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RELEASE-HF study: a protocol for an observational, registry-based study on the effectiveness of telemedicine in heart failure in the Netherlands

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ABSTRACT

Introduction Meta-analyses show postive effects of telemedicine in heart failure (HF) management on hospitalisation, mortality and costs. However, these effects are heterogeneous due to variation in the included HF population, the telemedicine components and the quality of the comparator usual care. Still, telemedicine is gaining acceptance in HF management. The current nationwide study aims to identify (1) in which subgroup(s) of patients with HF telemedicine is (cost-)effective and (2) which components of telemedicine are most (cost-) effective.

Methods and analysis The RELEASE-HF ('REsponsible roLl-out of E-heAlth through Systematic Evaluation – Heart Failure') study is a multicentre, observational, registry-based cohort study that plans to enrol 6480 patients with HF using data from the HF registry facilitated by the Netherlands Heart Registration. Collected data include patient characteristics, treatment information and clinical outcomes, and are measured at HF diagnosis and at 6 and 12 months afterwards. The components of telemedicine are described at the hospital level based on closed-ended interviews with clinicians and at the patient level based on additional data extracted from electronic health records and telemedicine-generated data. The costs of telemedicine are calculated using registration data and interviews with clinicians and finance department staff. To overcome missing data, additional national databases will be linked to the HF registry if feasible. Heterogeneity of the effects of offering telemedicine compared with not offering on days alive without unplanned hospitalisations in 1 year is assessed across predefined patient characteristics using exploratory stratified analyses. The effects of telemedicine components are assessed by fitting separate models for component contrasts.

Ethics and dissemination The study has been approved by the Medical Ethics Committee 2021 of the University Medical Center Utrecht (the Netherlands). Results will be published in peer-reviewed journals and presented at (inter)national conferences. Effective telemedicine scenarios will be proposed among hospitals throughout the country and abroad, if applicable and feasible.

Trial registration number NCT05654961.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A strength of this study is the use of nationwide routine clinical care data linked to national registry databases to capture current data on telemedicine use, the characteristics of patients with heart failure, treatments and clinically relevant outcomes with a 1-year follow-up.
⇒ Another strength is that data from the heart failure registry in the Netherlands and a separate data collection on telemedicine features using additional questionnaires allow consideration of heterogeneous treatment effects across the heart failure population and telemedicine components.
⇒ A limitation is that most data on telemedicine characteristics will be collected at the hospital level, rather than at the individual patient level.
⇒ Another limitation is that the cost-effectivity analyses are specific to the Dutch healthcare system, which may hamper generalisability of findings to other settings or countries.
⇒ A final limitation is that selection bias can occur when healthcare providers do not include all patients in the outpatient clinic in the heart failure registry because the registry is not incorporated in care pathways in electronic health record systems.

INTRODUCTION

Heart failure (HF) poses a major socioeconomic and patient burden, and healthcare systems are seeking innovative health models to support care. Optimised guideline-directed medical therapy, self-care (ie, healthy diet, medication adherence, exercise) and adequate monitoring of vital signs and symptoms may all help reduce HF-related morbidity.[1–3] Health models therefore use telemedicine as a tool to support patients in optimising HF management, self-care support and symptom monitoring to improve care and prevent (re)hospitalisation.[2–4]

'Telemedicine' is a heterogeneous intervention that includes a wide range of digital technologies (smartphones, mobile wireless devices/sensors, video connections, implantable devices, etc) exchanging digital health information between patients and clinicians to support and optimise the care process remotely.[5 6]

Many meta-analyses have evaluated the (cost-)effectiveness of telemedicine in patients with HF.[7–19] Overall, these meta-analyses point towards a positive effect of telemedicine on hospital admission, length of hospital stay, mortality and costs.[2 7–19] However, the effects are heterogeneous across subgroups[20–24] and vary with telemedicine components, such as type of monitored functions, number of alerts and risk of alert fatigue, contact with healthcare professional, type of device, and different quality of usual care.[7 14 15 19 25] This can lead to problems in comparability of studies. Understanding of the cost-effectiveness of telemedicine is fragmented because studies do not evaluate the same costs, with the focus shifting between the purchase costs of telemedicine, personnel costs and variation in the costs of telemedicine components.[4 12 16]

As a result, HF guidelines lack specific recommendations on *how*, *when* and in *whom* telemedicine should be provided. Despite the lack of solid evidence and advice, payers (eg, procurement officers, insurance companies) and patient organisations are advocating to accelerate the implementation of telemedicine for patients with HF in outpatient clinics.[26] Consequently, telemedicine is implemented in different formats with varying objectives, intervention components and implementation strategies. To reveal the real potential of telemedicine for patients with HF and its implementation in everyday practice, clarity on *how*, *when* and in *whom* and which telemedicine components are (cost-)effective is essential.

Here, we present the protocol for the RELEASE-HF ('REsponsible roLl-out of E-heAlth through Systematic Evaluation – Heart Failure') study. In this study, we focus on both patient-related uncertainties in telemedicine use and telemedicine intervention-related uncertainties from a clinical as well as an economic perspective. Our specific study objectives are to examine (1) which patient characteristics are related to an increase in the number of days spent alive without unplanned hospitalisations within 1 year when telemedicine is part of HF care compared with regular HF care; (2) which components of telemedicine as part of HF care lead to an increased number of days alive without unplanned hospitalisations within 1 year; (3) which characteristics of patients with HF are related to cost-effectiveness when telemedicine is part of HF care compared with regular HF care; and (4) which components of telemedicine as part of HF care are cost-effective.

METHODS AND ANALYSIS

Study design

RELEASE-HF is a nationwide, observational, registry-based cohort study across multiple hospitals in the Netherlands.[27] The study collects routine data longitudinally. We record the health status of and cardiac interventions in patients with HF and simultaneously observe the natural (de)implementation of telemedicine. RELEASE-HF is linked to the Heart4Data consortium which started in 2022 to create a national and sustainable infrastructure for cardiovascular registry-based research in the Netherlands.[28] This infrastructure will develop a framework for the governance, ethical, legal, financial, information technology and methodological factors necessary for registry-based research.

Progress and time plan

RELEASE-HF started in June 2021 and will last 4 years (figure 1). This study includes a collaboration with at least 29 hospitals that signed a letter of commitment. Additional hospitals may enter the study later if they can complete a 12-month follow-up per included patient through the HF registry.

Data sources

RELEASE-HF will combine various sources of data: the Netherlands Heart Registration (NHR) HF registry, other national databases, interviews, electronic health records (EHR) and telemedicine-generated data (figure 2). A detailed description of each data source is provided in the following:

HF registry

The HF registry is an ongoing quality registry in the Netherlands facilitated by the NHR, a non-profit organisation that aims to contribute to quality improvement and safety in cardiac care.[29 30] The HF registry serves as an ongoing learning healthcare system through benchmarking and quality control. Since 2019, it has been introduced as a voluntary, nationwide HF registration. Patient data are collected non-consecutively, and for the registry no informed consent is asked. Data of included patients are collected at three timepoints: at baseline, 6 months and 12 months from the time since diagnosis. The HF registry includes variables on three levels defined in a data dictionary: patient characteristics, treatment characteristics and clinically relevant outcomes. The data dictionary is a dynamic document (ie, the included variables and definitions may change over time) because it is based on current HF guidelines and compiled by a committee consisting of delegated cardiologists from Dutch hospitals. A detailed up-to-date data dictionary with an overview of the variables collected within the HF registry is always published on the NHR website. Online supplemental material 1 provides an overview of the data dictionary of the HF registry, September 2022 version; the content is subject to change.[31]

National registries and databases

If legally and technically feasible, we plan to link the HF registry data, specific to RELEASE-HF, to external data sources to (1) complement missing variables, (2) enrich and validate the HF registry, and (3) reduce registration burden for healthcare professionals/data managers. The

