2 (experimental intervention, related to the intervention group of the study) and E3 (comparator intervention, related to the comparator group of the study), it was sufficient if at least 80% of the patients included met these criteria. If for such studies subgroup analyses were available for patients who met the inclusion criteria, these analyses were used. Studies that met the inclusion criteria E1, E2 and E3 in fewer than 80% were included only if subgroup analyses were available for patients who met the inclusion criteria.

4.2 Comprehensive information retrieval

4.2.1 Sources of information

A systematic search for relevant studies and documents was performed for the comprehensive information retrieval. For part of the information retrieval (telemonitoring using active cardiac implantable devices), the results of the information retrieval for benefit assessment N16-02 [7] were included in the search results. The search was updated from August 2017 for the period not covered by commission N16-02. The following primary and further information sources as well as search techniques were considered:

Primary sources of information

- Bibliographic databases
  - MEDLINE
  - Embase
  - Cochrane Central Register of Controlled Trials
  - Cochrane Database of Systematic Reviews
- Trial registries
  - U.S. National Institutes of Health. ClinicalTrials.gov
  - World Health Organization. International Clinical Trials Registry Platform Search Portal

Further sources of information and search techniques

- Use of further search techniques
  - screening of reference lists of identified systematic reviews, including benefit assessment N16-02 [7]
  - author queries
  - documents sent by the G-BA
  - G-BA website and IQWiG website

4.2.2 Selection of relevant studies

Selection of relevant studies and documents from the results of the bibliographical search

In a first step, the hits identified in bibliographical databases were assessed for their potential relevance regarding the inclusion criteria (see Table 1) based on their title and, if available, abstracts. In a second step, the relevance of the documents considered potentially relevant was checked based on their full texts. The present project is part of a study investigating the efficiency of study selection [17]. Both steps were performed by 3 persons independently from one another in 3 different screening tools. The results of the selection were summarized after the full text evaluation.

Selection of relevant studies and documents from further sources of information

Search results from the following sources of information were assessed by 2 people independently from one another with regard to their relevance:

- trial registries
- documents sent by the G-BA

Search results from the information sources additionally considered were screened by 1 person with regard to studies. The identified studies were then checked for their relevance. The entire process was then reviewed by a second person. If discrepancies occurred in one of the selection steps mentioned, these were resolved by discussion between the 2 reviewers.

4.3 Information retrieval and synthesis

4.3.1 Presentation of the individual studies

All information necessary for the benefit assessment was extracted from the documents of the included studies into standardized tables. If discrepancies arose from the comparison of the information from different documents on a study (but also from multiple data on an aspect within a document itself), which could have considerable influence on the interpretation of the results, this is shown in the corresponding passages in the results section of the report.

The report provides a comparative description of the results regarding the patient-relevant outcomes reported in the studies.

The relevant results were to be assessed for their respective outcome-specific risk of bias for each study. The information was then combined and analysed. If possible, the procedures described in Sections 4.3.3 to 4.3.5 were used in addition to the comparison of the results of the individual studies. A final summarizing evaluation of the information was carried out in any case.

In general, results were not considered in the benefit assessment if they were based on fewer than 70% of patients to be considered in the analysis, that is, if the proportion of patients not considered in the analysis was more than 30%.

The results were also not considered in the benefit assessment if the difference of the proportions of patients not considered was greater than 15 percentage points between the groups.

4.3.2 Assessment of the risk of bias of the results

The outcome-specific risk of bias of the results was to be assessed for each study included in the benefit assessment. In particular, the following criteria across outcomes (A) and outcome-specific criteria (B) were to be systematically extracted and assessed:

A: Criteria for the assessment of the risk of bias of the results across outcomes

- randomization sequence generation
- allocation concealment
- blinding of patients and treating staff
- reporting independent of the results

B: Criteria for the outcome-specific assessment of the risk of bias of the results

- blinding of outcome assessors
- implementation of the intention-to-treat (ITT) principle
- reporting independent of the results

For the results of randomized studies, the risk of bias was summarized and classified as "high" or "low". If a high risk of bias had already been determined for the criteria listed under (A), the risk of bias was considered to be high for all results of all outcomes, regardless of the assessment of outcome-specific aspects. Otherwise, the criteria mentioned under (B) were subsequently taken into account for each outcome.

4.3.3 Meta-analyses

The estimated effects and confidence intervals (CIs) from the studies were summarized using forest plots. Subsequently, the heterogeneity of the study pool was examined for the presence of heterogeneity using the statistical test [18]. If the heterogeneity test showed a result that was not statistically significant ($p \geq 0.05$), it was assumed that the estimation of a common (pooled) effect was meaningful. In the case of at least 5 studies, the meta-analysis was performed using the random-effects model according to the method by Knapp and Hartung using the heterogeneity estimator by Paule and Mandel [19]. As a result, the joint effect including the CI is presented. Since heterogeneity cannot be reliably estimated in the case of fewer studies, fixed-effect models were used in 4 or fewer studies where appropriate. To do this, the studies had to be sufficiently similar and there had to be no reasons against the use of a fixed-effect model. A qualitative summary could also be prepared if appropriate.

If the heterogeneity test produced a statistically significant result ($p < 0.05$), only the prediction interval is shown in the case of at least 5 studies. In 4 or fewer studies, a qualitative summary was prepared. In both cases, it was also investigated which factors might cause this heterogeneity. This include methodological factors (see Section 4.3.4) and clinical factors, so-called potential effect modifiers (see Section 4.3.5).

Apart from the models mentioned above, it was possible to use alternatives such as the beta-binomial model for binary data [20] in certain situations and with particular justification.

4.3.4 Sensitivity analyses

If there were doubts about the robustness of results due to methodological factors such as the choice of certain cut-off values, imputation strategies for missing values, documentation times or effect measures, it was planned to investigate the influence of such factors in sensitivity analyses. The result of such sensitivity analyses can influence the certainty of the conclusions derived from the observed effects. An effect classified as not robust may, for example, result in the determination of only an indication, instead of proof, of a (greater) benefit (see Section 4.3.6 for the derivation of conclusions on the evidence base).

4.3.5 Subgroup characteristics and other effect modifiers

The results were investigated for potential effect modifiers, i.e. clinical factors that may influence the effects. The aim was to uncover possible effect differences between patient groups and treatment characteristics. Statistical significance based on a homogeneity or interaction test is a prerequisite for the detection of different effects. The available results from regression analyses, which include interaction terms, and from subgroup analyses were included in the investigation. In addition, the Institute performed its own analyses in the form of meta-regressions or meta-analyses, categorizing the studies with regard to possible effect modifiers. Subgroup analyses were only performed if each subgroup comprised at least 10 patients and, for binary data, if at least 10 events had occurred in one of the subgroups. It was planned to include the following factors in the analyses with regard to a possible effect modification:

- sex
- age
- disease severity
- type of telemonitoring (with implanted device or without)
- patients with good access to medical care (e.g. urban residence) versus patients with poor access to medical care (e.g. rural residence)

If further possible effect modifiers emerged from the available information, these could also be included if justified. If possible effect modifiers were identified, more precise conclusions derived from the observed effects were provided. For example, it was possible to limit the proof of a (greater) benefit to a specific subgroup of patients (for the derivation of conclusions on the evidence base, see Section 4.3.6).

4.3.6 Conclusions on the evidence base

For each outcome, a conclusion on the evidence base of the (greater) benefit and (greater) harm was drawn. with 4 possible levels of certainty: The data provided either “proof” (highest certainty), an “indication” (medium certainty), a “hint” (weakest certainty), or none of these 3 situations applied. The latter was the case if no data were available or the data available did not allow any of the other 3 conclusions to be drawn. In this case, the conclusion “There is no hint of (greater) benefit or (greater) harm” was drawn.

The certainty of conclusions regularly inferred depended on the criteria shown in Table 2. The qualitative certainty of results depended on the design of the study. Results of randomized trials with low risk of bias have a high, whereas results of randomized studies with high risk of bias have a moderate qualitative certainty of results. Results of non-randomized comparative studies have low qualitative certainty of results.

Table 2: Certainty of conclusions regularly inferred for different evidence situations if studies with the same qualitative certainty of results are available

		Number of studies				
		1 (with statistically significant effect)	≥ 2			
			Homogeneous	Heterogeneous		
			Meta-analysis statistically significant	Effects in the same direction[a]		
				Clear	Moderate	No
Qualitative certainty of results	High	Indication	Proof	Proof	Indication	–
	Moderate	Hint	Indication	Indication	Hint	–
	Minor	–	Hint	Hint	–	–
a: Effects in the same direction are present if a clear or moderate direction of the effects is notable despite heterogeneity.						

4.4 Specification of the methods

4.4.1 Study selection in trial registries

The information provided in trial registers was not detailed enough to assess the relevance for the research question with regard to the very specific intervention here. Therefore, the study selection from trial registries was performed as follows: Studies were excluded if they were identified exclusively from the search in trial registries, no result reports were available in the trial registry entry, and the data did not clearly show the relevance for the research question. In these cases, no author queries were made either.

4.4.2 Patient-relevant outcomes

Data were available for the following patient-relevant morbidity outcomes. They were therefore also taken into account:

- depressive symptoms
- health status
- morbidity due to cardiac failure

4.4.3 Meta-analyses

If the meta-analysis on an outcome revealed that heterogeneity was present in the study pool, qualitative evidence synthesis followed.

The Knapp-Hartung method is regularly used to perform meta-analyses with random effects. However, the analyses carried out in this report contain few studies. It is known that there are no good statistical methods for random-effects models in few studies; the Knapp-Hartung

method, for example, tends to produce very imprecise and therefore little informative estimations in few studies.

In addition, the included studies differ so much in the monitoring used (type 1 and type 2) that a fixed-effect model for both types of monitoring cannot be regarded as justified. First, it was examined whether the 95% CI according to Knapp-Hartung was narrower than the 95% CI according to DerSimonian-Laird. In this case, the effect estimation using Knapp-Hartung with variance correction would then have been considered further. This situation was not present in any of the meta-analyses. Furthermore, it was examined whether the Knapp-Hartung method produced an informative estimation. This is the case when the 95% CI of the pooled effect estimation is narrower than the union of the 95% CI of the individual studies. This situation was present in all meta-analyses. If the estimation of the effect according to Knapp-Hartung showed no significant difference between the treatment groups, but the estimation according to DerSimonian-Laird did, a qualitative evidence synthesis followed, where, for example, it was possible to derive a hint of a benefit or harm for this outcome in the case of so-called effects in the same direction.

4.4.4 Subgroup characteristics and other effect modifiers

The authors of the TIM-HF study conducted several prospectively planned subgroup analyses [21]. On the basis of the results on the subgroup characteristic “depressive symptoms” (Patient Health Questionnaire [PHQ] < 10), the study population was restricted to patients without depressive symptoms in the subsequent study of the same study group, TIM-HF2. For the present assessment, the characteristic “presence of depressive symptoms” was used as an additional possible effect modifier in the framework of a subgroup analysis because of its possible relevance.

5 Results

5.1 Comprehensive information retrieval

5.1.1 Primary sources of information

5.1.1.1 Bibliographic databases

Figure 1 shows the result of the systematic literature search in the bibliographical databases and of the study inclusion in accordance with the criteria for study inclusion. The search strategies for the search in bibliographical databases can be found in Section A.1. The last search was conducted on 29 April 2019.

Section 9.3 of the full report contains the citations of the hits that were checked as full texts, but were excluded, as well as the reasons for their exclusion.

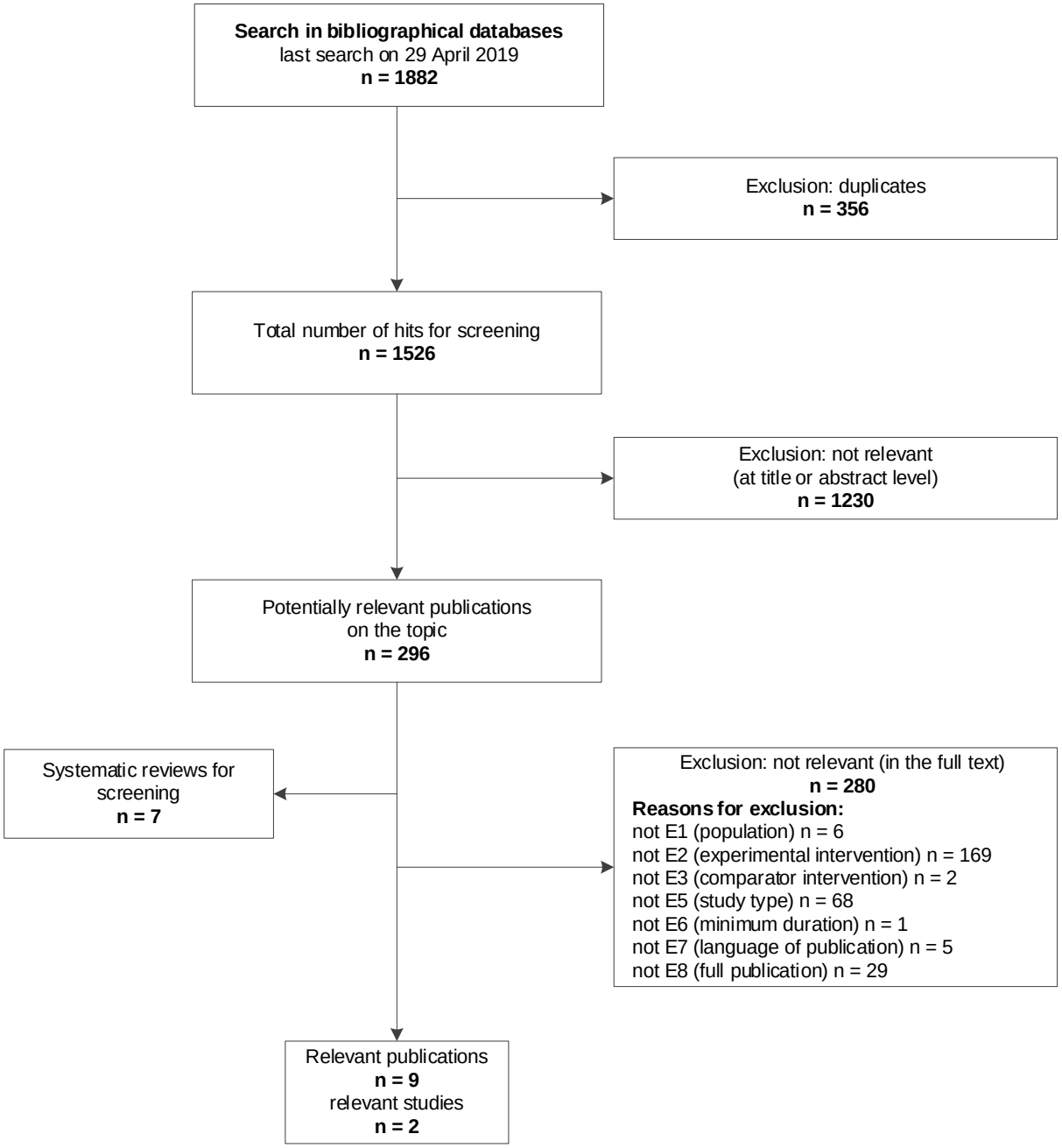

Figure 1: Result of the bibliographical search and of the study selection

5.1.1.2 Trial registries

The following relevant studies and documents were identified from the search in trial registries (Table 3):

Table 3: Relevant studies and documents identified in trial registries

Study	Trial registry ID	Trial registry	Result report available in the trial registry
TIM-HF	NCT00543881	ClinicalTrials.gov [22]	No
TIM-HF2	NCT01878630	ClinicalTrials.gov [23]	No
	DRKS00010239	German Clinical Trials Register [24]	No

The search strategies for the search in trial registries can be found in Section A.2. The last search in trial registries was conducted on 9 May 2019.