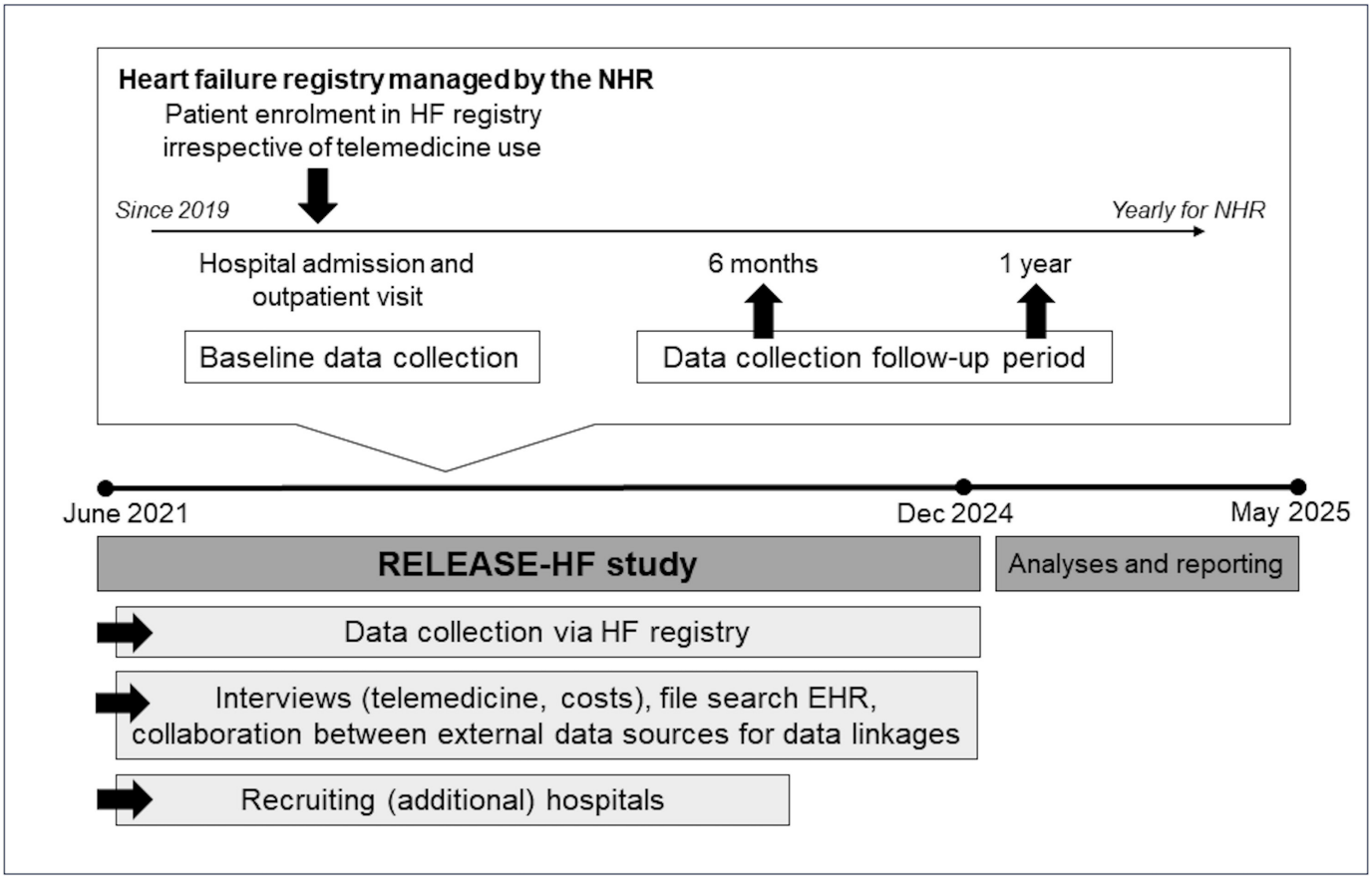

Figure 1 Overview of the time plan for the RELEASE-HF study. EHR, electronic health record; HF, heart failure; NHR, Netherlands Heart Registration; RELEASE-HF, REsponsible roLl-out of E-heAlth through Systematic Evaluation – Heart Failure.

external data sources considered are Statistics Netherlands (CBS), the national health insurance database (VEKTIS), the national registry for hospital care (Dutch Hospital Data) and the national database for drug utilisation and drug safety (PHARMO). The variables of interest are visits to the outpatient clinic, to the emergency room and to the general practitioner related to HF, admission days at an intensive care unit, and treatment characteristics specific to HF (ie, medication as class of diuretics).

Interviews on the use of telemedicine

Separate data collection will be performed using semi-structured interviews among clinicians and finance department staff on the features and costs of telemedicine at the hospital level. Online supplemental material 2 provides the interview guide.

EHR and telemedicine-generated data

File search in the EHR of patients and telemedicine-generated data will be used to identify telemedicine components at the patient level.

Study population

The HF registry comprises patients admitted to a Dutch hospital or to an outpatient clinic for HF irrespective of telemedicine use (figure 1). All patients who meet the diagnostic criteria for HF and its phenotype, according to the European Society of Cardiology (ESC) 2021 guidelines on HF, are included.[1] If a patient has been diagnosed with HF in a setting other than the one where the patient currently presents (primary, secondary or tertiary care), the patient will also be included.[31] Current HF registry is not yet incorporated and implemented in care pathways in EHR systems; therefore, selected patients fulfilling the NHR criteria are included in the HF registry and not on a consecutive basis or full coverage of all patients at the outpatient HF clinic. This may lead to selection bias. To prevent this selection bias, a researcher of RELEASE-HF is alerting healthcare professionals regularly to include all patients with HF in the HF registry, regardless of their telemedicine use, treatment and disease severity. Additionally, national working groups are progressing to fully incorporate the HF registry into the EHR.

Outcome measures

Primary outcome

The number of days alive without unplanned hospitalisation within 1 year of follow-up is derived from the number of unplanned hospital days as collected in the HF registry (table 1).

Secondary outcomes

The secondary outcomes are all-cause mortality, functional status, health status, health-related quality of life

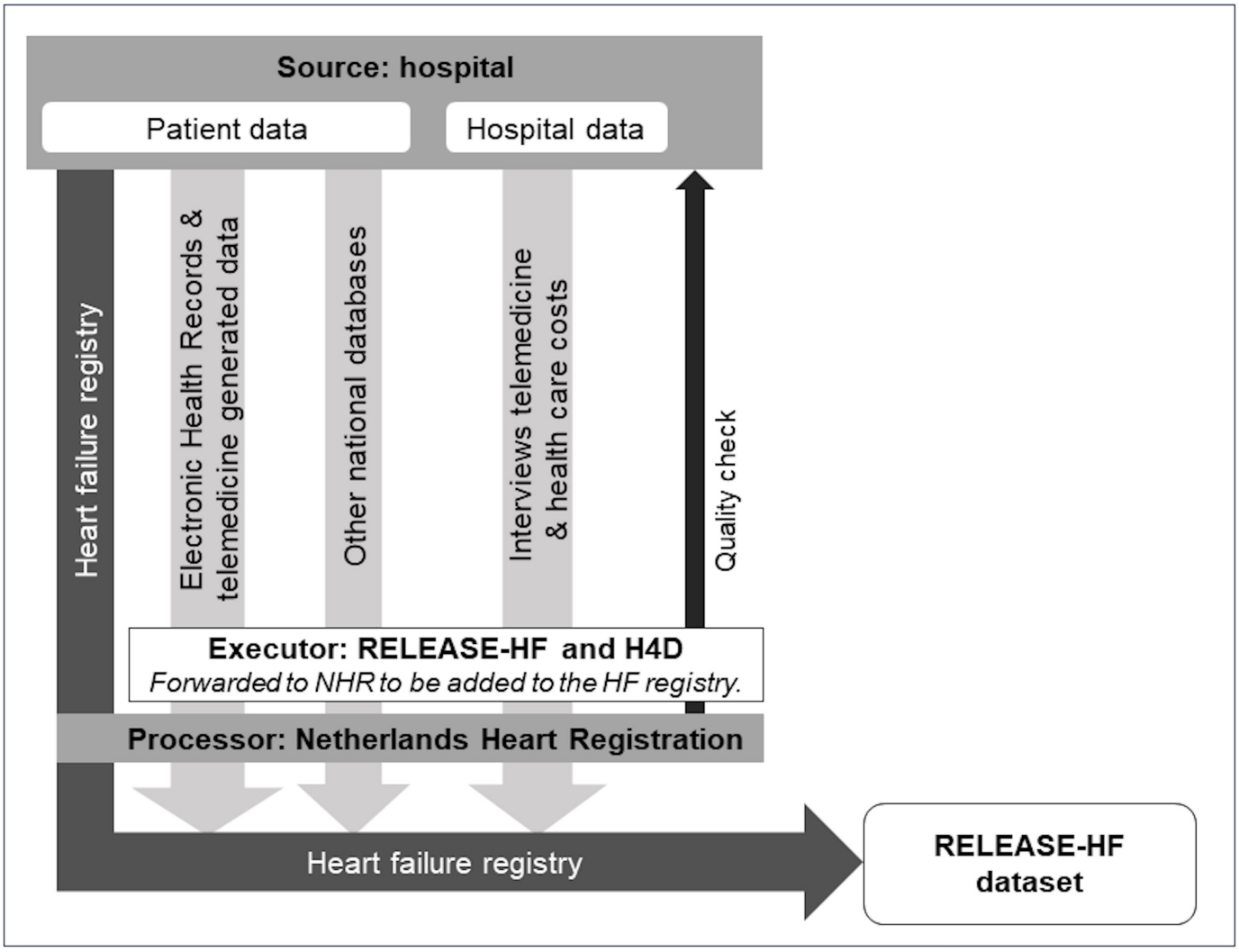

Figure 2 Data sources and flow to set up the final RELEASE-HF data set. H4D, Heart4Data consortium; HF, heart failure; NHR, Netherlands Heart Registration; RELEASE-HF, REsponsible roLl-out of E-heAlth through Systematic Evaluation – Heart Failure.

(hrQoL), healthcare utilisation within 1 year of follow-up and costs of care (table 1).

Exposure measurement

Exposure to telemedicine is measured in the HF registry at 6 months and 12 months of follow-up as non-use of telemedicine, telephone only, non-invasive telemedicine, implantable cardioverter defibrillator-based telemedicine or invasive telemedicine (table 1). Telemedicine output can be different from the closed-ended interviews that correspond to all outpatient clinic contacts in general. The components of the telemedicine intervention will be assessed at the hospital level at one time during the follow-up period. Table 2 provides an overview and operationalisation of the main components of the telemedicine intervention that have been described in existing literature or at the local (eg, hospital) level.[7 32–34] The components will be validated and possibly further refined based on the interviews. Figure 3 illustrates the flow of data collected at the hospital level and at the patient level.

Additional variables

Additional information includes age at HF diagnosis, sex, social economic status (SES), body mass index (BMI), New York Heart Association (NYHA) classification, left ventricular ejection fraction (LVEF), aetiology of HF, systolic and diastolic blood pressure, and heart rhythm and rate. The comorbidities are chronic respiratory disorders, obstructive sleep apnoea syndrome (OSAS), stroke, extra cardiac arterial vascular pathology, diabetes mellitus (DM), hypertension, anaemia, chronic kidney disease (CKD), malignancy, heart rhythm disorders, depression and thyroid disease. An overview of these variables can be found in online supplemental material 1 and published in detail at the NHR website.[31] Table 3 provides an overview and operationalisation of variables derived from this HF registry.

Data collection and quality control

Data of the HF registry will be remotely monitored for major outliers and missing variables using the NHR; these processes have been described elsewhere.[30 35] The NHR

Table 1 Operationalisation of exposure variable and study outcomes

Variable	Source	Time of collection	Operationalisation
Exposure			
Telemedicine	HF registry, telemedicine-generated data	T0, T1*, T2	Whether a patient receives telemedicine. Five categories: (1) no telemonitoring†; (2) telemonitoring by telephone; (3) telemonitoring, non-invasive based on traditional parameters (eg, blood pressure, ECG); (4) telemonitoring using ICD based on HF parameters; and (5) telemonitoring, invasive using sensors in the bloodstream or heart.
Primary outcome			
Number of days spent alive without unplanned hospitalisations within 1 year of follow-up	HF registry	T1*, T2	Number of days directly related to unplanned cardiac hospital admission due to HF. Number of admission days will be summed up over a period between follow-up moments and subtracted from 365 days.
Secondary outcomes			
Costs	Derived from HF registry, external data source, EHR, interviews	T0, T1*, T2	Costs estimated from patient, disease and treatment characteristics. Information taken into account includes medication use, whether the patient underwent cardiac interventions (eg, pacemaker implantation, percutaneous coronary intervention), use of telemedicine, hospital admission days, visits to the outpatient clinic, visits to the emergency room, admission days at an intensive care unit and visits to the GP related to HF.
All-cause mortality	HF registry, external data source	T1*, T2	Mortality status, determined after verification at the Personal Records Database (in Dutch: Basisregistratie Personen). Mortality is independent of HF (all-cause).
Functional status	HF registry	T0, T1*, T2	NYHA classification: a functional classification of patients based on severity of symptoms and physical activity, with specific attention to fatigue, palpitation and dyspnoea. Scores are linked to one of four NYHA classes: class I: no limitation; class II: slight limitation; class III: marked limitation; and class IV: unable to carry on any physical activity without discomfort.[1]
Health status	HF registry	T0, T1*, T2	SF-36 or SF-12 questionnaire (subset of SF-36)[54]: a validated patient-reported survey of patient health. Both questionnaires consist of eight sections with scores: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health. Each score is transformed into a scale of 0–100 on the assumption that each question carries equal weight. The lower the score, the more disability.
Health-related quality of life	HF registry	T0, T1*, T2	SF-36 or SF-12 questionnaire. QALY will be calculated based on the SF-6D, a model in which a single, preference-based score can be directly calculated for the SF-36 and SF-12.[55] Scores range from 0.0 (worst health state) to 1.0 (best health state).
Healthcare utilisation	External data source, EHR	T1, T2	Healthcare utilisation based on (1) the number of outpatient visits, plus (2) the number of visits to the general practice related to HF.

*The HF registry collects data standard at baseline (T0), after 6 months (T1) and after 12 months (T2). The RELEASE-HF study conforms to the timeframes of the HF registry. Therefore, data will be collected at 6 months, although the outcome measurements are after 12 months.
†The HF registry defines telemedicine as telemonitoring.
EHR, electronic health record; GP, general practitioner; HF, heart failure; ICD, implantable cardioverter defibrillator; NYHA, New York Heart Association; QALY, quality-adjusted life year; RELEASE-HF, REsponsible roLl-out of E-heAlth through Systematic Evaluation – Heart Failure; SF-12, 12-item short form health survey; SF-36, 36-item short form health survey; SF-6D, six-dimensional health state short form.

Table 2 Overview and operationalisation of telemedicine variables collected in the qualitative study

Component	Definition	Operationalisation (examples)
Supplier	(External) supplier of telemedicine for patients with HF.	Sanacoach, Luscii, Motiva/Philips, linked in personal environment in EHR.
Purpose of telemedicine	The intention/motives for which the telemedicine intervention is administered: patient level and/or hospital level.	Monitoring, prevent exacerbation, reduce workload, reduce costs, patient-centred care.
Considering telemedicine	First time a clinician considered telemedicine in HF management.	After diagnosis, (re)hospitalisation, titration phase.
Structured telephone support	Structured monitoring by telephone without using applications or devices specific to telemedicine and monitoring HF.	Present or not present.
Applications	Technologies or platforms on which the patient could receive telemedicine.	Smartphone, tablet, laptop, television, smartwatch.
Devices	Accessory a patient could use to perform telemedicine.	Blood pressure device (with or without Bluetooth), weight scale (with or without Bluetooth), smartwatch.
Involved healthcare workers	Involved healthcare workers and their role in considering and executing telemedicine.	HF nurse, nurse specialist, cardiologist.
Control centrum	The presence or absence of a control centrum to check the submitted measurements and questions.	Present or not present.
Use of telemedicine	When a patient could use telemedicine and have contact with clinicians.	24/7, office hours, during weekend, at night.
Type of contact	The manner of contact between the clinician and the patient.	Direct or indirect (store-and-forward) contact with a clinician.
Measurements	Type of measurements: vital functions and HF-related complaints, used to detect deterioration of and/or to monitor HF.	Blood pressure, heart rate, weight, temperature, oxygen level, HF complaints such as swelling ankles, nocturia, shortness of breath, tiredness, loss of appetite, coughing/wheezing, dizziness.
Notifications	Messages from the telemedicine intervention. Notifications can be two-sided: from patient to clinician and vice versa.	Automatic or non-automatic generated messages; notifications present or not present.
Modifiable aspects	The option to set up *thresholds* of monitored vital function, and the possibility to tailor these thresholds per patient, severity, type of HF or other aspects of the telemedicine intervention (eg, set up a tele-education environment).	Available or not available.
Connection with EHR	Feature of telemedicine if the intervention is integrated with the EHR. This means that data entered by the patient through the telemedicine intervention are visible to the clinician in the EHR without using other applications.	Connected or not connected with EHR.
Education	The presence or absence of an educational environment and the manner in which this is shaped.	Present or not present.
Educational topics	The covered topics in the educational environment of telemedicine.	Nutrition, behaviour, exercise, medication.
Self-care	The presence or absence of self-care modules and the actions taken by the patient based on a digital advice or measurement.	Available or not available.
Protocol	Local (hospital) protocol which consists of definitions about how often a patient should use telemedicine/ monitor the vital signs and HF complaints, depending on the HF complaints or phase (ie, titration, stable monitoring).	Low-intensity protocol defined as measurement of vital signs <2 times per week. High-intensity protocol defined as measurement of vital signs ≥2 times per week.

EHR, electronic health record; HF, heart failure.

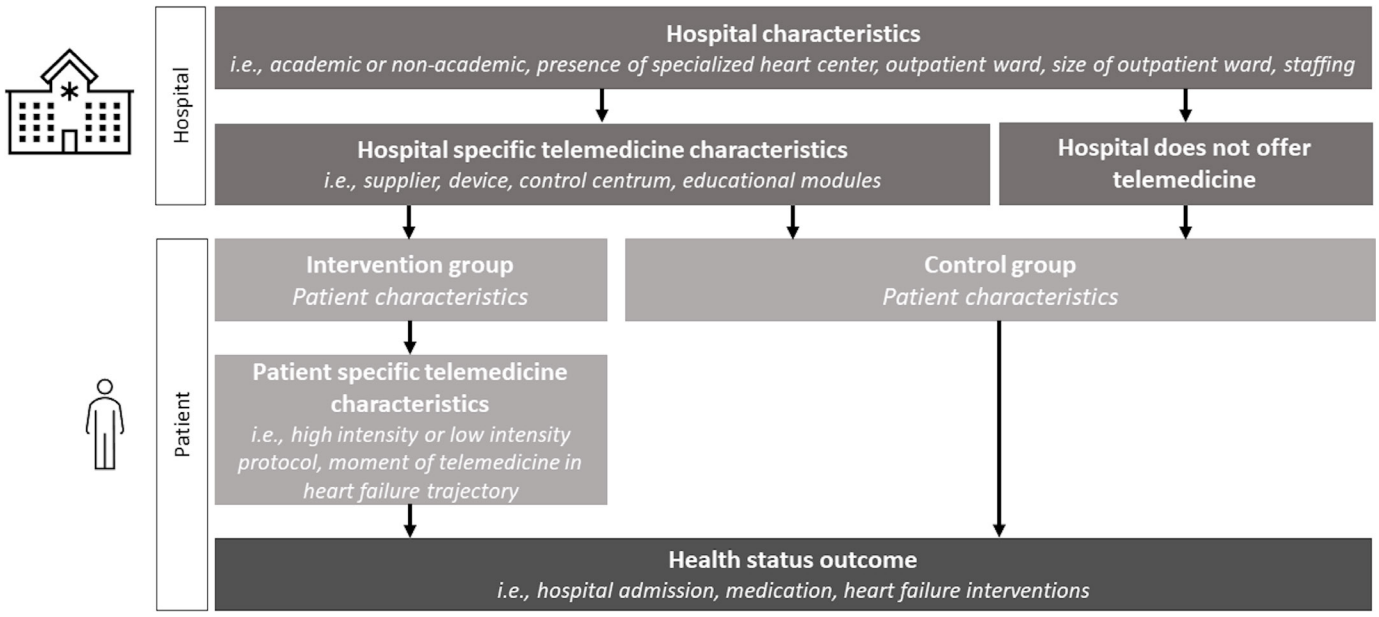

Figure 3 Figure depicting how telemedicine characteristics are collected at the hospital level and at the individual patient level. It clarifies the source of the collected clinical content used for the subgroup analyses rather than the type of data source.

uses a unique individual patient identifier (NHRpersonID) to deduplicate registrations of the same patient (at the same or different hospitals) in the HF registry.[36] During the RELEASE-HF study, researchers will perform an additional check on completed data and provide assistance to hospitals to reduce missing values, as well as assistance to reduce registration burden.

Telemedicine interviews, using an interview guide with closed-ended questions, will be performed by a RELEASE-HF investigator and conducted with clinicians (eg, cardiologist, HF nurse, nurse specialist, physician assistant). Interviews will be held during the 36-month period of data collection. All hospitals with telemedicine in HF care will be interviewed once, and the data will be checked with the hospitals once during the data collection period to be aware of changes in the components and status of telemedicine. For each hospital, the 6-monthly costs of telemedicine are determined via interviews and registration data (if at hand). The units will be linked to the unit cost guideline provided by the Dutch National Health Care Institute (Dutch: Zorginstituut Nederland).[37] These interviews will be performed by a health technology assessment (HTA) scientist and conducted with clinicians or finance department staff. All participants will provide informed consent.