5.1.2 Further sources of information and search techniques

Relevant studies and documents identified using further information sources and search techniques are only presented below if they had not already been found using the primary information sources.

5.1.2.1 Documents sent by the G-BA

In the framework of the work on the commission, the G-BA forwarded documents to IQWiG. These were checked for duplicates for the bibliographic literature research.

No relevant studies or documents were found that had not been identified by other search steps.

5.1.2.2 G-BA website and IQWiG website

No relevant studies or documents were identified on the websites of the G-BA and IQWiG that had not been found by other search steps. The screening of the IQWiG benefit assessment N16-02 is presented in Section 5.1.2.3.

5.1.2.3 Use of further search techniques

Systematic reviews were identified in the framework of the information retrieval. The reference lists of the systematic reviews from 2018 as well as the latest version of a Cochrane review were screened. The corresponding references can be found in Section 9.2 of the full report.

The following relevant studies and documents were found, which were identified by screening the IQWiG benefit assessment N16-02 [7]:

Table 4: Relevant studies and documents identified in benefit assessment N16-02

Study	Available documents ([reference])
IN-TIME	Publications [10,25] registry entry [26] clinical study report [27] study protocol [28]
TELECART	Publication [29]

5.1.2.4 Author queries

Author queries were sent for the present assessment (Table 5). The information from the responses received was included in the study evaluation.

Table 5: Overview of author queries

Study	Content of query	Response received yes/no	Content of response
Blum 2007 [30]	▪ Were the data transmitted daily? ▪ Did the transmitted parameters also include ▫ heart rate and rhythm, as well as ▫ information on the general health status? ▪ If a centre for TM was involved, was it supervised by a physician? ▪ Were reaction times defined for the centre for TM and the treating physician? ▪ Are data available on the actual reaction time of the centre for TM and the treating physician?	No[a]	
Cui 2013 [31]		No	
Diederichsen 2017 [32]		Yes	▪ Yes ▫ daily check for arrhythmias; mean heart rate and heart rate variability were not evaluated daily, but used for further research ▫ information on the general health status were not evaluated daily, but used for further research ▪ yes ▪ no ▪ no
Jerant 2001 [33]		No	
Jimenez 2018 [34]		No	
Kraai 2016 [35]		No[a]	
Lima 2016 [36]		No[a]	
RESULT [37]		No	
Schmidt 2018 [38]		No	

(continued)

Table 5: Overview of author queries (continued)

Study	Content of query	Response received yes/no	Content of response
TIM-HF/ TIM-HF2	Request for ▪ study protocol ▪ clinical study report ▪ SAP ▪ if applicable, post-hoc additional analyses	Yes[b]	Sending of ▪ study protocol [39,40] ▪ SAP [41,42] ▪ overview of planned and already published publications
	In particular request of results on ▪ depression ▪ EQ-5D visual analogue scale (outcome "health status") ▪ actual reaction times of the telemonitoring centre ▪ if already available: for all patient-relevant outcomes subgroup analyses on the characteristics ▫ sex ▫ age ▫ disease severity ▫ patients with good access to medical care (e.g. urban residence) versus patients with poor access to medical care (e.g. rural residence) Were the following outcomes also recorded? ▪ planned and unplanned cardiovascular hospitalization/hospitalization due to cardiac failure ▪ hospitalization overall (planned and unplanned) ▪ severe adverse events (SAEs)	Yes	▪ Publication of the results not yet published is planned

a: The message could not be delivered to the specified e-mail address.
b: Agreement on data transmission concluded.
EQ-5D: European Quality of Life-5 Dimensions; SAP: statistical analysis plan; TM: telemedicine

5.1.3 Resulting study pool

A total of 4 relevant studies were identified in the different search steps (see also Table 6).

Table 6: Study pool of the benefit assessment

Study	Available documents			
	Full publication (in scientific journals)	**Registry entry/result report from trial registries**	**Clinical study report from manufacturer documents (not publicly available)**	**Study protocol/SAP**
IN-TIME	Yes [10,25,43,44]	Yes [26]/no	Yes [27]	[28]
TELECART	Yes [29]	No/no	No	No
TIM-HF	Yes [21,45-48]	Yes [22]/no	No	[39,41]
TIM-HF2	Yes [49,50]	Yes [23,24]/no	No	[40,42]
SAP: statistical analysis plan				

5.1.4 Studies without reported results

No relevant studies without previously reported results were identified in the information retrieval.

5.2 Characteristics of the studies included in the assessment

The telemonitoring interventions used in the included studies can be grouped into 2 types.

In telemonitoring type 1, the data were automatically measured by the implanted device (ICD or CRT-D) and transmitted daily. Cardiac function was continuously monitored so that alarm signals could be transmitted immediately if cardiac arrhythmias (including atrial fibrillation) occurred. No involvement of the patient was necessary.

In telemonitoring type 2, it was the patient's task to measure the data once daily using external, non-invasive devices such as scales, blood pressure monitors or ECG event recorders; in addition, the patients were to provide a self-report of their state of health. The data were then transmitted automatically.

Studies with telemonitoring type 1

The **IN-TIME** study [10,25] included 716 patients with cardiac failure who had a therapeutic indication for implantation of an ICD or a CRT-D and left-ventricular ejection fraction (LVEF) ≤ 35%. An additional inclusion criterion was successful telemedical data transmission on ≥ 80% of all days of the 1-month run-in phase (or implementation of a corrective measure). However, the proportion of patients who, according to the clinical study report (CSR), were excluded on the basis of this inclusion criterion at the time of randomization was so low (0.5%) that no relevant transferability problem was to be expected. 664 patients were randomized and followed-up for 12 months (recruitment from 2007 to 2010).

Trend data on heart rate and heart rhythm, on patient activity and on technical parameters were transmitted daily by the implant. In addition, warning signals were transmitted after acute events such as cardiac arrhythmias and device/electrode malfunctions. A centre for telemedicine (TM) staffed by nurses, supported by a physician, checked on each working day whether warning signals were transmitted and analysed the trend data at least once a week (parallel to the investigator). If predefined warning signals or trends occurred, the centre for TM had to contact the person concerned by telephone on the same day using a standardized questionnaire. If the investigator was informed by the centre for TM about a warning signal or a specific trend, the investigator had to confirm receipt of the message within 48 hours. Both treatment groups received personal after-care; in addition to a general reference to care in compliance with guidelines made in the protocol, only the final visit after 12 months was mandatory. Hence, in the study, a relatively low frequency of after-care appointments was planned in the comparator group compared with the after-care intervals in the control groups of the other included studies (see also benefit assessment N16-02 [7]).

The **TELECART** study [29] included patients with chronic cardiac failure who had a therapeutic indication for de-novo implantation of a CRT-D, LVEF < 35%, and a left bundle branch block. 191 patients were randomized. Follow-up was 12 months (recruitment from 2010 to 2014). The study essentially provided for the same telemonitoring strategy as the IN-TIME study and had all the characteristics mentioned above. In both treatment groups, personal after-care was planned for the time points at 1, 3, 6 and 12 months.

Studies with telemonitoring type 2

The TIM-HF study [21,45,46] included 710 patients with chronic cardiac failure, LVEF ≤ 35% and a history of hospitalization or another characteristic to assess disease severity (see Table 8). Follow-up was 24 months (recruitment from 2008 to 2009). The patients in the intervention group were instructed to record daily data of their weight and blood pressure measurements, ECG and self-report of health. A centre for TM, staffed by physicians around the clock, checked the transmitted data daily and was able to initiate treatment measures (e.g. change of medication up to triggering emergency measures) if necessary. The participants in the intervention group were also provided with a home emergency call system. The intervention was additionally characterized by a monthly structured telephone call between the centre for TM and the patient on the topics of disease status, evaluation of depressive symptoms, behaviour in emergency situations and solution of technical problems. In both treatment groups, study visits were planned after 3, 6, 9, 12, 18 and 24 months.

The **TIM-HF2** study [49,50] included 1571 patients with chronic cardiac failure and a history of hospitalization. Follow-up was 12 months (recruitment from 2013 to 2017). Deviating from the other studies, patients with LVEF ≤ 45% were included; if the persons received a diuretic in permanent medicinal therapy, LVEF > 45% was also permitted. In addition, only patients without depressive symptoms (i.e. PHG-9 < 10 points) were eligible to participate in the study. The management strategy largely corresponded to that of the TIM-HF study: Besides the measurements planned there (weight, blood pressure, ECG and self-report of health), the TIM-

HF2 study also included oxygen saturation. In addition to the intervention characteristics of the TIM-HF study described above, the TIM-HF2 study also included disease-related training in the intervention group at the start of the study. In both treatment groups, study visits were planned after 3, 6, 9 and 12 months.

The average age in all studies was above 65 years. More than 70% of all study participants were men. Average LVEF was 26% in participants in the IN-TIME study and 27% in the TIM-HF study, whereas – concurring with the deviating inclusion criteria – it was notably higher in the TIM-HF2 study (41%). No information on LVEF is available for the TELECART study. All studies included practically only NYHA class II and III patients, with about half of the patients in each study having NYHA class II and half of them NYHA class III. The proportion of patients with depressive symptoms in the TIM-HF study was just over 20%, whereas in the TIM-HF2 study, in accordance with the inclusion criteria, no participant had depressive symptoms. No information regarding depressive symptoms of the participants was available for the studies IN-TIME and TELECART. The basic drug therapy in the 4 studies did not differ.

All studies except the TELECART study reported data on adherence. In the IN-TIME study, data submitted on 75% or more study days were available from 79.9% of all patients [44]. The studies TIM-HF and TIM-HF2 reported absolute adherence (i.e. complete transmission of all 4 parameters per measurement day) of at least 80% in 85.1% of all patients [47], and of at least 70% in 97% of all patients [49].

The following Table 7 describes the included RCTs regarding important characteristics that are relevant for the present benefit assessment. Table 8 describes the relevant criteria for patient inclusion and exclusion in the studies, and Table 9 shows the characteristics of the populations investigated in the studies. A detailed presentation of the interventions used in the studies is provided in Table 10.

Table 7: Characteristics of the studies included

Study	Study design	Patient number (randomized) N	Population	Location and period of study	Planned duration of follow-up	Relevant outcomes[a]
IN-TIME	RCT, unblinded, multicentre	664	Patients with indication for ICD or CRT-D implantation	Australia, Europe, Israel (36 centres) recruitment: 7/2007–12/2010	12 months	**Primary:** composite outcome of: all-cause mortality, hospitalization due to cardiac failure, NYHA class, health status **Secondary:** all-cause mortality, cardiovascular mortality, hospitalization due to cardiac failure, SAEs, health status, morbidity due to cardiac failure
TELECART	RCT, unblinded, multicentre	191	Patients with indication for CRT-D implantation	Italy recruitment: 9/2010–9/2014	12 months	**Primary:** all-cause mortality, cardiac mortality, hospitalization due to cardiac failure **Secondary:** stroke, shocks delivered
TIM-HF	RCT, unblinded, multicentre	710	Patients with chronic cardiac failure	Germany (165 centres) recruitment: 1/2008–6/2009	24 months	**Primary:** all-cause mortality **Secondary:** cardiovascular mortality, hospitalization overall, cardiovascular hospitalization, NYHA class, cardiac decompensation, health-related quality of life, depressive symptoms
TIM-HF2	RCT, unblinded, multicentre	1571	Patients with chronic cardiac failure	Germany (200 centres) recruitment: 8/2013–5/2017	12 months	**Primary:** days lost due to death or cardiovascular hospitalization **Secondary:** all-cause mortality, cardiovascular mortality, cardiovascular hospitalization, health-related quality of life

a: Primary outcomes include all available information without consideration of the relevance for this benefit assessment. Secondary outcomes contain exclusively information on the available outcomes relevant for this benefit assessment.