Patient-level telemedicine data are collected by a clinician, data manager or researcher at the hospital where the patient is being treated because these individuals

Table 3 Operationalisation of variables calculated from the included variables in the HF registry

Variable	Operationalisation
Social economic status	Score for socioeconomic status (including degree of education, wealth and employment history (WOA)) by zip code area according to the 2019 data from the Social Cultural Planning Agency; divided into quartiles or quintiles, where 1 is a low SES-WOA score.
Body mass index	Derived from weight in kilogram and length in centimetres, calculated as weight/(length×length).
CKD	Based on the cut-off values of eGFR calculated from serum creatinine level (collected by the HF registry). The HF registry calculates eGFR as the following: Male: (175×(creatinine level/88.4)^−1.154)×(age Tn^−0.203) Female: (175×(creatinine level/88.4)^−1.154)×(age Tn^−0.203)×0.742 CKD=eGFR ≥60 mL/min/1.73 m^2 No CKD=eGFR <60 mL/min/1.73 m^2
Depression	Health-related QoL derived from the SF-12 or SF-36 questionnaire. Scoring: 0–100; the lower the score, the more disability; the higher the score, the less disability; that is, a score of 0 is equivalent to maximum disability and a score of 100 is equivalent to no disability.

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HF, heart failure; QoL, quality of life; SES, social economic status; SF-12, 12-item short form health survey; SF-36, 36-item short form health survey; WOA, wealth, educational level and employment history (in Dutch: welvaart, opleidingsniveau, arbeidsverleden).

have access to the identification log of the HF registry. Collected data will include the start date of telemedicine use and the frequency at which measurements are sent to the treating hospital, with a high rate typically referred to as a high-intensity (or acute) protocol and a low rate as a low-intensity (or stable) protocol.

The Heart4Data consortium will establish opportunities for data linkage between the HF registry and other national registry databases, in collaboration with public partners (figure 2).[28] At the time of writing, a collaboration between these databases and the HF registry is not yet established for all external national databases.

Statistical analysis

Clinical effectiveness

Descriptives are presented for all variables of the HF registry and telemedicine components. We will present the number of days without unplanned hospitalisation for HF during 365 days after baseline, the average duration of unplanned HF-related hospital stays, the number of deaths and the time until death.

Preparation of the statistical model

As a first step, we describe how the overall effect of offering any type of telemedicine versus not offering telemedicine will be estimated. This analysis will subsequently be used for a comparison of telemedicine effects on days alive without unplanned HF-related hospitalisation during 1 year across subgroups.

The cohort is restricted to individuals with newly diagnosed HF, that is, at most 3 months prior to baseline. The exposure contrast is defined as offering any type of telemedicine after first presentation with HF at the hospital outpatient clinic versus patients not offered telemedicine. The telemedicine status for the entire follow-up is defined by 6 months after baseline measurement of telemedicine, used as an observational analogue of an 'intention to treat' analysis in which the stopping of telemedicine is disregarded.

Because telemedicine administration is dependent on patient characteristics, confounding by indication will be accounted for. Based on clinical consensus, the following patient-level confounding variables measured at baseline will be adjusted for: age, sex, SES, BMI, NYHA, LVEF, aetiology of HF, systolic blood pressure, diastolic blood pressure, heart rhythm, heart rate, chronic respiratory disorders, OSAS, stroke, extra cardiac arterial vascular pathology, DM, hypertension, anaemia, CKD, malignancy, heart rhythm disorders, depression and thyroid disease (see table 3 and online supplemental material 1).

The primary outcome model is a linear mixed model with a random intercept for the participating centre and is specified as follows. The outcome is measured in days, and because the final measurement may be less or more than 365 days after baseline, we rescale the number of days of unplanned hospitalisation to the number of days under follow-up to 365 days. The outcome is computed by subtracting the days of unplanned hospitalisation or death from 365. The earlier described confounding variables are added to the primary outcome model to adjust for confounding. Continuous covariates are modelled using splines. Multicollinearity between confounding variables and the telemedicine status is evaluated. The coefficient for telemedicine in the primary outcome model represents the average treatment effect of offering any telemedicine within 3 months after HF diagnosis compared with not offering telemedicine on days with unplanned HF-related hospitalisation during a year in the population of patients with newly diagnosed HF. Robust SEs are estimated to compute CIs.

For the secondary outcome functional status, a similar approach is taken to estimate the average treatment effect of offering any telemedicine within 3 months after HF diagnosis compared with not offering telemedicine on functional status after 1 year in the population of patients with newly diagnosed HF. For this analysis, the outcome model is a multinomial regression model, and baseline functional status is added as a covariate. The risk difference relative to the reference outcome category is assessed using the predicted outcomes of the primary outcome model offering of telemedicine versus not offering, to obtain the marginal risk difference.[38–40] Similarly, for the secondary outcomes health status and hrQoL, the outcome model is a probit regression model, with baseline measurements added as a covariate. Healthcare utilisation will be assessed using a Poisson regression model, and all-cause mortality will be assessed using binary logistic regression.

We plan to perform the following additional analyses. First, we plan to perform the analysis with the start of follow-up defined at the T1 (after 6 months) measurement and the outcome of unplanned hospitalisation days during 6 months. This is because telemedicine status can be misclassified when it is started shortly after baseline but is not registered in the data. Second, we plan to perform a per-protocol analysis of telemedicine use if detailed information on starting and stopping of telemedicine is available through linkage. Finally, we plan to perform all analyses in the entire cohort, rather than the cohort restricted on HF diagnosis, to a maximum of 3 months prior to T0 (baseline).

Research question 1: effectiveness of telemedicine in patient subgroups

Research question 1 investigates the effectiveness of telemedicine across subgroups of patients with HF. Patient-related subgroups were identified by a systematic literature review of randomised controlled trials (RCTs) of telemedicine: age, severity of HF (NYHA class at baseline), sex, SES, presence of depression, atrial fibrillation and type of HF (HF with preserved ejection fraction (HFpEF), HF with midrange ejection fraction (HFmrEF), HF with reduced ejection fraction (HFrEF)) (table 3).[20–24 41–49] Stratified analyses of the primary outcome model are performed to estimate the above-defined average treatment effect in each of the

subgroups. Heterogeneity in telemedicine effect across age is assessed on a continuous scale, where an interaction between age and telemedicine status is added to the primary outcome model, and the expected number of days out of hospital across age ranges from 50 to 90 years is predicted from this model under telemedicine offered versus not offered.

In an additional analysis, heterogeneity across time since diagnosis is explored for the entire cohort, without restricting to patients with a maximum of 3 months since HF diagnosis at baseline (diagnosed ≤3 months before baseline compared with >3 months before baseline).

The secondary outcomes functional status, health status and hrQoL are assessed using similar approaches but using multinomial, probit and probit regression model, respectively. Healthcare utilisation will be assessed using a Poisson regression model, and all-cause mortality will be assessed using binary logistic regression.

Research question 2: effectiveness of different telemedicine components

Research question 2 investigates the effectiveness of the different forms of telemedicine intervention. We assess this question by performing three separate analyses in which intervention aspects are contrasted in the subset of participants that received telemedicine. The presence or absence of a telemedicine component is determined at a hospital level. The components of telemedicine that are contrasted are presence versus absence of a service centre, presence versus absence of an educational module, and high-intensity versus low-intensity protocol (table 2).

The population of interest is patients with newly diagnosed HF (maximum 3 months prior to baseline) who received telemedicine. Offering of telemedicine is measured at 6 months after baseline.

In addition to the set of confounding variables at the patient level used in the analysis above, confounding variables at the hospital level are considered because indication for telemedicine is expected to differ across hospitals. Confounding variables include academic or non-academic hospital, presence of a specialised heart centre, presence of an outpatient ward, size of outpatient ward (number of patients/year), staffing of the HF outpatient clinic and full-time equivalent of outpatient-ward staff.

For each of the three contrasts, the primary outcome model is fitted to estimate the average treatment effect of a component relative to the corresponding reference component on days of unplanned hospitalisation during 1 year in the population of patients with newly diagnosed HF that initiated telemedicine.

The secondary outcomes functional status, health status and hrQoL are assessed using similar approaches but using multinomial, probit and probit regression model, respectively. Healthcare utilisation and all-cause mortality will be assessed using Poisson regression model and binary logistic regression, respectively.

Cost-effectiveness

Costs will be estimated by computing the average costs (using cost guideline provided by the National Health Care Institute) per individual based on the information collected by the NHR and in the interviews with hospitals. Since 2023, Dutch hospitals can claim costs of telemedicine using the National Health Care Institute's Diagnosis Treatment Combination (DBC). This DBC can be used to estimate the average costs.[37] A 95% credible interval (CE) will be computed using the percentiles of a Monte Carlo bootstrap analysis with 5000 resamplings. This average cost represents a sum of the costs of telemedicine use, inpatient days, days at intensive care unit, HF-related hospital procedures and outpatient visits. In a secondary analysis, we will re-estimate the average costs and 95% CE using data enriched with VEKTIS data (if linking is available), meaning that the costs of visits to the general practitioner, pharmacy and care at home are also taken into account.

Linkage with CBS may be incomplete for several participants because of missing values or incomplete data sets (eg, twins, different available time windows between registries of collected data). If the number of non-linked participants is below 10%, we will perform multiple imputation; if it is above 10%, we will perform HTA analysis on the complete subset.

Utility values will be estimated using the average hrQoL score collected in the HF registry and, if needed, from the literature. The difference in average QoL score between the group that uses telemedicine versus the group that does not represents the difference in disutility between the groups under the assumption that the collected hrQoL is a good representation of the utility of the particular health state that individuals were in.

Quality-adjusted life years (QALYs) are estimated by multiplying the observed number of follow-up years by the corresponding hrQoL score. Subsequently, the incremental cost-effectiveness ratio (ICER) is computed by taking the ratio between the difference of the costs of the average patient in the telemedicine group and those not in the telemedicine group, and the difference in QALY of both groups, thereby providing the cost per additional QALY gained. The 95% CEs are obtained using the Monte Carlo percentile methods described above. Both deterministic and probabilistic sensitivity analyses will be performed to completely outline uncertainty on individual and combined parameters in the model.

In addition, willingness-to-pay curves will be drawn to highlight the impact of different thresholds on cost-effectiveness outcomes.

Research question 3: cost-effectiveness of telemedicine in patient subgroups

For research question 3, costs, utility, QALYs, ICER and willingness-to-pay curves will be computed to estimate the difference in cost-effectiveness between users and non-users of telemedicine in general. Subsequently, the analyses will be repeated to estimate cost-effectiveness

in subgroups, similar to the groups defined for research question 2 in the clinical effectiveness analysis.

Research question 4: cost-effectiveness of different telemedicine components

For research question 4, costs, utility, QALYs, ICER and willingness-to-pay curves will be computed to estimate the difference in cost-effectiveness between components of telemedicine, similar to the comparisons defined for research question 3 in the clinical effectiveness analysis.

Sample size calculation

The primary focus in RELEASE-HF is on the clinical effectiveness of telemedicine in HF management. Hence, the sample size calculation is based on parameters relevant to this analysis. The sample size calculation was conducted in three steps: (1) computing the required sample size for the main effect of telemedicine on the primary outcome, (2) taking into account that subgroup effects are of primary interest and (3) anticipating the accrual rate.

For the first part, we assumed a mean increase in the number of days spent alive without unplanned hospitalisation of 6.4 (SD 21.1) days based on the findings of the TIM-HF2 study.[44] This corresponds to a required sample size of 432 patients in total, based on a type I error probability of 5%, a type II error probability of 20% and accounting for 20% dropout.

Such a sample size would allow for an overall estimate of the difference between telemedicine and no telemedicine in days spent alive without unplanned hospitalisation in the overall patient population; however, our interest is in heterogeneous intervention effects. Hence, for the second part, the sample size was inflated to estimate subgroup effects.[50 51] To detect interaction effects that are 50%–60% of the size of the overall effect (ie, increase of more than 3.2–3.8 days spent outside the hospital due to the interaction given the main effect) with a power of 80%, the required sample size is inflated by a factor of 12.[50] This results in a required sample size of 5184 individuals.

Finally, from the HF registry pilot study (CHECK-HF), we know that, in view of the estimated average number of patients per hospital, the average proportion of included outpatient clinic patients with HF was above 80%.[52] Taking this accrual rate into account, we would require the inclusion of 6480 patients with HF.

Patient and public involvement

Patient and public organisations were involved during grant application. Public organisations were involved in recruiting hospitals, and in legal support and advice. Healthcare professionals' involvement in the study includes participating in an interview about telemedicine and motives about telemedicine choice and use. Patients with HF and patient organisations will be involved in formulating and prioritising relevant research questions which are in line with the need of the patient and the aim of the RELEASE-HF study. The results will be disseminated with involvement of patient and public organisations.

ETHICS AND DISSEMINATION

Management and storage of data

RELEASE-HF is an observational, retrospective multicentre cohort study of prospectively collected data registered within the NHR. A waiver for informed consent for analysis of data from the NHR data registry was obtained. Data collection and registration is performed by the participating centres in a secured online environment. Detailed information on the process of data acquisition, completeness, data quality and analysis of the NHR has been published previously.[30] To obtain reliable data, the NHR has an advanced, certified data quality control system in place to ensure completeness and quality of data.[35]

Participants of the interview study will sign informed consent. Data will be stored in the secured environment at the University Medical Center (UMC) Utrecht, the Netherlands. Data will be pseudonymised at the participant and setting level. A secured identification log will be used, only accessible to the main RELEASE-HF researcher. Because the interview data will be linked to the HF registry, pseudonymised data will also be stored at the Medical Informatics Department of University Medical Centers Amsterdam (the Netherlands).

Storage of linked data sets (HF registry with other national databases) will be part of the infrastructure established by the Heart4Data consortium.[28] The RELEASE-HF study will follow these principles.

The Medical Ethics Committee of UMC Utrecht (the Netherlands) reviewed the study protocol and confirmed that the study does not fall under the scope of the Medical Research Involving Human Subjects Act. RELEASE-HF complies with the rules of the General Data Protection Regulation.

Dissemination

The results will be published in peer-reviewed journals and presented at (inter)national conferences as deemed relevant for HF and telemedicine. The HF registry data underlying this article were provided by the NHR with the permission of the participating hospitals. Data are available on reasonable request to the corresponding author and with permission of the NHR. The hospital-specific telemedicine characteristics, which are added to the HF registry data, will also only be available on reasonable request to the corresponding author and with permission of the participating hospitals.

DISCUSSION

The RELEASE-HF study is a large-scale, observational study used to better understand heterogeneity in clinical effectiveness between patients using telemedicine. To our knowledge, this is the first study using routine clinical care data.

The current design has been chosen because telemedicine is already implemented in various ways in healthcare settings in the Netherlands. Therefore, conducting an RCT does not fit the current care for patients with HF. Additionally, using a national registry instead of an RCT allows us to observe all patients with HF, reducing selection bias that would otherwise be introduced by an RCT. A Dutch registry study previously showed that routinely collected data lead to a representative sample.[52] However, we have to be aware of confounding bias introduced by physicians or nurses who decide which patients may use telemedicine. We cannot completely avoid this bias, although we perform extensive confounding correction and conduct interviews with these healthcare professionals, asking about their local guidelines so we understand the selection of patients in that hospital. Consequently, it has been argued that results from observational studies describe a patient outcome when using the intervention rather than assessing the response to the intervention.[53] Another limitation of registry-based studies is that the data to be collected are predetermined, which can lead to relevant missing variables. To overcome the missing data, such as telemedicine data at the patient level or outcome measures, we aim to link other data sources to enrich the RELEASE-HF data set.

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Contributors JvE contributed to protocol conception and design and to the development of statistical analyses, obtained ethics approval, and contributed to writing the protocol manuscript and critical revision of the protocol manuscript. KL contributed to protocol conception and design and to the development of statistical analyses, provided statistical and methodological support, and contributed to writing the statistical analyses paragraph and critical revision of the protocol manuscript. JBR contributed to protocol conception and design, obtaining funding, and development of statistical analyses, provided statistical and methodological support, and critically revised the manuscript. ES contributed to the development of statistical analyses, provided statistical and methodological support, and critically revised the manuscript. GWJF contributed to protocol conception and design, obtaining funding, and writing the economic evaluation paragraph, and critically revised the manuscript. LD contributed to protocol conception for data collection combined with the use of the HF registry data, and critically revised the manuscript. JS and JB are also local investigators and assisted with the data collection. TJ, JS, JB, FHR and RAdB contributed to protocol conception and design and obtaining funding, and critically revised the manuscript. FWA and JCAT contributed to protocol conception and design, secured funding for the project and critically revised the manuscript. All authors approved the final version of the manuscript. The RELEASE-HF investigators consist of all local investigators who are responsible for ethical board approval and data collection. They have all read, refined and approved the final version of the manuscript.

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Competing interests JB received an independent research grant from Abbott for ISS paid to institution, and has had speaker engagements or advisory boards for AstraZeneca, Abbott, Bayer, Boehringer, Daiichi Sankyo, Novartis and Vifor in the past 5 years. RAdB has received research grants and/or fees from AstraZeneca, Abbott, Boehringer Ingelheim, Cardior Pharmaceuticals, Ionis Pharmaceuticals, Novo Nordisk and Roche, and has had speaker engagements with Abbott, AstraZeneca, Bayer, Bristol Myers Squibb, Novartis and Roche. CJWB has received speaker fees from AstraZeneca, Boehringer Ingelheim and Novartis. MLH is supported by the Dutch Heart Foundation (Dr E Dekker Senior Clinical Scientist Grant 2020T058) and CVON (2020B008 RECONNEXT). He received an investigator-initiated research grant from Vifor Pharma, an educational grant from Boehringer Ingelheim and Novartis, and speaker/consultancy fees from Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, MSD, Novartis, Sankyo, Daiichi, Quinn and Vifor Pharma, all of which were not related to this study.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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Supplementary material 1 Variables of the heart failure registry

NOTE: Based on the dynamic data dictionary version 22.1.4 September 9, 2022. Definitions of variables and included variables are subject to change, since data dictionary depends on the current HF guidelines and is compiled by a committee consisting of delegated cardiologists from Dutch hospitals.

	Variables	Answer possibilities	Baseline (T0)	6 months (T1)	12 months (T2)
Identifying variables	Diagnosis number *	Unique number set up by the hospital	**X**		
	Date of diagnosis *	Date (DD-MM-YYYY)	**X**		
	Patient number*	Identification number in the hospital	**X**		
	Maiden name*	Name	**X**		
	Surname*	Name	**X**		
	Date of birth[$]	Date (DD-MM-YYYY)	**X**		
	Sex	Male Female	**X**		
	Zip code*	1000 AA – 9999 ZZ= the Netherlands 0000= Abroad -1= Unknown	**X**		
Diagnostic variables	Setting of inclusion	10= Outpatient clinic 20= Hospital, novo patient 30= Hospital, acute/chronic HF patient -1 = Unknown	**X**		
	Previous HF diagnosis	0= No 1= Yes -1= Unknown	**X**		
	Date of previous diagnosis (if applicable)	Date (DD-MM-YYYY)	**X**		
	Location diagnosis HF	10= Not earlier diagnosed with HF 10= Primary care 20= Secondary care 30= Tertiary care -1= Unknown	**X**		
	Type of HF	10= HFrEF 20= HFmrEF 30= HFpEF -1= Unknown	**X**		
	Etiology HFrEF	0= No HFrEF 10= Ischemic cardiomyopathy 20= Non-ischemic, hypertensive cardiomyopathy 50= Non-ischemic, arrhythmia/tachycardia mediated 60= Non-ischemic, hypertrophic cardiomyopathy 70= Non-ischemic, dilated cardiomyopathy (eci) 80= Non-ischemic, inflammation/infection (i.e., myocarditis) 90= Nonischemic, restrictive cardiomyopathy and/or accumulation 111= Nonischemic, familiar cq. genetic cardiomyopathy with proven DNA mutation	**X**		