CRT-D: cardiac resynchronization therapy defibrillator; ICD: implantable cardioverter defibrillator; NYHA: New York Heart Association; PGA: patient global assessment; RCT: randomized controlled trial; SAE: serious adverse event

Table 8: Inclusion and exclusion criteria for patients in the studies

Study	Key inclusion criteria	Key exclusion criteria
IN-TIME	▪ Indication for ICD or CRT-D implantation ▪ chronic cardiac failure (for at least 3 months) ▪ NYHA class II or III for 1 month prior to screening ▪ LVEF ≤ 35% within 3 months prior to screening ▪ indication for therapy with diuretics The following criteria had to be met after the end of the 1-month run-in phase (before randomization): ▪ stable optimum drug therapy ▪ successful telemedical data transmission on ≥ 80% of all days (or implementation of a corrective measure)	▪ Age ≤ 18 years ▪ uncontrolled hypertension ▪ permanent atrial fibrillation ▪ life expectancy < 1 year ▪ restrictive, infiltrative or hypertrophic cardiomyopathy, constrictive pericarditis, acute myocarditis The following criterion was not allowed to be met after the end of the run-in phase (before randomization): ▪ acute coronary syndrome, cardiac surgery or stroke within the last 6 weeks
TELECART	▪ Indication for CRT-D implantation ▪ chronic cardiac failure for at least 3 months ▪ NYHA class II or III ▪ left bundle branch block ▪ LVEF < 35%	▪ Age < 18 or > 75 years ▪ prior implantation of an ICD, a CRT-D or a cardiac pacemaker ▪ prior cardiac surgery ▪ life expectancy ≤ 1 year
TIM-HF	▪ Age ≥ 18 years ▪ chronic cardiac failure NYHA stage II–III ▪ LVEF ≤ 35% ▪ cardiac decompensation with hospitalization *or* therapy with intravenous loop diuretics (> 40 mg/dL, equivalent dose of furosemide) due to beginning cardiac congestion *or* LVEF ≤ 25%, measured twice at intervals of at least 6 months ▪ optimal medical treatment for cardiac failure with ACE inhibitor or AT1 receptor antagonist, beta blocker and spironolactone as well as diuretic therapy concurring with tolerability at the investigator's discretion ▪ ICD and/or CRT therapy if indicated and consented by patient	▪ Life expectancy ≤ 1 year ▪ hospitalization for cardiac decompensation within 7 days before inclusion in study ▪ implanted cardiac assist system ▪ unstable angina pectoris ▪ congenital heart defect ▪ primary heart valve disease, hypertrophic/restrictive/arrhythmogenic right ventricular cardiomyopathy, acute myocarditis (diagnosis < 1 year) ▪ listed for heart transplantation ▪ planned revascularization or CRT implantation

(continued)

Table 8: Inclusion and exclusion criteria for patients in the studies (continued)

Study	▪ Key inclusion criteria	▪ Key exclusion criteria
TIM-HF2	▪ Chronic cardiac failure (NYHA class II or III) ▪ LVEF ≤ 45% or > 45% + minimum 1 diuretic in permanent medicinal therapy ▪ hospitalization due to cardiac decompensation < 12 months before inclusion in the study (unrelated to proven myocardial infarction without known moderate reduction in LVEF) ▪ depression score PHQ-9 < 10	▪ Age < 18 years ▪ hospitalization within the last 7 days before randomization ▪ implanted mechanical cardiac assist system ▪ acute coronary syndrome within the last 7 days before randomization ▪ high urgent listed for heart transplantation ▪ planned revascularization, transcatheter aortic valve implantation (TAVI), planned mitral clip and/or planned CRT implantation within 3 months after randomization ▪ revascularization and/or CRT implantation within 28 days before randomization ▪ life expectancy < 12 months

CRT: cardiac resynchronization therapy; CRT-D: cardiac resynchronization therapy defibrillator; ICD: implantable cardioverter defibrillator; LVEF: left-ventricular ejection fraction; NYHA: New York Heart Association; PHQ-9: Patient Health Questionnaire-9

Table 9: Characteristics of the study populations

Study	N	Age [years], mean (SD)	Sex [F/M], %	BMI [kg/m²], mean (SD)	LVEF (%), mean (SD)	NYHA class, %	Implanted device, %	Depressive symptoms[a], %	Coronary/ ischaemic heart disease, %	Study discontin-uations, n (%)
IN-TIME										
TM	333	65.3 (9.3)	17.7/82.3	28 (4.4)	26 (6.5)	▪ II: 45.2 ▪ III: 54.8	▪ Dual chamber ICD: 42.9 ▪ CRT-D: 57.1	ND	70.0	20 (6.0[b])[c]
Control	331	65.8 (9.6)	20.8/79.2	28.1 (4.7)	25.6 (6.6)	▪ II: 40.8 ▪ III: 59.2	▪ Dual chamber ICD: 39.6 ▪ CRT-D: 60.4	ND	68.0	25 (7.6[b])[c]
TELECART										
TM	89[d, e]	71.8 (8.5)	28.1[a]/71.9	ND	ND	▪ II: 41.6[a] ▪ III: 58.4[a]	▪ Dual chamber CRT-D: 100.0	ND	ND	2 (2[b])
Control	94[d, e]	72.6 (5.7)	20.2[a]/79.8	ND	ND	▪ II: 48.9[a] ▪ III: 51.1[a]	▪ Dual chamber CRT-D: 100.0	ND	ND	6[a] (6[b])
TIM-HF										
TM	354	66.9 (10.8)	19.5[a]/80.5	28.4 (5.4)	26.9 (5.7)	▪ II: 49.7 ▪ III: 50.3	▪ ICD: 46.3 ▪ CRT: 15.3	80 (22.6[a])	57.1	4 (1.1[b])
Control	356	66.9 (10.5)	18.0[a]/82.0	28.2 (5.3)	27.0 (5.9)	▪ II: 50.6 ▪ III: 49.4	▪ ICD: 44.9 ▪ CRT: 16.9	78 (21.9[a])	54.5	4 (1.1[b])
TIM-HF2										
TM	796[f]	70 (11)	30/70	30 (6)	41 (13)	▪ I: 0 ▪ II: 52 ▪ III: 47	▪ ICD: 29 ▪ CRT: 15	0 (0)	39	37 (4.8[b])
Control	775[f]	70 (10)	31/69	30 (6)	41 (13)	▪ I: 1 ▪ II: 51 ▪ III: 47	▪ ICD: 30 ▪ CRT: 16	0 (0)	42	15 (1.9[b])

(continued)

Table 9: Characteristics of the study populations (continued)

a: Operationalized as PHQ-9 ≥ 10.
b: Institute's calculation.
c: 23 additional patients were excluded. Distribution to the 2 treatment groups unclear.
d: Number of analysed patients.
e: Data are only available for a total of 183 patients from the 191 randomized patients.
f: The data on the characteristics of the study populations refer to the full analysis set with 765 patients (TM) and 773 patients (control). The full analysis set included all randomized patients with valid informed consent and initiated assigned treatment. 31 randomized patients (TM) and 2 randomized patients (control) from the ITT population were not included in this analysis.

BMI: body mass index; CRT: cardiac resynchronization therapy; CRT-D: cardiac resynchronization therapy defibrillator; F: female; ICD: implantable cardioverter defibrillator; ITT: intention to treat; LVEF: left-ventricular ejection fraction; M: male; N: number of randomized patients; ND: no data; NYHA: New York Heart Association; PHQ-9: Patient Health Questionnaire-9; SD: standard deviation; TM: telemonitoring

Table 10: Characteristics of the interventions in the studies included

Study	Intervention	Comparison
IN-TIME	**Implant** ▪ ICD or CRT-D (device by BIOTRONIK)	**Implant** ▪ ICD or CRT-D (device by BIOTRONIK)
	Telemonitoring ▪ daily transmission of trend data: ▫ automatic measurement and transmission of parameters on heart rate and rhythm (including mean heart rate, heart rate variability, ventricular extrasystoles per hour), patient activity and technical parameters by ICD or CRT-D ▪ immediate transmission of warning signals after acute events such as cardiac arrhythmias and device/electrode malfunctions by ICD or CRT-D ***Centre for telemedicine (TM)*** ▪ daily check for warning signals (on working days) ▪ at least weekly check of trend data (at least patient activity and ventricular ectopy) ▪ in case of predefined warning signals/trend data: contacting the treating physician within 1 hour (on working days) ▪ staffed by a physician and 2 nurses (on working days) ***Treating physician*** ▪ In case of warning signals, the treating physician received a fax, an e-mail or an SMS. ▪ check of trend data depending on clinical routine ▪ In case of predefined warning signals/trend data, the physician contacted the patient by telephone on the same day (standardized interview). ▫ reaction as determined by the treating physician ▪ feedback to the centre for TM within 48 hours, otherwise request made by the centre for TM to the study centre	
	Personal after-care ▪ 12 months after randomization ▪ additional after-care possible	

(continued)

Table 10: Characteristics of the interventions in the studies included (continued)

Study	Intervention	Comparison
TELECART	**Implant** ▪ CRT-D with telemonitoring function (device by BIOTRONIK)	**Implant** ▪ CRT-D without telemonitoring function (device by Boston Scientific, St. Jude Medical or Medtronic)
	Telemonitoring[a] ▪ daily[b] transmission of trend data: ▫ automatic measurement and transmission of parameters on heart rate and rhythm (including mean heart rate, heart rate variability, ventricular extrasystoles per hour), patient activity and technical parameters by CRT-D ▪ immediate transmission of warning signals after acute events such as cardiac arrhythmias and in case of device/electrode malfunctions by CRT-D ***Treating physician*** ▪ transmitted data were monitored by the investigator depending on clinical routine ▪ in case of predefined events: contacting the patient on the same day[c] using a standardized telephone interview followed by clinical examination ▪ reaction as determined by the investigators ▪ feedback to the centre for TM within 48 hours ***Centre for telemedicine*** ▪ daily check for warning signals (on working days) ▪ at least weekly check of trend data[c] ▪ in case of predefined events: redundant forwarding of these events to the treating physician (on working days) ▪ staffed by nurses and supporting physician (on working days)	
	Personal after-care ▪ at months 1, 3, 6 and 12 after implantation	

(continued)

Table 10: Characteristics of the interventions in the studies included (continued)

Study	Intervention	Comparison
TIM-HF	**Basic therapy in compliance with guidelines** ▪ drug therapy ▪ if indicated: implantation of ICD/CRT before baseline visit	
	Telemonitoring ▪ daily measurement of ECG, weight and blood pressure and self-report of health by the patient[d] ▪ automatic transmission ▪ home emergency call allows direct connection to the physician on duty at the centre for TM ***Centre for telemedicine (TM)*** ▪ daily check of transmitted data (prioritized according to urgency) ▪ in case of missing measurements: telephone enquiry with the patient ▪ in case of abnormal measurements: ▫ the centre for TM contacts the patient by telephone within 24 hours after knowledge (in case of unstable status immediate contacting of the patient and the study centre) and ▫ initiates various measures up to change of medication (combined with referral to the investigator) or the initiation of emergency measures (e.g. alerting an emergency physician) ▪ staffed by at least 1 physician and at least 1 nurse (24 hours/7 days a week)	
	Telephone support ▪ monthly structured telephone call between the centre for TM and the patient on the topics of disease status, evaluation of depressive symptoms, behaviour in emergency situations and solution of technical problems	
	Personal after-care ▪ at months 3, 6, 9, 12, 18 and 24 ▪ additional after-care possible	

(continued)

Table 10: Characteristics of the interventions in the studies included (continued)

Study	Intervention	Comparison
TIM-HF2	**Basic therapy in compliance with guidelines** ▪ drug therapy ▪ regular check whether implantation of ICD/CRT is indicated	
	Telemonitoring ▪ daily transmission of data on ECG, oxygen saturation, weight and blood pressure and self-report of health by the patient[e] ▪ automatic transmission ▪ home emergency call allows direct connection to the physician on duty at the centre for TM ***Centre for telemedicine (TM)*** ▪ daily check of transmitted data (prioritized according to urgency) ▪ in case of missing measurements: telephone enquiry with the patient within 1 day ▪ in case of abnormal measurements: ▫ the centre for TM contacts the patient by telephone within 24 hours after knowledge (in case of unstable status immediately) and ▫ initiates various measures up to change of medication (in consultation with the treating physician) or initiation of emergency measures (e.g. alerting an emergency physician) ▪ structured optimization of the medication to achieve target values, e.g. of blood pressure (in consultation with the investigator) ▪ staffed by physicians and nurses (24 hours/7 days a week) ▫ in high-risk patients (MR-proADM level > 1.2 nmol/L) care primarily provided by physician	
	Training ▪ at start of the study: ▫ training of patients in the handling of the telemedicine devices ▫ patient training on the monitoring of symptoms and self-management in cardiac failure	
	Telephone support ▪ monthly structured telephone call between the centre for TM and the patient on the topics of disease-related symptoms, self-care behaviour, problems in association with the disease and/or the devices	
	Personal after-care ▪ planned visits at 3, 6, 9 and 12 months after randomization ▪ additional after-care possible	

(continued)

Table 10: Characteristics of the interventions in the studies included (continued)

a: The authors of the TELECART study described the tasks of the central monitoring unit and essential event and trend data of interest that should be monitored and passed on to the investigator on weekdays [29]. For further details on the monitoring, the publication referred to the design publication of the IN-TIME study [25]. In summary, it was therefore assumed that the telemonitoring used in the TELECART study essentially corresponded to the telemonitoring used in the IN-TIME study.
b: According to publication [29], 3 specific types of devices were used in the intervention group. The instructions for use of the devices [51,52] show that data were transmitted daily.
c: The information was found only in the design publication of the IN-TIME study [25], which was referred to in the publication of the TELECART study [29].
d: The telemonitoring system consisted of a scale, a blood pressure monitor, an ECG event recorder, a modified personal digital assistant (PDA), and a home emergency call system. The health self-assessment was measured by entering a numerical value between 1 and 5 (1 = best state, 5 = worst state, as perceived by the patient) into the modified PDA.
e: The telemonitoring system consisted of a scale, a blood pressure monitor, an ECG event recorder, a digital tablet, and a home emergency call system. The health self-assessment was measured by entering a numerical value between 1 and 5 (1 = best state, 5 = worst state, as perceived by the patient).
CRT: cardiac resynchronization therapy; CRT-D: cardiac resynchronization therapy defibrillator; ECG: electrocardiogram; ICD: implantable cardioverter defibrillator; MR-proADM: mid-regional pro-atrial natriuretic peptide; TM: telemedicine

5.3 Assessment of criteria of the risk of bias across outcomes

The assessment of criteria of the risk of bias across outcomes is presented in the following Table 11.