		120= Non-ischemic, pericardial 135= Non-ischemic, toxic cardiomyopathy due to alcohol/drugs 136= Non-ischemic, toxic cardiomyopathy due to chemotherapy/radiation 139= Non-ischemic, toxic cardiomyopathy due to other 140= Non-ischemic, eci or (as yet) undetermined 900= Other (i.e., valve disease, metabolic, peripartum) -1= Unknown			
	Etiology HFpEF	0= No HFpEF 10= Secondary HFpEF 20= Isolated hypertensive heart disease 30= Genetic HCM 40= Amyloidosis 50= Sarcoidosis 60= Hemochromatosis 70= Immune/inflammatory 80= Aortic valve stenosis 90= Pericardial diseases 900= Other -1= Unknown	**X**		
Patient characteristics	***Identifying variables***				
	Follow-up moment	0 = T0 6 = T1 12 = T2 24 = T3 36 = T4 48 = T5	**X**	**X**	**X**
	Comorbidities				
	Hypertension	0= No 1= Yes -1= Unknown	**X**	**X**	**X**
	Cardiovascular accident	0= No 1= Yes -1= Unknown	**X**	**X**	**X**
	Extracardiac arterial vascular pathology	0= No 1= Yes -1= Unknown	**X**	**X**	**X**
	Chronic respiratory disease	0= No 1= Yes -1= Unknown	**X**	**X**	**X**
	Obstructive Sleep Apnea Syndrome	0= No 1= Yes -1= Unknown	**X**	**X**	**X**
	Diabetes Mellitus	0= No 1= Diabetes, treatment unknown 2= Diabetes, no treatment 10= Diabetes, diet 20= Diabetes, oral medication 30= Diabetes, insulin 90= Diabetes, other -1= Unknown	**X**	**X**	**X**
	Thyroid disorder	0= No 10= Yes, hypothyroidism 20= Yes, hyperthyroidism	**X**	**X**	**X**

		-1= Unknown			
	Malignancy	0= No 10= Yes, in the past 20= Yes, currently -1= Unknown	**X**	**X**	**X**
	Measurements				
	Length	Measurement in centimeters	**X**	**X**	**X**
	Weight	Measurement in kilogram	**X**	**X**	**X**
	Systolic blood pressure	Measurement in mmHg	**X**	**X**	**X**
	Diastolic blood pressure	Measurement in mmHg	**X**	**X**	**X**
	Heart rhythm	10= Sinus rhythm 20= Atrium fibrillation 30= Atrial pacing 90= Other -1= Unknown	**X**	**X**	**X**
	Heartrate	Measurement in beats per minute	**X**	**X**	**X**
	Atrial heart rhythm disorder	0= No 1= Yes -1= Unknown	**X**	**X**	**X**
	Left bundle branch block	0= No 10= Yes, own heart's electrical conduction 20= Yes, pacing rhythm -1= Unknown	**X**	**X**	**X**
	QRS complex duration	Measurement in milliseconds	**X**	**X**	**X**
	Left ventricle ejection fraction, NYHA classification and laboratory parameters				
	Left ventricle ejection fraction	Measurement in percentages	**X**	**X**	**X**
	NYHA class	1= Class I 2= Class II 3= Class III 4= Class IV -1= Unknown	**X**	**X**	**X**
	NT-proBNP	1 t/m 8000= Value in pmol/l 0= No NT-proBNP measurement -1= Unknown	**X**	**X**	**X**
	Date measurement NT-proBNP[$]	Date (DD-MM-YYYY)	**X**	**X**	**X**
	Serum creatinine	Value in µmol/l	**X**	**X**	**X**
	Iron deficiency	1= No 2= Yes, absolute ferritin < 100 µg/L 3= Yes, relative ferritin 100-300 µg/L with transferrin saturation < 20% -1= Unknown	**X**	**X**	**X**
	Anemia	0= No 1= Yes -1= Unknown	**X**	**X**	**X**
Medication	***Medication with target dose***				
	Type ACE inhibitor	0= No ACE inhibitor prescribed at Tn 10= Captopril (td in ESC 2021 = 150 mg) 20= Enalapril (td in ESC 2021= 20-40 mg) 3-= Lisinopril (td in ESC 2021 = 20-35 mg) 40= Ramipril (td in ESC 2021 = 10 mg) 50= Perindopril (td in ESC 2021 = 8 mg)	**(X)**	**X**	**X**

		60= Quinapril (td in ESC 2021 = 20 mg) 70= Fosinopril (td in ESC 2021 = 20-40 mg) 90= Other -1= Unknown			
	Target dose ACE inhibitor	0= No ACE inhibitor prescribed at Tn 1= No, target dose in ESC 2021 not reached due to contraindication or otherwise 2= No, target dose in ESC 2021 not reached due to titration phase 10= Yes, target dose in ESC 2021 reached or maximally tolerable for this patient -1= Unknown	**(X)**	**X**	**X**
	Type ARB	0= No ARB prescribed at Tn 10= Candesartan (td in ESC 2021 = 32 mg) 20= Losartan (td in ESC 2021 = 150 mg) 30= Valsartan (td in ESC 2021 = 320 mg) 40= Telmisartan (td in ESC 2021 = 80 mg) 50= Irbesartan (td in ESC 2021 = 300 mg) 90= Other -1= Unknown	**(X)**	**X**	**X**
	Target dose ARB	0= No ARB prescribed at Tn 1= No, target dose in ESC 2021 not reached due to contraindication or otherwise 2= No, target dose in ESC 2021 not reached due to titration phase 10= Yes, target dose in ESC 2021 reached or maximally tolerable for this patient -1= Unknown	**(X)**	**X**	**X**
	ARNI	0= No 1= Yes (td in ESC 2021 = 194-206 mg) -1= Unknown	**(X)**	**X**	**X**
	Target dose ARNI	0= No ARNI prescribed at Tn 1= No, target dose in ESC 2021 not reached due to contraindication or otherwise 2= No, target dose in ESC 2021 not reached due to titration phase 10= Yes, target dose in ESC 2021 reached or maximally tolerable for this patient -1= Unknown	**(X)**	**X**	**X**
	Type beta-blocker	0 = No beta blocker prescribed at Tn 10= Bisoprolol (td in ESC 2021 = 10 mg) 20= Metoprolol (td in ESC 2021 = 200 mg) 30= Carvedilol (td in ESC 2021 = 50 mg)	**(X)**	**X**	**X**

		40= Nebivolol (td in ESC 2021 = 10 mg) 50= Atenolol (td in ESC 2021 = 100 mg) 60= Pindolol (td in ESC 2021 = 20 mg) 70= Propranolol (td in ESC 2021 = 160 mg) 90= Other -1= Unknown			
	Target dose beta-blocker	0= No beta blocker prescribed at Tn 1= No, target dose in ESC 2021 not reached due to contraindication or otherwise 2= No, target dose in ESC 2021 not reached due to titration phase 10= Yes, target dose in ESC 2021 reached or maximally tolerable for this patient -1= Unknown	**(X)**	**X**	**X**
	Type MRA	0= No MRA prescribed at Tn 10= Eplerenone (td in ESC 2021= 50 mg) 20= Spironolactone (td in ESC 2021= 50 mg) 90= Other -1= Unknown	**(X)**	**X**	**X**
	Target dose MRA	0= No MRA prescribed at Tn 1= No, target dose in ESC 2021 not reached due to contraindication or otherwise 2= No, target dose in ESC 2021 not reached due to titration phase 10= Yes, target dose in ESC 2021 reached or maximally tolerable for this patient -1= Unknown	**(X)**	**X**	**X**
	Type SGLT2 inhibitor	0= No SGLT2 inhibitor prescribed at Tn 10= Canagliflozin (td in ESC 2021 = 10 mg) 20= Dapagliflozin (td in ESC 2021 = 10 mg) 30= Empagliflozin (td in ESC 2021 = 10 mg) 90= Other -1= Unknown	**(X)**	**X**	**X**
	Target dose SGLT2 inhibitor	0= No SGLT2 inhibitor prescribed at Tn 1= No, target dose in ESC 2021 not reached due to contraindication or otherwise 2= No, target dose in ESC 2021 not reached due to titration phase 10= Yes, target dose in ESC 2021 reached or maximally tolerable for this patient -1= Unknown	**(X)**	**X**	**X**
	Ivabradine	0= No 1= Yes	**(X)**	**X**	**X**

		-1= Unknown			
	Target dose Ivabradine	0= No ivabradine prescribed at Tn 1= No, target dose in ESC 2021 not reached due to contraindication or otherwise 2= No, target dose in ESC 2021 not reached due to titration phase 10= Yes, target dose in ESC 2021 reached or maximally tolerable for this patient -1= Unknown	**(X)**	**X**	**X**
	Additional medication				
	Diuretic	0= No 1= Yes (target dose in ESC 2021 = 15mg) -1= Unknown	**(X)**	**X**	**X**
	Vericiguat	0= No 1= Yes -1= Unknown	**(X)**	**X**	**X**
	Digoxin	0= No 1= Yes -1= Unknown	**(X)**	**X**	**X**
	Amiodarone	0= No 1= Yes -1= Unknown	**(X)**	**X**	**X**
	Sotalol	0= No 1= Yes -1= Unknown	**(X)**	**X**	**X**
	Hydralazine / Isosorbide dinitrate	0= No 1= Yes -1= Unknown	**(X)**	**X**	**X**
Outcome variables	***Cardiac intervention and implantable***				
	Pacemaker – VVI	0= No 1= Yes -1= Unknown	**(X)**	**X**	**X**
	Pacemaker – VVI date[$]	Date (DD-MM-YYYY)	**(X)**	**X**	**X**
	Pacemaker – DDD	0= No 1= Yes -1= Unknown	**(X)**	**X**	**X**
	Pacemaker – DDD date[$]	Date (DD-MM-YYYY)	**(X)**	**X**	**X**
	CRT-P	0= No 1= Yes -1= Unknown	**(X)**	**X**	**X**
	CRT-P date[$]	Date (DD-MM-YYYY)	**(X)**	**X**	**X**
	CRT-D	0= No 1= No, because of medical condition 2= No, because of patients' wish 10= Yes -1= Unknown	**(X)**	**X**	**X**
	CRT-D date[$]	Date (DD-MM-YYYY)	**(X)**	**X**	**X**
	ICD – VVI	0= No 1= No, because of medical condition 2= No, because of patients' wish 10= Yes -1= Unknown	**(X)**	**X**	**X**
	ICD – VVI date[$]	Date (DD-MM-YYYY)	**(X)**	**X**	**X**
	ICD – DDD	0= No 1= No, because of medical condition 2= No, because of patients' wish	**(X)**	**X**	**X**

		10= Yes -1= Unknown			
	ICD – DDD date[$]	Date (DD-MM-YYYY)	**(X)**	**X**	**X**
	PCI	0= No 1= Yes -1= Unknown	**(X)**	**X**	**X**
	PCI date[$]	Date (DD-MM-YYYY)	**(X)**	**X**	**X**
	CABG	0= No 1= Yes -1= Unknown	**(X)**	**X**	**X**
	CABG date[$]	Date (DD-MM-YYYY)	**(X)**	**X**	**X**
	LVAD	0= No 1= Yes -1= Unknown	**(X)**	**X**	**X**
	LVAD date[$]	Date (DD-MM-YYYY)	**(X)**	**X**	**X**
	Heart transplantation	0= No 1= Yes -1= Unknown	**(X)**	**X**	**X**
	Heart transplantation date[$]	Date (DD-MM-YYYY)	**(X)**	**X**	**X**
	Heart revalidation	0= No 1= Yes -1= Unknown	**(X)**	**X**	**X**
	Telemonitoring	0= No telemonitoring 10= Telemonitoring by telephone 20= Telemonitoring, non-invasive based on traditional parameters (e.g., blood pressure, ECG) 30= Telemonitoring, using ICD based on HF parameters 40= Telemonitoring, invasive by sensors in the blood stream or heart -1= Unknown	**(X)**	**X**	**X**
	Patient status and quality of life				
	Mortality	0= Alive 1= Deceased -1= Unknown		**X**	**X**
	Date mortality[$]	Date (DD-MM-YYYY)		**X**	**X**
	Number of hospitalizations	Number		**X**	**X**
	Date hospitalization[$]	Date (DD-MM-YYYY)		**X**	**X**
	Number of hospitalization days	Number		**X**	**X**
	Location follow-up	0= No follow-up, because of mortality 10= Patient stays in secondary care, outpatient HF clinic 20= Patient stays in tertiary care, outpatient HF clinic 30= Patient transferred to primary care 40= Patient transferred to the cardiology outpatient clinic 90= Other -1= Unknown		**X**	**X**
	Type quality of life questionnaire	0= Not measured 10= SF12-2 20= SF36-2 30= SF36-1 -1= Unknown	**X**	**X**	**X**
	Quality of life	Coding depends on questionnaire	**X**	**X**	**X**
*Variables are collected in the Heart failure registry, but the data is not distributed and available for research.					

[$]All variables which consist of a date will be transformed to number of days since diagnosed with HF. The actual date is not available in research.

HF: Heart Failure; HFrEF: Heart Failure with reduced Ejection Fraction; HFmrEF: Heart Failure with mildly reduced Ejection Fraction; HFpEF: Heart failure with preserved Ejection Fraction; NYHA: New York Heart Association; eci: e causa ignota (unknown cause); NT-proBNP: N-Terminal pro B-type Natriuretic Peptide; ACE: Angiotensin Converting Enzyme; td: target dose; ARB: Angiotensin Receptor Blocker; ARNI: Angiotensin Receptor-Neprilysin Inhibitor; MRA: Mineralocorticoid Receptor Antagonists; SGLT2: Sodium-glucose co-transporter-2; VVI: Ventricular pacing; DDD: dual-chamber antibradycardia pacing; CRT-P: Cardiac Resynchronization Therapy with a Pacemaker; CRT-D: Cardiac Resynchronization Therapy with a pacemaker and an ICD; ICD: Implantable Cardioverter-Defibrillator; PCI: Percutaneous Coronary Intervention; CABG: Coronary Artery Bypass Graft; LVAD: Left Ventricular Assist Device; ECG: Electro Cardio Gram; SF12/SF36: Short Form Health Survey with 12 questions or 36 questions.

Supplementary material 2 Interview guide telemedicine

Introduction

What do we mean by telemedicine?

With telemedicine, we mean the provision of care at a distance. The healthcare provider and the patient are not physically present with each other at that moment. Telemedicine can consist of telemonitoring or tele-education (according to the Collaboration Agreement and Quality Criteria for Telemedicine).

- *Telemonitoring* involves monitoring heart failure symptoms and relevant parameters used to support patients and healthcare providers in the treatment of heart failure.
- *Tele-education* is a service that allows the patient/user to receive remote education. Receiving this education can be accessed through a variety of applications and devices.

Background Information: Use of Telemedicine

1) Does your hospital offer telemedicine to outpatient heart failure patients?
    - Yes, we offer telemedicine.
        i. Why do you offer telemedicine?
            - *Possibilities: monitoring, education, self-care/self-management, consultation, cost reduction, reduction in hospital admissions, improvement in quality of life, reducing workload.*
    - No, we do not offer telemedicine.
        i. Why don't you offer telemedicine? (How strong is the influence of [x] in this?)
            - *Possibilities: no patient/clinician demand, costs, evidence, user-unfriendly technology, no connection to EHR, HF care pathway is different, time, shortage of healthcare professionals, significant investment compared to the amount of patients, legal/privacy concerns, others.*
        ii. Have you considered using telemedicine for HF patients?
            - What prompted you to consider it but not proceed?
        iii. Which professionals were involved in this decision?
    - No, but we plan to start telemedicine.
        i. Why are you planning to start telemedicine?
            - *Possibilities: patient/clinician desire, guidelines, COVID-19, funding, others.*
        ii. To what extent did COVID-19 influence this decision?
        iii. Which professionals are involved in this decision?
    - No, we stopped telemedicine.
        i. Why did you stop telemedicine?
            - *Possibilities: no patient demand, didn't meet expectations, more time, moderate positive effects, cost, lack of staff, others.*
        ii. Who were involved in this decision? (Professionals)

Users of Telemedicine

From this point on, the conversation continues with the focus on the performers of telemedicine from the perspective of healthcare professional.

2) Which system do you use for telemedicine?
    - Luscii
    - Sananet/SanaCoach
    - Motiva (Philips)
    - 24Care
    - Hartwacht
    - CardioMEMS
    - Empower
    - Other, namely: ...

3) Why do you use telemedicine for heart failure patients?
    - Why is telemedicine used for [goal X]?
        i. *Functionalities: monitoring, education, self-care/self-management, consultation.*
        ii. *Endpoints: cost reduction, reduction in hospital admissions, improvement in quality of life, reducing workload for healthcare professionals.*
        iii. *Other, namely: ...*

Offering Telemedicine

4) Which patients visit the heart failure outpatient clinic?
    i. *Severity, age, duration of illness.*

5) Which heart failure patients at your outpatient clinic are eligible for telemedicine?
    i. What factors are considered in the decision to use telemedicine?
    ii. *Telemedicine guideline: Chronic HF, recently diagnosed, readmission due to exacerbation, anxious/uncertain/depressive patients, assistance in early detection of deterioration.*
    iii. *Characteristics: caregiver network, patient/donor digital skills, language proficiency, patient mobility, internet connection, distance to hospital, other.*
    - Does the severity of heart failure play a role in initiating telemedicine?
        - Yes
        - No
    - At which NYHA class is telemedicine used?
        - NYHA 1
        - NYHA 2
        - NYHA 3
        - NYHA 4
    - Why this NYHA class?

6) Which heart failure patients at your outpatient clinic are not eligible for telemedicine?
    - Why are these patients not eligible?
        i. *Telemedicine guideline: Chronic HF, recently diagnosed, readmission due to exacerbation, anxious/uncertain/depressive patients, assistance in early detection of deterioration.*
        ii. *Characteristics: caregiver network, patient/donor digital skills, language proficiency, patient mobility, internet connection, distance to hospital, other.*

7) When is telemedicine for the first time considered for heart failure patients? (multiple answers possible)
    - For every newly diagnosed heart failure patient
    - After a hospital admission

- For patients attending the heart failure outpatient clinic (regardless of previous hospital admission)
- After an exacerbation (patient is already diagnosed with heart failure)
    i. When is telemedicine offered after an exacerbation?
        - After 1 exacerbation
        - After ... exacerbations
        - If the patient has more than ... exacerbations
    i. Does the time period in which the patient has an exacerbation play a role in offering telemedicine?
        - Yes, when ... exacerbations in ... weeks
        - No
        - In the titration phase
    i. Is telemedicine offered during the titration phase?
        - Yes, every time there is a change in medication
        - Yes, only when the patient is newly diagnosed with the disease
        - Sometimes, depending on the situation, ease of titration, patient's distance, pandemic, etc.
        - No
    i. For which medication?
- In the stable phase of HF
    i. Is telemedicine offered in every stable phase of heart failure?
        - Yes
        - No
- Others, namely: ...

8) Which healthcare professionals are involved in determining whether or not to use telemedicine for the patient? (multiple answers possible)
    - Cardiologist
    - Heart failure nurse
    - Nurse Specialist / Physician Assistant
    - General Practitioner
    - Home care nurse
    - General practice nurse
    - Other, namely: ...

Stopping/On-Off principle of telemedicine

9) Is telemedicine offered multiple times in a heart failure care trajectory?
    - Yes
        i. How is this offered?
        ii. For which patients?
        iii. What determines the on/off/on/off principle?
        iv. Is the equipment removed?
    - No

10) When is telemedicine stopped?
    i. Patient request, death, healthcare professional's assessment, disease severity, treatment phase, established time period, other
    - Does NYHA class play a role in this?