Table 11: Risk of bias across outcomes

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias across outcomes
			Patients	Treating staff			
IN-TIME	Yes	Yes	No	No	No[a]	No[b]	High
TELECART	Yes	Yes	Unclear	No	Unclear[c]	Yes	High
TIM-HF	Yes	Yes	No	No	Unclear[d]	No[e]	High
TIM-HF2	Yes	Yes	No	No	Unclear[f]	No[e]	High

a: Unplanned interim analysis, which led to an increase in sample size.
b: Non-transparent patient flow.
c: No sample-size planning reported.
d: Although data on cardiac decompensation and health-related quality of life were recorded, they were not or only incompletely available.
e: The centre for telemedicine conducted a monthly structured telephone call on disease-related topics with the patients in the intervention group.
f: Data on depressive symptoms and health status were not available.

The risk of bias at study level was rated as high for all 4 studies. It was unclear for 3 studies whether there was selective reporting. Due to the lack of transparency in the patient flow, the risk of bias of the results of the IN-TIME study was rated as high. No sample size planning was reported for the TELECART study, which also resulted in a high risk of bias. In the studies TIM-HF and TIM-HF2, patients in the telemonitoring group received intensified monthly training in the form of a structured telephone call on disease-related topics, among others. Patients in the control arm did not receive comparable intensified training. Since this caused differences in the backbone therapy between the 2 groups, a potential cointervention bias could not be ruled out. The risk of bias of both studies was therefore rated as high.

Since the high risk of bias at study level has a direct impact at outcome level, all reported outcomes had a high risk of bias.

5.4 Patient-relevant outcomes

Table 12 shows an overview of the available data on patient-relevant outcomes from the included studies. It was possible to extract data on patient-relevant outcomes from 4 studies. For the outcome categories “mortality” and “hospitalization”, separate analyses were performed for the total number of patients with event (all-cause mortality or hospitalization) and for the number of patients with cardiovascular event (cardiovascular mortality or cardiovascular hospitalization). If only data on cardiac mortality or hospitalization due to cardiac failure instead of cardiovascular mortality or hospitalization were available in the studies, these data were used. Data on the outcomes “depressive symptoms”, “health status” and “health-related quality of life” were planned in 2 studies, but were partly not reported or reported incompletely. One study reported data on the outcome “SAEs”, but these were not usable for the benefit assessment.

Incomplete data for several outcomes

Some studies had planned the recording of data on health status (IN-TIME, TIM-HF2), depressive symptoms (TIM-HF, TIM-HF2), cardiac decompensation (TIM-HF) and health-related quality of life (TIM-HF). However, these data were either not or not completely reported. For example, the proportion of missing values was about 70% for the outcome “health status”, and about 75% for the outcome “depressive symptoms”.

In all 4 studies included, adverse events (AEs) were to be recorded according to the study-specific methods. Data on SAEs were only reported in the CSR of the IN-TIME study. However, these data were not usable for the benefit assessment as the presentation also included values of 52 non-randomized patients. Results on SAEs were missing completely in the remaining 3 studies with a total of 2472 patients.

Table 12: Overview of the extraction of patient-relevant outcomes, data availability

Outcome / Study	Mortality		Morbidity							Hospitalization		Health-related quality of life			
	Mortality/overall survival	Cardiovascular	Stroke	Cardiac decompensation	Cardiac arrhythmia requiring treatment	Health status	Morbidity due to cardiac failure	Thromboembolic events	Depressive symptoms	Total	Cardiovascular	MLHF	SF-36	Shocks delivered	SAEs
IN-TIME	●	●	–	–	–	⭘	⭘	–	–	–	●[b]	–	–	–	(–)[d]
TELECART	●	●[a]	⭘	–	⭘	–	–	–	–	–	●[b]	–	–	⭘	–
TIM-HF	●	●	–	(●)	–	–	–	–	⭘	⭘	●	–	(●)	–	–
TIM-HF2	●	●	–	–	–	(●)	⭘[c]	–	(●)	–	●	⭘	–	–	–

–: no data available; (–): data not usable; (●): data recorded, but not or incompletely reported; ⭘: data available and usable; ●: data considered in meta-analysis

a: Only results on cardiac mortality were available; these were used as a substitute for the outcome "cardiovascular mortality".

b: Only results on hospitalization due to cardiac failure were available; these were used as a substitute for the outcome "cardiovascular hospitalization".

c: No change in NYHA class reported, only proportion of patients per NYHA class.

d: Data not usable as the data of 52 non-randomized patients were included in addition to the randomized patients.

MHLF: Minnesota Living with Heart Failure; NYHA: New York Heart Association; SAE: serious adverse event; SF-36: Short Form (36) Health Survey

5.4.1 Outcome-specific risk of bias

A high risk of bias across outcomes was determined for all included studies (see Section 5.3). Hence, there was a high risk of bias also for all outcomes. Therefore, the risk of bias at outcome level is not assessed and presented in this report.

5.4.2 Results on all-cause mortality

Table 13 shows the results on the outcome "all-cause mortality".

Table 13: Results – all-cause mortality

Study Date of analysis	TM N	TM Patients with events n (%)	Control N	Control Patients with events n (%)	TM vs. control OR [95% CI]; p-value
IN-TIME					
12 months	333	10 (3.0)	331	27 (8.1)	See meta-analysis (Figure 2)
TELECART					
12 months	89	7 (7.9)	94	8 (8.5)	See meta-analysis (Figure 2)
TIM-HF					
26 months[a]	354	54 (15.3)[b]	356	55 (15.4)[b]	See meta-analysis (Figure 2)
TIM-HF2					
12 months	765	61 (8)	773	89 (12)	See meta-analysis (Figure 2)

a: Median follow-up.
b: Institute's calculation.
CI: confidence interval; n: patients with events; N: number of analysed patients; OR: odds ratio; TM: telemonitoring; vs.: versus

Meta-analysis

Figure 2 shows the meta-analysis on the outcome "all-cause mortality".

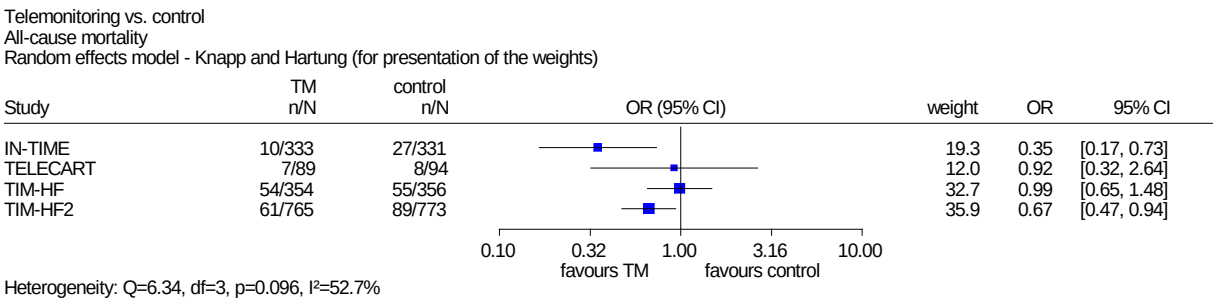

Figure 2: All-cause mortality (meta-analysis)

The meta-analysis of the data of the 4 studies on all-cause mortality according to Knapp and Hartung and DerSimonian-Laird found no statistically significant effect. Whereas the studies IN-TIME and TIM-HF2 showed a statistically significant advantage of telemonitoring, there

were no statistically significant effects for the studies TELECART and TIM-HF. There was no hint of a benefit or harm of telemonitoring regarding all-cause mortality.

Subgroup characteristics and other effect modifiers

For the outcome "all-cause mortality", it was possible to calculate interaction tests from the available data for the characteristic "telemonitoring type 1 versus type 2" (see Section 5.2) and for the characteristic "depressive symptoms".

There was an indication of an interaction with the intervention only for the characteristic "depressive symptoms" (p = 0.014). The analysis was based only on data on telemonitoring type 2 (studies TIM-HF and TIM-HF2) as no information on depressive symptoms was available from the 2 other studies. For patients without depressive symptoms, there was a statistically significant advantage of telemonitoring for the outcome "all-cause mortality". For patients with depressive symptoms, there was no statistically significant effect, the numerical result was to the disadvantage of telemonitoring (Figure 3).

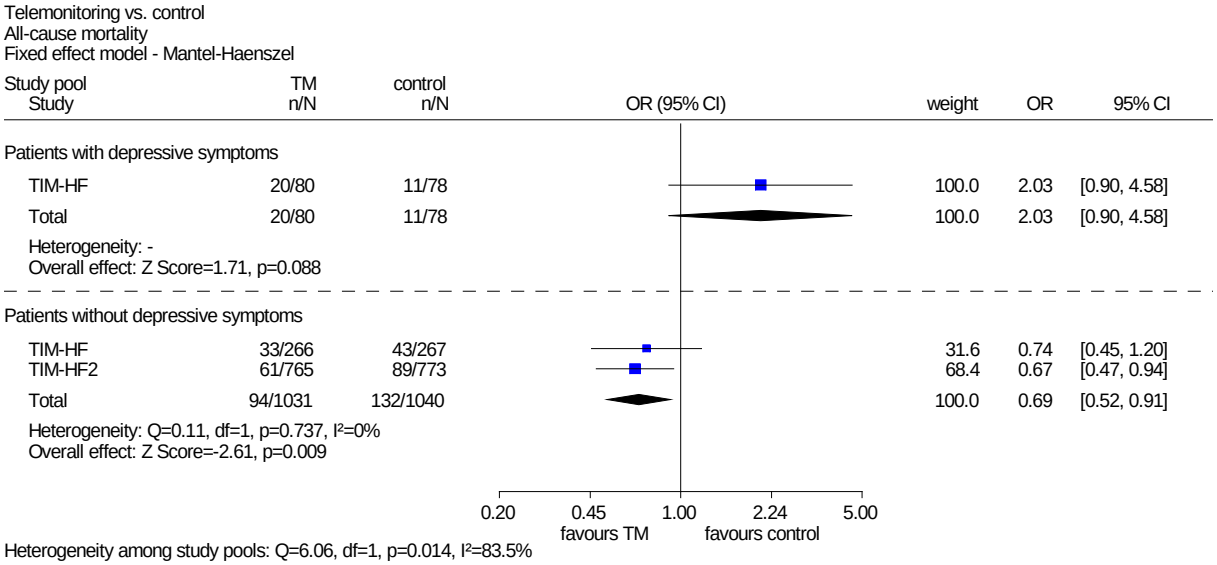

Figure 3: Subgroup analysis according to presence of depressive symptoms for the outcome "all-cause mortality" (meta-analysis)

Further operationalizations

There were survival time data on the outcome "all-cause mortality", which were pooled in a meta-analysis in the framework of a sensitivity analysis (without presentation) and which did not contradict the result of the analyses based on the odds ratio (OR).

Conclusion on the benefit for all-cause mortality

For the outcome "all-cause mortality", no advantage of telemonitoring was found at the overall study level, i.e. it remains unclear whether the use of the telemonitoring procedures investigated

offers a survival advantage or whether there is no difference in the probability of dying with and without telemonitoring. An advantage was shown in the subgroup of patients without depressive symptoms who received telemonitoring type 2, however (based on 2 studies with a high risk of bias). Hence, there is an indication of a benefit of telemonitoring type 2 for patients without depressive symptoms for the outcome "cardiovascular mortality".

5.4.3 Results on cardiovascular mortality

Table 14 shows the results on the outcome "cardiovascular mortality".

Table 14: Results – cardiovascular mortality

Study Date of analysis	TM N	TM Patients with events n (%)	Control N	Control Patients with events n (%)	TM vs. control OR [95% CI]; p-value
Cardiovascular mortality					
IN-TIME					
12 months	333	8 (2.4)[a]	331	21 (6.3)[a]	See meta-analysis (Figure 4)
TIM-HF					
26 months[b]	354	40 (11.3)[a]	356	46 (12.9)[a]	See meta-analysis (Figure 4)
TIM-HF2					
12 months	765	39 (5)	773	59 (8)	See meta-analysis (Figure 4)
Cardiac mortality					
TELECART					
12 months	89	3 (3.4)	94	5 (5.3)	See meta-analysis (Figure 4)

a: Institute's calculation.
b: Median follow-up.
CI: confidence interval; n: patients with events; N: number of analysed patients; OR: odds ratio; TM: telemonitoring; vs.: versus

Meta-analysis

Figure 4 shows the meta-analysis on the outcome "cardiovascular mortality".

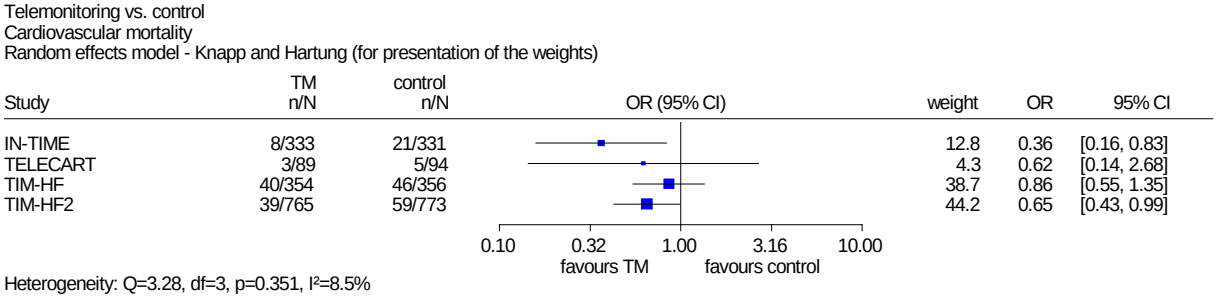

Figure 4: Cardiovascular mortality (meta-analysis)

Using the method according to Knapp and Hartung, the meta-analysis on cardiovascular mortality showed no statistically significant difference between the 2 treatment groups; but using the method of DerSimonian-Laird, it did. The qualitative consideration showed effects, which were moderately in the same direction, and that showed an advantage of telemonitoring for the outcome "cardiovascular mortality".

Subgroup characteristics and other effect modifiers

For the outcome "cardiovascular mortality", it was possible to calculate an interaction test from the available data for the characteristic "telemonitoring type 1 versus type 2" (see Section 5.2). This resulted in no indication of an interaction with the intervention.

Further operationalizations

There were survival time data on the outcome "cardiovascular mortality", which were pooled in a meta-analysis in the framework of a sensitivity analysis (without presentation) and which did not contradict the result of the analyses based on the OR.

Conclusion on the benefit for cardiovascular mortality

For the outcome "cardiovascular mortality", the consideration of individual studies (qualitative evidence synthesis) showed an advantage of telemonitoring, i.e. cardiovascular deaths were less frequent. This resulted in a hint of a benefit of telemonitoring for the outcome "cardiovascular mortality".

5.4.4 Results on stroke

Table 15 shows the results on the outcome "stroke".

Table 15: Results – stroke

Study Date of analysis	TM N	TM Patients with events n (%)	Control N	Control Patients with events n (%)	TM vs. control OR [95% CI]; p-value
TELECART					
12 months	89	3[a] (3.4)[b]	94	4[a] (4.3)[b]	0.87 [0.17; 3.61][c]; p = 0.549[d]

a: Unclear whether the numbers provided refer to patients with events or to the number of events. Strokes reported as SAEs.
b: Institute's calculation.
c: Institute's calculation of OR and CI (asymptotic), unconditional exact test (CSZ method according to [53]).
d: Pearson's χ^2 test
CI: confidence interval; CSZ: convexity, symmetry, z score; n: patients with events; N: number of analysed patients; OR: odds ratio; TM: telemonitoring; vs.: versus

No statistically significant difference was shown between the treatment groups for the outcome "stroke".

Subgroup characteristics and other effect modifiers

None of the planned subgroup analyses was possible for the outcome "stroke".

Conclusion on the benefit for stroke

This resulted in no hint of a benefit or harm of telemonitoring for the outcome "stroke".

5.4.5 Results on cardiac decompensation

According to the study protocol, it was planned to record results on the outcome "cardiac decompensation" in the TIM-HF study [39]. No results were available, however. Due to the incomplete data (see Section 5.4), no conclusion on the benefit was drawn for the outcome "cardiac decompensation".

5.4.6 Results on cardiac arrhythmia requiring treatment

Table 16 shows the results on ventricular arrhythmias.

Table 16: Results – ventricular arrhythmias

Study Date of analysis	TM		Control		TM vs. control
	N	Patients with events n (%)	N	Patients with events n (%)	OR [95% CI]; p-value[a]
TELECART[a]					
12 months	89	6[b] (6.7)[c]	94	11[b] (11.7)[c]	0.55 [0.19; 1.54][c]; 0.262[d]

a: Event operationalized as persistent ventricular tachycardia/persistent ventricular fibrillation.
b: Unclear whether the numbers provided refer to patients with events or to the number of events.
c: Institute's calculation under the assumption that the provided numbers refer to patients with events.
d: Institute's calculation, unconditional exact test (CSZ method according to [53]).
CI: confidence interval; CSZ: convexity, symmetry, z score; n: patients with events; N: number of analysed patients; OR: odds ratio; TM: telemonitoring; vs.: versus

There was no statistically significant difference between the treatment groups with regard to ventricular arrhythmias.

Subgroup characteristics and other effect modifiers

None of the planned subgroup analyses was possible for the outcome "cardiac arrhythmia requiring treatment".

Conclusion on the benefit for cardiac arrhythmia requiring treatment

This resulted in no hint of a benefit or harm of telemonitoring for the outcome "cardiac arrhythmia requiring treatment".

5.4.7 Results on venous and/or arterial thromboembolic events

No results were available on venous and/or arterial thromboembolic events. This resulted in no hint of a benefit or harm of telemonitoring for this outcome.

5.4.8 Results on hospitalization overall

Table 17 shows the results on the outcome "hospitalization overall".

Table 17: Results – hospitalization overall

Study	TM		Control		TM vs. control
Date of analysis	N	Patients with events n (%)	N	Patients with events n (%)	OR [95% CI]; p-value
TIM-HF					
26 months[a]	354	192 (54.2)[b]	356	179 (50.3)[b]	1.17 [0.87; 1.57]; 0.300

a: Median follow-up.
b: Institute's calculation.
CI: confidence interval; CSZ: convexity, symmetry, z score; n: patients with events; N: number of analysed patients; OR: odds ratio; TM: telemonitoring; vs.: versus

No statistically significant difference was shown between the treatment groups for the outcome "hospitalization overall". Hence, there was no hint of a benefit or harm of telemonitoring regarding hospitalization overall.

Subgroup characteristics and other effect modifiers

No planned subgroup analyses were possible for the outcome "hospitalization overall" due to missing data.

Further operationalizations

In addition, survival time data were available for the outcome "hospitalization overall", but they would not have had a relevant influence on the conclusion of the benefit.

Conclusion on the benefit for hospitalization overall

No advantage of telemonitoring was shown for the outcome "hospitalization overall". This resulted in no hint of a benefit or harm of telemonitoring for the outcome "hospitalization overall".

5.4.9 Results on cardiovascular hospitalization

Table 18 shows the results on the outcome "cardiovascular hospitalization". As described in Section 5.4, the data on hospitalization due to cardiac failure were used as a substitute if no data were available for cardiovascular hospitalization. This applied to the studies IN-TIME and TELECART.

Table 18: Results – cardiovascular hospitalization

Study Date of analysis	TM N	TM Patients with events n (%)	Control N	Control Patients with events n (%)	TM vs. control OR [95% CI]; p-value
Cardiovascular hospitalization					
TIM-HF					
26 months[a]	354	141 (39.8)	356	132 (37.1)	See meta-analysis (Figure 5)
TIM-HF2					
12 months	765	252 (32.9)	773	269 (34.8)	See meta-analysis (Figure 5)
Hospitalization due to cardiac failure					
IN-TIME[b]					
12 months	333	28 (8.4)[c]	331	35 (10.6)[c]	See meta-analysis (Figure 5)
TELECART					
12 months	89	14[d] (15.7)	94	27[d] (28.7)	See meta-analysis (Figure 5)

a: Median follow-up.
b: Any hospitalization due to cardiac failure that was associated with at least 1 overnight stay and led to a medication adjustment.
c: Institute's calculation.
d: Unclear whether the numbers provided refer to patients with events or to the number of events.
CI: confidence interval; CSZ: convexity, symmetry, z score; n: patients with events; N: number of analysed patients; OR: odds ratio; TM: telemonitoring; vs.: versus

Meta-analysis

Figure 5 shows the meta-analysis on the outcome "cardiovascular hospitalization".

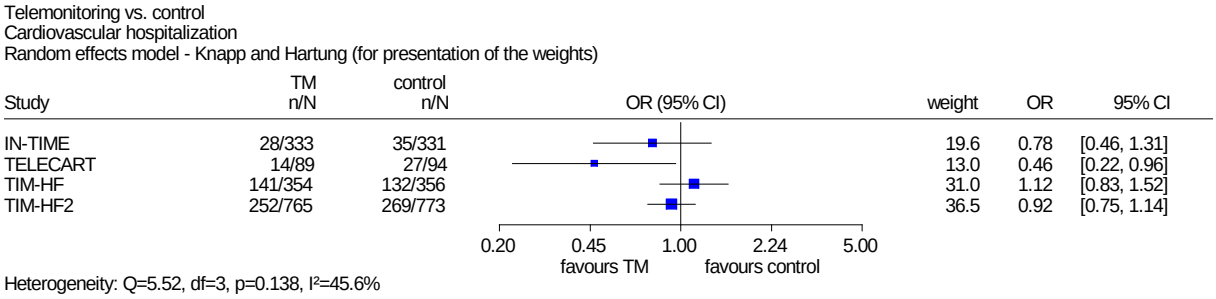

Figure 5: Cardiovascular hospitalization (meta-analysis)

Using the methods according to Knapp and Hartung and DerSimonian-Laird, the meta-analysis on the outcome "cardiovascular hospitalization" showed no statistically significant difference between the 2 treatment groups. In addition, the results were not in the same direction.

Subgroup characteristics and other effect modifiers

For the outcome "cardiovascular hospitalization", it was possible to calculate an interaction test from the available data for the characteristic "telemonitoring type 1 versus type 2" (see Section 5.2). This resulted in no indication of an interaction.

Further operationalizations

In addition, survival time data were available for cardiovascular hospitalization, but they would not have had a relevant influence on the conclusion of the benefit.

Conclusion on the benefit for cardiovascular hospitalization

No advantage or disadvantage of telemonitoring was shown for the outcome "cardiovascular hospitalization". Hence, there was no hint of a benefit or harm of telemonitoring regarding cardiovascular hospitalization.

5.4.10 Results on shocks delivered

Table 19 shows the results on the outcome "shocks delivered".

Table 19: Results – patients with shocks

Study	TM		Control		TM vs. control
Date of analysis	N	Patients with events n (%)	N	Patients with events n (%)	OR [95% CI]; p-value
TELECART					
12 months	89	10[a] (11.2[b])	94	16[a] (17.0[b])	ND [ND]; 0.208[c]

a: Unclear whether the numbers provided refer to patients with events or to the number of events.
b: Institute's calculation of the percentages.
c: Pearson's χ^2 test.
CI: confidence interval; n: patients with events; N: number of analysed patients; ND: no data; OR: odds ratio; TM: telemonitoring; vs.: versus

No statistically significant difference was shown between the treatment groups for the outcome "shocks delivered".

Subgroup characteristics and other effect modifiers

No planned subgroup analyses were possible for the outcome "shocks delivered" due to missing data.

Conclusion on the benefit for shocks delivered

This resulted in no hint of a benefit or harm of telemonitoring for the outcome "shocks delivered".

5.4.11 Results on serious adverse events

Table 20 shows the results on the outcome "SAEs".

Table 20: Results – serious adverse events

Study	TM		Control		TM vs. control
Date of analysis	N	Patients with events n (%)	N	Patients with events n (%)	OR [95% CI]; p-value[a]
IN-TIME					
12 months	333[a]	145	331[a]	160	NC

a: The analysis contains 52 additional patients whose randomization allocation was not provided.
CI: confidence interval; n: patients with events; N: number of analysed patients; NC: not calculated; OR: odds ratio; TM: telemonitoring; vs.: versus

No effect was calculated for the outcome "SAEs" because 52 additional patients whose randomization allocation was not provided were included in the analysis of the IN-TIME study.

Subgroup characteristics and other effect modifiers

No planned subgroup analyses were possible for the outcome "SAEs" due to missing data.

Conclusion on the benefit for serious adverse events

Due to the incomplete data (see Section 5.4), no conclusion on the benefit was drawn for the outcome "SAEs".

5.4.12 Results on health-related quality of life

Table 21 and Table 22 show the results on the outcome "health-related quality of life".

Table 21: Results – health-related quality of life, MLHFQ

Questionnaire	Study (date of analysis)	n/N	Values at baseline mean (SD)	Values at end of study mean (SD)	Change compared with baseline mean [95% CI]	TM vs. control Difference of the changes [95% CI]; p-value[a]
MLHFQ[b]	**TIM-HF2 (12 M)**					
	TM	649/796	ND	ND	−3.08 [−4.42; −1.75]	−1.11 [−3.01; 0.80]; 0.26
	Control	624/775	ND	ND	−1.98 [−3.34; −0.61]	

a: Estimated using ANCOVA, adjusted for baseline value.
b: Higher values indicate deterioration in quality of life (range between 0 and 105 [54]).
CI: confidence interval; M: months; MLHFQ: Minnesota Living with Heart Failure Questionnaire; n: number of analysed patients; N: number of randomized patients; ND: no data; SD: standard deviation; TM: telemonitoring; vs.: versus

Table 22: Results – health-related quality of life, SF-36

Questionnaire	Study Subscale	N	Values 12 months		Values 24 months	
			Mean (SD)[a]	TM vs. control difference[a] [95% CI]; p-value[a]	Mean (SD)[a]	TM vs. control difference[a] [95% CI]; p-value[a]
SF-36[a]	TIM-HF					
	PCS sum score					
	TM	ND	54.3 (1.2)[c]	ND [ND]; 0.01	53.8 (1.4)[b]	ND [ND]; 0.3
	Control	ND	49.9 (1.2)[c]		51.7 (1.4)[b]	
	MCS sum score					
	TM	ND	ND	ND	ND	ND
	Control	ND	ND		ND	

a: Estimated using a model for repeated measures with the variables treatment, time point, baseline value and interaction between treatment and time point.
b: Higher values indicate improvement in quality of life.
c: No information on the number of patients the information refers to.
CI: confidence interval; MCS: Mental Health Composite Scale; N: number of analysed patients; ND: no data; PCS: Physical Composite Scale; SD: standard deviation; SF-36: Short Form (36) Health Survey; TM: telemonitoring; vs.: versus

The TIM-HF2 study (Minnesota Living with Heart Failure Questionnaire [MLHFQ]) produced no statistically significant results.

The results on the outcome "health-related quality of life" in the TIM-HF study were incomplete. Results on the Mental Health Composite Scale (MCS) sum score of the Short Form (36) Health Survey (SF-36) were missing. The authors reported only results on the Physical Composite Scale (PCS) sum score. The difference between the groups for the PCS at the time point of 12 months was statistically significant. The clinical relevance of the effect remained unclear, however, because, due to a lack of data on the number of patients, Hedges' g could not be calculated. There was no statistically significant effect at the time point of 24 months.

Subgroup characteristics and other effect modifiers

None of the planned subgroup analyses was possible for the outcome "health-related quality of life".

Conclusion on the benefit for health-related quality of life

Due to the incomplete data – complete data were only available for 56% of the patients – no conclusion on the benefit was drawn for the outcome "health-related quality of life".

5.4.13 Results on depressive symptoms

Table 23 shows the results on the outcome "depressive symptoms".

Table 23: Results – depressive symptoms

Study Date of analysis	TM		Control		TM vs. control
PHQ-9 score	N	Patients with events n (%)	N	Patients with events n (%)	OR [95% CI]; p-value[b]
TIM-HF					
12 months	285[a]		281[a]		
No depression		222 (78)		208 (74)	1.27 [0.85; 1.89]; 0.24
Minor depression		29 (10)		27 (10)	
Major depression		34 (12)		46 (16)	

a: Institute's calculation.
b: Estimated using logistic regression for ordinal outcomes.
CI: confidence interval; n: patients with events; N: number of analysed patients; ND: no data; OR: odds ratio; PHQ-9: Patient Health Questionnaire-9; TM: telemonitoring; vs.: versus

From the TIM-HF study, data at 24 months were also available. These could not be used for the assessment, however, as > 30% of the patients were missing at this time point.

According to the study protocol, it was planned to record results on the outcome "depressive symptoms" also in the TIM-HF2 study [40]. No results were available, however.

Subgroup characteristics and other effect modifiers

None of the planned subgroup analyses was possible for the outcome "depressive symptoms".

Conclusion on the benefit for depressive symptoms

Due to the incomplete data – data were only available for 25% of the patients – no conclusion on the benefit was drawn for the outcome "depressive symptoms".

5.4.14 Results on health status

It was planned for the benefit assessment to include the result on the visual analogue scale (VAS) of the European Quality of Life-5 Dimensions (EQ-5D) (TIM-HF2) and the result on deterioration in the patient global assessment (PGA) (IN-TIME) for the outcome "health status".

Table 24 shows the available results on deterioration in PGA.

Table 24: Results – deterioration in patient global assessment

Study Date of analysis	TM		Control		TM vs. control
	N	Patients with events n (%)	N	Patients with events n (%)	OR [95% CI]; p-value
IN-TIME[a]					
12 months	333	10 (3.0)[b]	331	8 (2.4)[b]	1.25 [0.49; 3.21]; 0.683

a: Moderately to notably worse values in patient global assessment.
b: Institute's calculation.
CI: confidence interval; n: patients with events; N: number of analysed patients; ND: no data; OR: odds ratio; TM: telemonitoring; vs.: versus

According to the study protocol, it was planned to record results on the outcome "EQ-5D" in the TIM-HF2 study [40]. No results were available, however.

Subgroup characteristics and other effect modifiers

None of the planned subgroup analyses was possible for the outcome "health status".

Conclusion on the benefit for health status

Due to the incomplete data – data were only available for 30% of the patients – no conclusion on the benefit was drawn for the outcome "health status".

5.4.15 Results on morbidity due to cardiac failure

Table 25 and Table 26 show the results on morbidity due to cardiac failure.

Table 25: Results – deterioration in NYHA class

Study Date of analysis	TM		Control		TM vs. control
	N	Patients with events n (%)	N	Patients with events n (%)	OR [95% CI]; p-value
IN-TIME					
12 months	333	29 (8.7)[a]	331	35 (10.6)[a]	ND [ND]; 0.43[b]

a: Institute's calculation.
b: Pearson's χ^2 test.
CI: confidence interval; n: patients with events; N: number of analysed patients; ND: no data; OR: odds ratio; TM: telemonitoring; vs.: versus

Table 26: Results – distribution of NYHA classes

Study Time point of analysis NYHA class	TM N	TM Patients with events n (%)	Control N	Control Patients with events n (%)	TM vs. control Effect measure [95% CI]; p-value
TIM-HF					
12 months	318[a, b]		318[a, b]		
I		37 (11)		27 (8)	ND [ND]; 0.589[c]
II		160 (46)		170 (49)	
III		111 (32)		112 (32)	
IV		10 (3)		9 (3)	
24 months	233[a, d]		241[a, b]		
I		21 (8)		19 (8)	ND [ND]; 0.613[c]
II		114 (45)		124 (49)	
III		90 (35)		75 (30)	
IV		8 (3)		7 (3)	

a: Institute's calculation.
b: 28 patients in this group had already died at the time point of recording.
c: Pearson's χ^2 test, Institute's calculation.
d: 21 patients in this group had already died at the time point of recording. Since 28 patients had already died at the time point of 12 months, it can be assumed that this number is incorrect.

CI: confidence interval; n: patients with events; N: number of analysed patients; ND: no data; NYHA: New York Heart Association; OR: odds ratio; TM: telemonitoring; vs.: versus

No statistically significant difference was shown between the treatment groups for the outcome "morbidity due to cardiac failure".

Subgroup characteristics and other effect modifiers

None of the planned subgroup analyses was possible for the outcome "morbidity due to cardiac failure".

Conclusion on the benefit for morbidity due to cardiac failure

This resulted in no hint of a benefit or harm of telemonitoring for the outcome "morbidity due to cardiac failure".

5.5 Evidence map

The following Table 27 shows the evidence map regarding patient-relevant outcomes.

Table 27: Evidence map regarding patient-relevant outcomes

Mortality		**Morbidity**							**Hospital-ization**				
All-cause mortality	**Cardiovascular**	**Stroke**	**Cardiac decompensation**	**Cardiac arrhythmia requiring treatment**	**Thromboembolic events**	**Health status**	**Morbidity due to cardiac failure**	**Depressive symptoms**	**Total**	**Cardiovascular**	**Shocks delivered**	**Serious adverse events**	**Health-related quality of life**
⇔ / ⇑[a]	⇗	(⇔)	(–)	⇔	–	(–)	⇔	(–)	⇔	⇔	⇔	(–)	(–)

⇑: indication of benefit
⇗: hint of benefit
⇔: no hint, indication or proof, homogeneous result
(⇔): no hint, indication or proof, homogeneous result; the 95% confidence interval for the relative effect is so imprecise that neither halving nor doubling of the effect can be ruled out
(–): no conclusion on the benefit as data were recorded, but not or incompletely reported, or data were not usable
–: no data available
a: Indication of benefit in the subgroup of patients who have no depressive symptoms.

6 Discussion

The present report investigated the benefit of telemonitoring with defined minimum requirements in patients with advanced cardiac failure. In comparison with benefit assessment N16-02, special requirements were placed on the implementation of telemonitoring in order to assess only those strategies with particularly intensive monitoring.

Overall, there was a hint of a benefit of telemonitoring with defined minimum requirements for the outcome "cardiovascular mortality". An indication of a benefit regarding all-cause mortality was only shown for patients without depressive symptoms, based on studies that investigated telemonitoring type 2. A conclusion on the benefit for SAEs and health-related quality of life was not possible due to incomplete or unusable data. Hence, a balancing of the conclusions on the benefit of all outcomes is not possible.

Conclusions on the benefit for mortality

The aim of telemonitoring is to reduce cardiovascular mortality. This was verified in the present benefit assessment with a hint of a benefit for cardiovascular mortality.

In the analysis of all-cause mortality, however, the positive effect of telemonitoring cannot be shown, although the results point in the same direction as the results on cardiovascular mortality. It remains unclear from the analysis whether overall survival between the two groups is the same or whether there is an advantage for telemonitoring. An unfavourable effect of telemonitoring on all-cause mortality appears unlikely when all patients with and without depressive symptoms and both types of monitoring are considered together. If only patients without depressive symptoms are considered, there is a survival advantage in the group with telemonitoring type 2. An unfavourable effect in the group of patients with depressive symptoms and telemonitoring type 2 cannot be excluded. For this reason, the authors of the earlier study on telemonitoring type 2 (TIM-HF), from which the subgroup results on depressive symptoms originate, did not include patients with depressive symptoms in the subsequently planned study (TIM-HF2) and recommended screening for depressive symptoms in this context.

Cardiovascular deaths account for about 2 thirds of all-cause mortality. Overall, the benefit in cardiovascular mortality does not have a (sufficient) impact on all-cause mortality. Since the patients with this disease often have multimorbidities, a certain proportion of patients die from other than cardiovascular causes. This could explain, in terms of dilution, why no effect of telemonitoring is shown in all-cause mortality. A subgroup that does not benefit from telemonitoring, e.g. patients with depressive symptoms, could also have a similar effect.

The data for all-cause mortality point numerically in the same direction: The OR was about 0.7 for both the model according to DerSimonian-Laird and the model according to Knapp-Hartung. Thus, this does not contradict the result for cardiovascular mortality.

Report in comparison with other systematic reviews

The benefit of telemonitoring in cardiac failure has already been investigated in numerous systematic reviews. In accordance with the results of the present benefit assessment, some systematic reviews described a benefit of telemonitoring due to reduced mortality [55]. However, other reviews reported no [56] or only a temporary benefit (180 days) of telemonitoring for this outcome [57]. None of the systematic reviews focused on telemonitoring with defined minimum requirements, as investigated in this benefit assessment. Restrictions of the method were rather made with regard to the telemonitoring systems used. Inglis 2015 [58] and Brons 2018 [59] investigated exclusively non-invasive telemonitoring methods, whereas Health Quality Ontario 2018 investigated telemonitoring with implanted systems [56]. None of the systematic reviews contains data from all 4 studies included in this benefit assessment. Moreover, the subgroup characteristic of depressive symptoms was not considered in any systematic review.

Differences of the studies included

The publication on the TELECART study largely referred to the methods of telemonitoring of the IN-TIME study. Even though the TELECART study lacked some details on the methods of telemonitoring, it was assumed that the telemonitoring strategy in both studies was largely comparable. In contrast, there were differences in comparison with the management strategy in the studies TIM-HF and TIM-HF2, which had a largely comparable approach.

These differences and their possible consequences are discussed below.

Automated and patient-initiated measurements

In contrast to the studies IN-TIME and TELECART, in which the examination parameters were measured and transmitted continuously and fully automatically by means of implanted defibrillators (ICDs or CRT-Ds) and therefore did not require any active involvement of the patients, these measurements were initiated once a day by the patients themselves in the studies TIM-HF and TIM-HF2, which could have affected the completeness of the transmitted data.

One might assume that systems that require the cooperation of patients are less reliable in the daily transfer to the centre for TM than automated systems. As can be inferred from the data, however, a transfer rate was achieved that comes close to that of automated procedures – possibly due to the intensified form of patient involvement in the form of regular telephone support and training. Thus, both approaches seem suitable to maintain the telemonitoring intensity to be investigated here.

Training as part of telemonitoring

The TIM-HF study and, to an even greater extent, the TIM-HF2 study conducted regular trainings for the participants in the intervention group to accompany telemonitoring.

Patient training is an important part of treatment in the therapeutic indication of cardiac failure [60] and is recommended in the current guidelines [61]. Since all patients in both groups of the

studies TIM-HF and TIM-HF2 were to receive treatment in accordance with the guidelines, it can be assumed that a certain extent of training was also carried out in the respective control groups. However, due to the monthly structured telephone calls, it can be expected that the intensity of training in these studies was higher in the intervention groups than in the control groups. It is unclear whether the training units were an essential active component of the telemonitoring strategy of the studies TIM-HF and TIM-HF2 and whether, in systems requiring patient involvement, only intensified training might ensure sufficient adherence for intensive telemonitoring. It can be assumed that intensified training and support tailored to the individual needs of the patients also influences the perception and behaviour of the patients with regard to their disease. Due to the complexity of this telemonitoring strategy, however, the respective contribution of the individual components to the overall effect cannot be determined.

Since patients in the control arms of the studies TIM-HF and TIM-HF2 did not receive comparable intensified training and there was therefore a difference in the backbone therapy between the 2 groups, a potential cointervention bias was assumed for these studies. In order to take this into account in the assessment, the risk of bias across outcomes was rated as high in both studies. Particularly in the case of telemonitoring strategies that – as in the studies TIM-HF and TIM-HF2 – require patient involvement, it seems sensible to supplement telemonitoring with intensified patient training. If, in the framework of the present benefit assessment, intensified training had been regarded as a mandatory characteristic of telemonitoring with defined minimum requirements, the risk of bias across outcomes in both studies would have been rated as low. This might have resulted in a higher certainty of conclusions on the benefit of such a telemonitoring strategy.

Patient populations of the studies included

Ejection fraction

The TIM-HF2 study included patients with lower reduction in LVEF (LVEF < 45% or LVEF > 45% for permanent medicinal therapy with a diuretic) than the other 3 studies (LVEF ≤ 35%).

Based on the ejection fraction, current guidelines classify cardiac failure into different degrees of severity, which differ in their aetiology, the comorbidities and response to therapy [61]. The proportion of patients in the TIM-HF2 study who had an LVEF < 40% (heart failure with preserved ejection fraction), which was comparable to the one in the other studies, was only 44%. More than 30% of the patients had an LVEF between 40% and 50%. They fall into the group of heart failure with mid-range ejection fraction (HFmrEF) – called “grey zone” in the literature – for which no uniform treatment standards have been defined to date [61]. More than 20% of the patients had an LVEF > 50% and can therefore, according to the guidelines, be classified as having heart failure with preserved ejection fraction, which is associated with a lower mortality rate [4,61]. In contrast to the other 3 studies, the patient population in the TIM-HF2 study was mixed with respect to the severity of cardiac failure. It could therefore be assumed that the majority of patients in the TIM-HF2 study were less seriously affected than

patients in the other studies. This seems unlikely, however, as both the distribution of patients among NYHA classes and the rates of all-cause mortality were comparable between the studies.

Presence of depressive symptoms

Based on a prospective subgroup analysis, the authors of the TIM-HF study concluded that the benefit of telemonitoring was significantly influenced by the presence of depressive symptoms [21]. In the study, these patients benefited less from telemonitoring than those without depressive symptoms. Consequently, only patients without depressive symptoms were included in the TIM-HF2 study [50].

In order to determine in the present benefit assessment whether the effect of telemonitoring on overall survival is influenced by the presence of depressive symptoms, an additional subgroup analysis for the characteristic "depressive symptoms" was performed for this report, including the data from the studies TIM-HF and TIM-HF2. A statistically significant advantage for telemonitoring was shown for the group of patients without depressive symptoms. In patients with depressive symptoms, the result was clearly opposite and not statistically significant.

The result of the subgroup analysis is based only on data on telemonitoring type 2 because data from the studies IN-TIME and TELECART (both type 1) are not available separately for the presence of depressive symptoms. It is unclear whether the characteristic "depressive symptoms" also leads to different effects in telemonitoring type 1 or whether the interaction is due to a combination of the characteristics "depressive symptoms" and "telemonitoring type 2". However, it can be assumed that the benefit of telemonitoring by means of an implant that does not require regular patient involvement due to the fully automated measurement and transmission of data is less affected by the presence of depressive symptoms than telemonitoring type 2.

Regardless of the type of telemonitoring, it is quite possible that patients with depressive symptoms do not benefit to the same extent from telemonitoring due to the large number of possible associations between a cardiac disorder and a psychiatric disorder. For several years, the relationship between cardiac failure and the presence of depression has been discussed [62] and the presence of depression has been associated with greater mortality [63].

7 Conclusion

The 4 studies included investigated 2 different strategies of telemonitoring with defined minimum requirements. In telemonitoring type 1, the data were automatically measured by the implanted device (ICD or CRT-D), no involvement of the patient was necessary. In telemonitoring type 2, it was the patient's task to measure the data using external, non-invasive devices.

Including all studies, there was no hint of a benefit or harm of telemonitoring for the outcome "all-cause mortality". Data for the subgroups of patients with and without depressive symptoms were only available for telemonitoring type 2. For the outcome "all-cause mortality", there was an indication of a benefit for patients without depressive symptoms.

The joint consideration of telemonitoring type 1 and type 2 showed a hint of a benefit for the outcome "cardiovascular mortality".

There was no hint of a benefit or harm of telemonitoring with defined minimum requirements for the following outcomes: hospitalization overall, cardiovascular hospitalization, stroke, cardiac arrhythmia requiring treatment, thromboembolic events, shocks delivered by a cardiac device and morbidity due to cardiac failure. Due to the incomplete data, no conclusion on the benefit was drawn for the following outcomes: SAEs, depressive symptoms, cardiac decompensation, health status and health-related quality of life.

8 References

1. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG et al. 2009 focused update incorporated into the ACC/AHA 2005 guidelines for the diagnosis and management of heart failure in adults: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. Circulation 2009; 119(14): e391-e479.

2. Bundesministerium für Gesundheit. Zwanzigste Verordnung zur Änderung der Risikostruktur-Ausgleichsverordnung (20. RSA-ÄndV). Bundesgesetzblatt Teil 1 2009; (35): 1542-1569.

3. Robert Koch-Institut (Ed). Gesundheit in Deutschland: Gesundheitsberichterstattung des Bundes; gemeinsam getragen von RKI und Destatis. Berlin: RKI; 2015. URL: http://www.gbe-bund.de/pdf/GESBER2015.pdf.

4. Bundesärztekammer, Kassenärztliche Bundesvereinigung, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften. Nationale VersorgungsLeitlinie: chronische Herzinsuffizienz; Langfassung; Version 3 [online]. 04.2018 [Accessed: 23.07.2019]. URL: https://www.leitlinien.de/mdb/downloads/nvl/herzinsuffizienz/herzinsuffizienz-2aufl-vers3-lang.pdf.

5. Raphael C, Briscoe C, Davies J, Ian Whinnett Z, Manisty C, Sutton R et al. Limitations of the New York Heart Association functional classification system and self-reported walking distances in chronic heart failure. Heart 2007; 93(4): 476-482.

6. Palaniswamy C, Mishkin A, Aronow WS, Kalra A, Frishman WH. Remote patient monitoring in chronic heart failure. Cardiol Rev 2013; 21(3): 141-150.

7. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Telemonitoring mithilfe von aktiven kardialen implantierbaren Aggregaten bei ventrikulärer Tachyarrhythmie sowie Herzinsuffizienz: Abschlussbericht: Auftrag N16-02; Version 1.2 [online]. 04.07.2018 [Accessed: 18.07.2018]. (IQWiG-Berichte; Volume 577). URL: https://www.iqwig.de/download/N16-02_Telemonitoring-mithilfe-von-aktiven-kardialen-implantierbaren-Aggregaten_Abschlussbericht_V1-2.pdf.

8. Helms TM, Stockburger M, Köhler F, Leonhardt V, Müller A, Rybak K et al. Basic structural features of a cardiac telemedicine center for patients with heart failure and implanted devices, cardiac arrhythmias, and increased risk of sudden cardiac death. Herzschrittmacherther Elektrophysiol 2019; 30(1): 136-142.

9. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Telemonitoring mithilfe von aktiven kardialen implantierbaren Aggregaten bei ventrikulärer Tachyarrhythmie sowie Herzinsuffizienz: Dokumentation der Anhörung zum Vorbericht; Auftrag N16-02 [online]. 02.01.2018 [Accessed: 26.03.2018]. URL: https://www.iqwig.de/download/N16-02_Telemonitoring-mithilfe-von-aktiven-kardialen-implantierbaren-Agg....pdf.

10. Hindricks G, Taborsky M, Glikson M, Heinrich U, Schumacher B, Katz A et al. Implant-based multiparameter telemonitoring of patients with heart failure (IN-TIME): a randomised controlled trial. Lancet 2014; 384(9943): 583-590.

11. Tompkins C, Orwat J. A randomized trial of telemonitoring heart failure patients. J Healthc Manag 2010; 55(5): 312-322.

12. Kielblock B, Frye C, Kottmair S, Hudler T, Siegmund-Schultze E, Middeke M. Impact of telemetric management on overall treatment costs and mortality rate among patients with chronic heart failure. Dtsch Med Wochenschr 2007; 132(9): 417-422.

13. Gemeinsamer Bundesausschuss. Konkretisierung des Auftrags des Gemeinsamen Bundesausschusses an das Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen: Bewertung eines datengestützten, zeitnahen Managements in Zusammenarbeit mit einem ärztlichen telemedizinischen Zentrum für Patientinnen und Patienten mit einer fortgeschrittenen Herzinsuffizienz gemäß § 135 Absatz 1 SGB V [online]. 28.03.2019 [Accessed: 24.04.2019]. URL: https://www.g-ba.de/downloads/40-268-5678/2019-03-28_IQWiG-Beauftragung_Telekardiologie_Konkretisierung.pdf.

14. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 13.09.2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

15. ICH Expert Working Group. ICH harmonised tripartite guideline: structure and content of clinical study reports; E3; current step 4 version [online]. 30.11.1995 [Accessed: 05.09.2018]. URL: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_Guideline.pdf.

16. Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ et al. CONSORT 2010: explanation and elaboration; updated guidelines for reporting parallel group randomised trials. BMJ 2010; 340: c869.

17. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. [GA17-01] Steigerung der Effizienz der Studienselektion [online]. [Accessed: 12.09.2018]. URL: https://www.iqwig.de/de/projekte-ergebnisse/projekte/institutsleitung/ga17-01-steigerung-der-effizienz-der-studienselektion.7847.html.

18. Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F. Methods for meta-analysis in medical research. Chichester: Wiley; 2000.

19. Veroniki AA, Jackson D, Viechtbauer W, Bender R, Knapp G, Kuss O et al. Recommendations for quantifying the uncertainty in the summary intervention effect and estimating the between-study heterogeneity variance in random-effects meta-analysis. Cochrane Database Syst Rev 2015; (Suppl 1): 25-27.

20. Kuss O. Statistical methods for meta-analyses including information from studies without any events: add nothing to nothing and succeed nevertheless. Stat Med 2015; 34(7): 1097-1116.

21. Koehler F, Winkler S, Schieber M, Sechtem U, Stangl K, Böhm M et al. Telemedicine in heart failure: pre-specified and exploratory subgroup analyses from the TIM-HF trial. Int J Cardiol 2012; 161(3): 143-150.

22. Charite University, Berlin. Telemedical interventional monitoring in heart failure (TIM-HF): study details [online]. In: ClinicalTrials.gov. 21.12.2016 [Accessed: 03.07.2019]. URL: https://ClinicalTrials.gov/show/NCT00543881.

23. Charite University, Berlin. Telemedical interventional management in heart failure II (TIM-HF2): study details [online]. In: ClinicalTrials.gov. 03.08.2018 [Accessed: 03.07.2019]. URL: https://ClinicalTrials.gov/show/NCT01878630.

24. Charité Campus Charité Mitte. Telemedizinische Mitbetreuung bei chronischer Herzinsuffizienz [online]. In: Deutsches Register Klinischer Studien. 22.05.2019 [Accessed: 03.07.2019]. URL: http://www.drks.de/DRKS00010239.

25. Arya A, Block M, Kautzner J, Lewalter T, Mörtel H, Sack S et al. Influence of home monitoring on the clinical status of heart failure patients: design and rationale of the IN-TIME study. Eur J Heart Fail 2008; 10(11): 1143-1148.

26. Biotronik. Influence of home monitoring on the clinical status of heart failure patients with an impaired left ventricular function (IN-TIME): study details [online]. In: ClinicalTrials.gov. 23.12.2014 [Accessed: 03.07.2019]. URL: https://ClinicalTrials.gov/show/NCT00538356.

27. Biotronik. Influence of home monitoring on mortality and morbidity in heart failure patients with an impaired left ventricular function; study IN-TIME; clinical investigation report [unpublished]. 2013.

28. Biotronik. Influence of home monitoring on mortality and morbidity in heart failure patients with an impaired left ventricular function; study IN-TIME; protocol; version 1.2 [unpublished]. 2010.

29. Sardu C, Santamaria M, Rizzo MR, Barbieri M, Di Marino M, Paolisso G et al. Telemonitoring in heart failure patients treated by cardiac resynchronisation therapy with defibrillator (CRT-D): the TELECART study. Int J Clin Pract 2016; 70(7): 569-576.

30. Blum K, Janowick F, Gottlieb SS. One year changes in quality of life for heart failure patients in a home telemonitoring program. J Card Fail 2006; 12(6 Suppl): S122.

31. Cui Y, Doupe M, Katz A, Nyhof P, Forget EL. Economic evaluation of Manitoba Health Lines in the management of congestive heart failure. Healthc Policy 2013; 9(2): 36-50.

32. Diederichsen SZ, Haugan KJ, Kober L, Hojberg S, Brandes A, Kronborg C et al. Atrial fibrillation detected by continuous electrocardiographic monitoring using implantable loop recorder to prevent stroke in individuals at risk (the LOOP study): rationale and design of a large randomized controlled trial. Am Heart J 2017; 187: 122-132.

33. Jerant AF, Azari R, Nesbitt TS. Reducing the cost of frequent hospital admissions for congestive heart failure: a randomized trial of a home telecare intervention. Med Care 2001; 39(11): 1234-1245.

34. Jimenez-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 07.09.2018 [Epub ahead of print].

35. Kraai I, De Vries A, Vermeulen K, Van Deursen V, Van der Wal M, De Jong R et al. The value of telemonitoring and ICT-guided disease management in heart failure: results from the IN TOUCH study. Int J Med Inf 2016; 85(1): 53-60.

36. Lima CEB, Martinelli M, Peixoto GL, Siqueira SF, Wajngarten M, Silva RT et al. Silent atrial fibrillation in elderly pacemaker users: a randomized trial using home monitoring. Ann Noninvasive Electrocardiol 2016; 21(3): 246-255.

37. Tajstra M, Sokal A, Gwozdz A, Wilczek M, Gacek A, Wojciechowski K et al. Remote supervision to decrease hospitalization rate: unified and integrated platform for data collected from devices manufactured by different companies; design and rationale of the RESULT study. Ann Noninvasive Electrocardiol 2017; 22(4).

38. Schmidt C, Öner A, Mann M, Krockenberger K, Abbondanzieri M, Brandewiede B et al. A novel integrated care concept (NICC) versus standard care in the treatment of chronic cardiovascular diseases: protocol for the randomized controlled trial CardioCare MV. Trials 2018; 19(1): 120.

39. Charité - Universitätsmedizin Berlin. Telemedical interventional monitoring in heart failure: telemedizinische Betreuung bei chronischer Herzinsuffizienz; study TIM-HF; Studienprotokoll [unpublished]. 2007.

40. Charité - Universitätsmedizin Berlin. Telemedical interventional management in heart failure II: telemedizinische Mitbetreuung bei chronischer Herzinsuffizienz; study TIM-HF II; Studienprotokoll [unpublished]. 2013.

41. Charité - Universitätsmedizin Berlin. Telemedical interventional monitoring in heart failure (TIM-HF); study TIM-HF; statistical analysis plan [unpublished]. 2010.

42. Charité - Universitätsmedizin Berlin. Telemedical interventional management in heart failure II: study TIM-HF II; statistical analysis plan [unpublished]. 2018.

43. Geller JC, Lewalter T, Bruun NE, Taborsky M, Bode F, Nielsen JC et al. Implant-based multi-parameter telemonitoring of patients with heart failure and a defibrillator with vs. without cardiac resynchronization therapy option: a subanalysis of the IN-TIME trial. Clin Res Cardiol 14.03.2019 [Epub ahead of print].

44. Husser D, Christoph Geller J, Taborsky M, Schomburg R, Bode F, Nielsen JC et al. Remote monitoring and clinical outcomes: details on information flow and workflow in the IN-TIME study. Eur Heart J Qual Care Clin Outcomes 2019; 5(2): 136-144.

45. Koehler F, Winkler S, Schieber M, Sechtem U, Stangl K, Böhm M et al. Impact of remote telemedical management on mortality and hospitalizations in ambulatory patients with chronic heart failure: the telemedical interventional monitoring in heart failure study. Circulation 2011; 123(17): 1873-1880.

46. Koehler F, Winkler S, Schieber M, Sechtem U, Stangl K, Böhm M et al. Telemedical interventional monitoring in heart failure (TIM-HF), a randomized, controlled intervention trial investigating the impact of telemedicine on mortality in ambulatory patients with heart failure: study design. Eur J Heart Fail 2010; 12(12): 1354-1362.

47. Prescher S, Deckwart O, Koehler K, Lücke S, Schieber M, Wellge B et al. Will telemonitoring be adopted by patients with chronic heart failure? Dtsch Med Wochenschr 2014; 139(16): 829-834.

48. Prescher S, Schoebel C, Koehler K, Deckwart O, Wellge B, Honold M et al. Prognostic value of serial six-minute walk tests using tele-accelerometry in patients with chronic heart failure: a pre-specified sub-study of the TIM-HF-Trial. Eur J Prev Cardiol 2016; 23(2 Suppl): 21-26.

49. Koehler F, Koehler K, Deckwart O, Prescher S, Wegscheider K, Kirwan BA et al. Efficacy of telemedical interventional management in patients with heart failure (TIM-HF2): a randomised, controlled, parallel-group, unmasked trial. Lancet 2018; 392(10152): 1047-1057.

50. Koehler F, Koehler K, Deckwart O, Prescher S, Wegscheider K, Winkler S et al. Telemedical interventional management in heart failure II (TIM-HF2), a randomised, controlled trial investigating the impact of telemedicine on unplanned cardiovascular hospitalisations and mortality in heart failure patients: study design and description of the intervention. Eur J Heart Fail 2018; 20(10): 1485-1493.

51. Biotronik. Iforia 3/5/7 Gebrauchsanweisung: Revision J [online]. 27.11.2017 [Accessed: 19.06.2018]. URL: https://manuals.biotronik.com/wps/proxy/https/aurum.biotronik.com/emanuals/manual/Icd/Iforia/Iforia/DE/de/J?type=manual.

52. Biotronik. Lumax 540 Gebrauchsanweisung: Revision G [online]. 01.02.2013 [Accessed: 19.06.2018]. URL: https://manuals.biotronik.com/wps/proxy/https/aurum.biotronik.com/emanuals/manual/Icd/Lumax/Lumax540/SE/de/G?type=manual.

53. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574.

54. Bilbao A, Escobar A, García-Perez L, Navarro G, Quirós R. The Minnesota Living with Heart Failure Questionnaire: comparison of different factor structures. Health Qual Life Outcomes 2016; 14: 23-23.

55. Inglis SC, Clark RA, McAlister FA, Stewart S, Cleland JG. Which components of heart failure programmes are effective? A systematic review and meta-analysis of the outcomes of structured telephone support or telemonitoring as the primary component of chronic heart failure management in 8323 patients; abridged Cochrane Review. Eur J Heart Fail 2011; 13(9): 1028-1040.

56. Health Quality Ontario. Remote monitoring of implantable cardioverter-defibrillators, cardiac resynchronization therapy and permanent pacemakers: a health technology assessment. Ont Health Technol Assess Ser 2018; 18(7): 1-199.

57. Pekmezaris R, Tortez L, Williams M, Patel V, Makaryus A, Zeltser R et al. Home telemonitoring in heart failure: a systematic review and meta-analysis. Health Aff (Millwood) 2018; 37(12): 1983-1989.

58. Inglis SC, Clark RA, Dierckx R, Prieto-Merino D, Cleland JGF. Structured telephone support or non-invasive telemonitoring for patients with heart failure. Cochrane Database Syst Rev 2015; (10): CD007228.

59. Brons M, Koudstaal S, Asselbergs FW. Algorithms used in telemonitoring programmes for patients with chronic heart failure: a systematic review. Eur J Cardiovasc Nurs 2018; 17(7): 580-588.

60. Riegel B, Moser DK, Anker SD, Appel LJ, Dunbar SB, Grady KL et al. State of the science: promoting self-care in persons with heart failure: a scientific statement from the American Heart Association. Circulation 2009; 120(12): 1141-1163.

61. 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: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2016; 37(27): 2129-2200.

62. Silver MA. Depression and heart failure: an overview of what we know and don't know. Cleve Clin J Med 2010; 77(Suppl 3): S7-S11.

63. Gathright EC, Goldstein CM, Josephson RA, Hughes JW. Depression increases the risk of mortality in patients with heart failure: a meta-analysis. J Psychosom Res 2017; 94: 82-89.

64. Wong SSL, Wilczynski NL, Haynes RB. Comparison of top-performing search strategies for detecting clinically sound treatment studies and systematic reviews in MEDLINE and EMBASE. J Med Libr Assoc 2006; 94(4): 451-455.

65. Lefebvre C, Manheimer E, Glanville J. Searching for studies [online]. In: Higgings JPT, Green S (Ed). Cochrane handbook for systematic reviews of interventions: version 5.1.0. 03.2011 [Accessed: 05.09.2018]. URL: http://handbook-5-1.cochrane.org/chapter_6/6_searching_for_studies.htm.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/non-drug-interventions/n-projekte/n19-01-data-supported-timely-management-in-cooperation-with-a-centre-for-telemedicine-for-patients-with-advanced-cardiac-failure-rapid-report.11591.html.

Appendix A – Search strategies

A.1 – Searches in bibliographic databases

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) 1946 to April 26, 2019

The following filters were adopted:

- Systematic review: Wong [64] – High specificity strategy
- RCT: Lefebvre [65] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision)

Search for telemonitoring type 1

#	**Searches**
1	exp Heart Failure/
2	(heart adj1 failure).ti,ab.
3	1 or 2
4	exp Telemedicine/
5	exp Telemetry/
6	Monitoring, Physiologic/
7	exp Monitoring, Ambulatory/
8	(monitoring* adj5 (remote* or home* or automatic*)).ti,ab.
9	(telemonitoring* or telehomecare* or telecare* or telehealth* or telemedicine* or telecardiology* or telemanagement* or telemedical* or telemetric*).ti,ab.
10	or/4-9
11	randomized controlled trial.pt.
12	controlled clinical trial.pt.
13	(randomized or placebo or randomly or trial or groups).ab.
14	drug therapy.fs.
15	or/11-14
16	15 not (exp animals/ not humans.sh.)
17	Cochrane database of systematic reviews.jn.
18	(search or MEDLINE or systematic review).tw.
19	meta analysis.pt.
20	or/17-19
21	or/16,20
22	and/3,10,21

#	**Searches**
23	22 not (comment or editorial).pt.
24	23 and (english or german).lg.

Search for telemonitoring type 2 (update of the search for benefit assessment N16-02)

#	**Searches**
1	Defibrillators, Implantable/
2	Cardiac Resynchronization Therapy Devices/
3	((implant* or (cardiac adj1 resynchroni#ation*)) adj4 (defibrillator* or device*)).ti,ab.
4	(resynchroni#ation* adj1 therapy*).ti,ab.
5	or/1-4
6	Monitoring, Physiologic/
7	exp Monitoring, Ambulatory/
8	exp Telemetry/
9	exp Telemedicine/
10	Automation/
11	((remote* or home* or ambulatory*) adj3 monitoring*).ti,ab.
12	telemonitoring*.ti,ab.
13	(automatic* adj3 alert*).ti,ab.
14	or/6-13
15	5 and 14
16	randomized controlled trial.pt.
17	controlled clinical trial.pt.
18	(randomized or placebo or randomly or trial or groups).ab.
19	drug therapy.fs.
20	or/16-19
21	exp animals/ not humans.sh.
22	20 not 21
23	Cochrane database of systematic reviews.jn.
24	meta analysis.pt.
25	(search or MEDLINE or systematic review).tw.
26	or/23-25
27	22 or 26
28	15 and 27
29	28 not (comment or editorial).pt.

#	Searches
30	29 and (english or german).lg.
31	30 and 20170807:3000.(dt).

Search interface: Ovid

- Ovid MEDLINE(R) Epub Ahead of Print and In-Process & Other Non-Indexed Citations April 26, 2019

Search for telemonitoring type 1

#	Searches
1	(heart adj1 failure).ti,ab.
2	(monitoring* and (remote* or home* or automatic*)).ti,ab.
3	(telemonitoring* or telehomecare* or telecare* or telehealth* or telemedicine* or telecardiology* or telemanagement* or telemedical* or telemetric*).ti,ab.
4	or/2-3
5	(clinical trial* or random* or placebo).ti,ab.
6	trial.ti.
7	or/5-6
8	(search or meta analysis or medline or systematic review).ti,ab.
9	or/7-8
10	and/1,4,9
11	10 not (comment or editorial).pt.
12	11 and (english or german).lg.

Search for telemonitoring type 2 (update of the search for benefit assessment N16-02)

#	Searches
1	((implant* or (cardiac and resynchroni#ation*)) and (defibrillator* or device*)).ti,ab.
2	(resynchroni#ation* and therapy*).ti,ab.
3	or/1-2
4	((remote* or home* or ambulatory*) and monitoring*).ti,ab.
5	telemonitoring*.ti,ab.
6	(automatic* and alert*).ti,ab.
7	or/4-6
8	(clinical trial* or random* or placebo).ti,ab.
9	trial.ti.

#	**Searches**
10	(search or meta analysis or medline or systematic review).ti,ab.
11	or/8-10
12	and/3,7,11
13	12 not (comment or editorial).pt.
14	13 and (english or german).lg.
15	14 and 20170807:3000.(dt).

2. Embase

Search interface: Ovid

- Embase 1974 to 2019 April 26

The following filters were adopted:

- Systematic review: Wong [64] – High specificity strategy
- RCT: Wong [64] – Strategy minimizing difference between sensitivity and specificity

Search for telemonitoring type 1

#	**Searches**
1	exp heart failure/
2	(heart adj1 failure).ti,ab.
3	or/1-2
4	exp telemedicine/
5	*patient monitoring/
6	Home monitoring/
7	exp remote sensing/
8	ambulatory monitoring/
9	(monitoring* adj5 (remote* or home* or automatic*)).ti,ab.
10	(telemonitoring* or telehomecare* or telecare* or telehealth* or telemedicine* or telecardiology* or telemanagement* or telemedical* or telemetric*).mp.
11	or/4-10
12	(random* or double-blind*).tw.
13	placebo*.mp.
14	or/12-13
15	(meta analysis or systematic review or MEDLINE).tw.
16	or/14-15
17	and/3,11,16

#	**Searches**
18	17 not medline.cr.
19	18 not (exp animal/ not exp human/)
20	19 not (Conference Abstract or Conference Review or Editorial).pt.
21	20 and (english or german).lg.

Search for telemonitoring typ 2 (update of the search for benefit assessment N16-02)

#	**Searches**
1	implantable cardioverter defibrillator/
2	cardiac resynchronization therapy device/
3	cardiac resynchronization therapy/
4	((implant* or (cardiac adj1 resynchroni#ation*)) adj4 (defibrillator* or device*)).ti,ab.
5	(resynchroni#ation* adj1 therapy*).ti,ab.
6	or/1-5
7	exp remote sensing/
8	home monitoring/
9	exp telemedicine/
10	*patient monitoring/
11	ambulatory monitoring/
12	((remote* or home* or ambulatory*) adj3 monitoring*).ti,ab.
13	telemonitoring*.ti,ab.
14	(automatic* adj3 alert*).ti,ab.
15	or/7-14
16	6 and 15
17	(random* or double-blind*).tw.
18	placebo*.mp.
19	or/17-18
20	(meta analysis or systematic review or MEDLINE).tw.
21	19 or 20
22	16 and 21
23	22 not medline.cr.
24	23 not (exp animal/ not exp human/)
25	24 and (english or german).lg.
26	25 not (Conference Abstract or Conference Review or Editorial).pt.
27	26 and 20170807:3000.(dc).

3. The Cochrane Library

Search interface: Wiley

- Cochrane Database of Systematic Reviews: Issue 4 of 12, April 2019
- Cochrane Central Register of Controlled Trials: Issue 4 of 12, April 2019

Search for telemonitoring type 1

ID	Search
#1	[mh "Heart Failure"]
#2	(heart NEAR/1 failure):ti,ab
#3	#1 or #2
#4	[mh "Telemedicine"]
#5	[mh "Telemetry"]
#6	[mh ^"Monitoring, Physiologic"]
#7	[mh "Monitoring, Ambulatory"]
#8	(monitoring* NEAR/5 (remote* or home* or automatic*)):ti,ab
#9	(telemonitoring* or telehomecare* or telecare* or telehealth* or telemedicine* or telecardiology* or telemanagement* or telemedical* or telemetric*):ti,ab
#10	#8 or #9
#11	#3 and #10 in Cochrane Reviews, Cochrane Protocols
#12	#3 and #10 in Trials

Search for telemonitoring type 2 (update of the search for benefit assessment N16-02)

ID	Search
#1	[mh ^"Defibrillators, Implantable"]
#2	[mh ^"Cardiac Resynchronization Therapy Devices"]
#3	((implant* or (cardiac* near/1 (resynchronisation* or resynchronization*))) near/4 (defibrillator* or device*)):ti,ab
#4	((resynchronisation* or resynchronization*) near/1 therapy*):ti,ab
#5	#1 or #2 or #3 or #4
#6	[mh ^"Monitoring, Physiologic"]
#7	[mh "Monitoring, Ambulatory"]
#8	[mh Telemetry]
#9	[mh Telemedicine]
#10	[mh ^Automation]
#11	((remote* or home* or ambulatory*) near/3 monitoring*):ti,ab
#12	telemonitoring*:ti,ab

ID	Search
#13	(automatic* near/3 alert*):ti,ab
#14	#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
#15	#5 and #14 with Cochrane Library publication date from Aug 2017 to present, in Cochrane Reviews, Cochrane Protocols
#16	#5 and #14 with Cochrane Library publication date from Aug 2017 to present, in Trials

A.2 – Searches in study registries

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Advanced Search

Search strategies
(defibrillator OR resynchronization OR desynchronization OR ICD OR CRT OR CRT-D) AND (monitoring OR telemonitoring OR alert OR remote OR home OR ambulatory)
(heart failure OR tachycardia) AND (home monitoring OR remote monitoring OR telemonitoring)
((monitoring AND (remote OR home OR automatic)) OR (telemonitoring OR telehomecare OR telecare OR telehealth OR telemedicine OR telecardiology OR telemanagement OR telemedical OR telemetric)) AND heart failure [DISEASE]

2. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: http://apps.who.int/trialsearch/
- Type of search: Standard Search

Search strategies
defibrillator OR defibrillators OR resynchronization OR desynchronization
remote monitoring AND heart failure OR home monitoring AND heart failure OR telemonitoring AND heart failure OR remote monitoring AND tachycardia OR home monitoring AND tachycardia OR telemonitoring AND tachycardia
remote AND monitoring AND heart failure OR home AND monitoring AND heart failure OR automatic AND monitoring AND heart failure OR remote AND care AND heart failure
telemonitoring AND heart failure OR telehomecare AND heart failure OR telecare AND heart failure OR telehealth AND heart failure OR telemedicine AND heart failure OR telecardiology AND heart failure OR telemanagement AND heart failure OR telemedical AND heart failure OR telemetric AND heart failure