Modules of the Telemedicine System

11) On which device can the patient receive telemedicine? *(multiple answers possible)*
    - Application on a mobile phone (smartphone)
    - Computer
    - Television
    - Watch (smartwatch)
    - iPad
    - Other, namely: ...

Telemonitoring

12) Does your telemedicine system include telemonitoring (e.g., vital signs, nutrition, medication, heart failure symptoms)?
    - Yes
        i. What is the main reason for using telemonitoring?
            - *Early detection of exacerbation, titration, longitudinal follow-up, self-management, other*
    - No

13) What type of telemonitoring do you use?
    - Non-invasive
    - Invasive
    - Non-invasive and invasive

14) Which measurements are monitored via telemonitoring?
    - Weight
    - Blood pressure
    - Heart rate
    - Heart rhythm (irregular, regular)
    - Temperature
    - Saturation
    - Intake (e.g., in the context of sodium restriction)
    - Fluid intake
    - Medication
    - Heart failure-related symptoms
        i. What symptoms do you monitor?
            - *Fatigue, decreased appetite, shortness of breath, swollen legs and ankles, cold hands and feet, a full feeling in the upper abdomen, palpitations, nocturia, constipation, tickling cough, restless sleep, memory and concentration problems, dizziness*
            - *Other, namely: ….*
    - Other, namely: ....

15) What equipment has the patient received for telemonitoring? *(multiple answers possible)*
    - No equipment
    - Patient uses their own equipment
        i. What equipment?
    - Weight scale
    - Bluetooth-enabled weight scale
    - Blood pressure monitor
    - Bluetooth-enabled blood pressure monitor
    - Pulse oximeter
    - Bluetooth-enabled pulse oximeter
    - ECG device

van Eijk J, *et al*. *BMJ Open* 2024; 14:e078021. doi: 10.1136/bmjopen-2023-078021

- CardioMEMS
- Other, namely: ....

16) Can a patient transmit monitored (vital) signs via the telemonitoring system to the healthcare provider?
    - Yes
        i. When can the patient transmit these monitored (vital) signs? (time of day)
            - *Possible options: 24/7, office hours, weekend, evening, night, set times, other, namely*

        ii. How does the patient transmit the monitored (vital) signs to the healthcare professional? (communication)
            - *Possible options: letter, phone call, video call, chat, SMS, email, via applications, other*
    - No

17) Does the healthcare professional receive a notification when monitored (vital) signs are entered into the telemonitoring system?
    - Yes
        i. When does the healthcare professional receive a notification?
            - *Possible options: always, when threshold values are exceeded, other*

        i. Where does the healthcare professional receive the notification?
            - *Possible options: Electronic Patient Record (EPD), standalone applications, email inbox, other*

        ii. Does the healthcare professional always receive the notification in the same manner, or does severity of exceeding the threshold play a role?
            - Yes
            - No
                i. What is the difference?

        iii. Which healthcare professional receives these messages?
            - *Possible options: cardiologist, heart failure nurse, nurse practitioner, physician assistant, general practitioner (GP), practice nurse, home care worker, other*

        iv. Are there erroneous notifications?
            - *How do you handle them?*
    - No
        v. How often does the healthcare professional evaluate the monitored vital signs, questionnaires, outcomes filled in by the patient in the telemonitoring system?
            a. Per week: ....
            b. Per day: ....
            c. Per patient: ....

18) Can a healthcare professional respond to the received monitored (vital) signs?
    - Yes
        i. Which healthcare professional responds to the received results?
            - *Possible options: cardiologist, heart failure nurse, nurse practitioner, physician assistant, general practitioner (GP), practice nurse, home care worker, other*

        ii. When can the healthcare professional respond to these monitored (vital) signs? (time of the day)
            - *Possible options: 24/7, office hours, weekend, evening, night, set times, other*

        iii. How does the healthcare professional respond to the monitored (vital) signs?
            - *Possible options: letter, phone call, video call, chat, SMS, email, via applications, other*

        iv. Does the patient receive a notification if the healthcare professional has sent a message to the patient?
    - No

19) Can thresholds be set for the monitored (vital) signs in the telemonitoring system?
    - No
    - Yes, general thresholds (not patient-specific)
        i. What are the thresholds based on? / How are the thresholds formulated?
    - Yes, patient-specific thresholds
        i. Can the thresholds be adjusted per patient, per situation, per moment?
            - Yes
            - No
        i. What are the thresholds based on? / How are the thresholds formulated?

20) Is there always contact between the patient and the healthcare professional for the monitored (vital) signs transmitted via the telemonitoring system?
    - Yes
        i. Is the contact direct or indirect (store-and-forward) between the patient and the healthcare professional?
            - *Direct: The patient and healthcare professional are using the system simultaneously, allowing for direct contact via one of the techniques provided by the telemonitoring system.*
            - *Indirect: The patient and healthcare professional have asynchronous contact with each other. The patient/healthcare professional sends their information to the recipient. The recipient reads the message later and responds to the sender.*
            - *Combination of direct and indirect contact*
    - No
        i. When is there contact between the patient and healthcare professional?

21) What actions does the healthcare professional take with the received monitored (vital) signs?
        i. How do you initiate these actions?
            - *Possible options: letter, phone call, video call, chat, SMS, email, via applications, other*
        ii. Does the telemonitoring system provide automatically generated advice to the patient when they enter data in a module in the telemonitoring system?
            - *Yes*
            - *No*

22) What is your experience with the telemonitoring provided by the telemonitoring system?

Education and self-care

23) Does your telemedicine system include the modules education and self-care?
    - Yes
        i. Does the education module need to be actively activated for each patient by the healthcare professional? (Note: Can the telemonitoring system also exist without the education module?)
            - Yes
            - No
        ii. Which topics are included in the education?
            - General medical information about heart failure
            - Information about treatment
            - Prevention of symptoms/exacerbations
            - Medication use
            - Fluid and dietary management
            - Physical activity
            - Other, namely: ...

iii. Do you actively refer the patient to the education module in the telemedicine system? (Note: Do you discuss this topic in your consultation?)
- Yes
- No

i. Is the education module the same for every patient?

ii. Which self-care components are included in the telemedicine system?
- Lifestyle interventions,
  - Which behaviors/lifestyle interventions are included?
    - *Possible answers: exercise, nutrition, stress management*
- Psychological well-being: information, knowledge, tools
- Patient's medication overview
- Medication explanation (medication glossary)
- Medication intake reminder as per prescription
- Referral to external sources and links related to heart failure
- Knowledge quiz/ability to test knowledge about heart failure
- Monitoring
- Self-detection and the ability to anticipate/adjust medication (e.g., detecting weight gain through monitoring and then taking and recording medication [diuretics])
- Other, namely: ...

- No

24) To what extent does the patient make decisions based on the telemedicine system?
   - Are efforts made that the patient take independent action / anticipate in response to measured (vital) signs?

25) To what extent does the telemedicine system promote the patient's self-care? / What is the effect of this module on the patient's self-care (skills)?

26) What are your experiences with the built-in self-care and education modules in the telemedicine system?

Heart Failure Community

27) Can the patient use the telemedicine system to get in touch with peers (for example, a heart failure community)?
   - Yes, always
   - Yes, but this module needs to be activated
     i. How is the heart failure community organized?
     - *Local (hospital)*
     - *Regional*
     - *National*
   - No, this is not possible

Analog Telemonitoring (via telephone)

28) Do you have contact with heart failure patients by phone (hospital to patient)?
    - Yes
        i. Who initiates contact with these patients by phone?
            - *Possible options: cardiologist, heart failure nurse, nurse practitioner (NP), physician assistant (PA), general practitioner (GP), general practice nurse (POH), home care nurse, other*
        ii. When do you have contact with the patient by phone?
        iii. What is the purpose of contact by phone?
        iv. How often do you have contact with the patient by phone?
        v. Which patients receive telephone guidance?
        vi. Why these patients?
    - No

29) Can the patient initiate contact by phone with the heart failure outpatient clinic (patient to hospital)?
    - Yes
        i. When can/may the patient initiate this type of contact?
        ii. Who does the patient have telephone contact with?
            - *Possible options: cardiologist, heart failure nurse, nurse practitioner (NP), physician assistant (PA), general practitioner (GP), general practice nurse (POH), home care nurse, other*
    - No

30) Can a heart failure patient or healthcare professional seek contact in any other way?
    - Through which channel does this contact occur?
        - *Possible answer: patient portal*
    - When does this contact occur via this channel?

31) What is your experience with telemonitoring by phone?

External Influences on the Use of Telemonitoring

Evaluation

32) Is the telemedicine system evaluated (experiences, application in HF care, impact on objectives) among healthcare professionals?
    - Yes
    - No

33) What is the influence of telemedicine on the patient population that visits the (regular) heart failure outpatient clinic?
    - What are the characteristics of these patients?

34) Is the telemedicine system evaluated (experiences, application in their disease, usage) between the healthcare professional and the patient?
    - Yes
    - No
        i. Are expectations discussed with the patient regarding the use of telemedicine?
        ii. What feedback do you receive?
        iii. What is the experience of telemedicine from the patients' perspective?

Experience

35) Do you believe that telemedicine in your hospital has led to efficiency?
    - Yes
        i. On which outcomes?
        ii. Has this been objectively assessed?
    - No
        i. What makes you say that?

36) Would you recommend the telemedicine system you use?
    - Why?

37) What would you like to change/improve about your telemedicine system?

38) If you could choose a telemedicine system again, what would it look like?

COVID-19

39) Does COVID-19 have an impact on the use of telemedicine in your heart failure outpatient clinic? (multiple answers possible)
    - Yes, telemedicine is used for more patients as an intervention.
    - Yes, telemedicine is used less frequently for patients as an intervention.
    - Yes, telemedicine is used differently by patients who were already using this intervention before COVID-19.
        i. Which devices of the telemedicine system are used differently since COVID-19?
            - *Possible answers: phone calls, video calls, chat, email, SMS, chatbot, other.*
        i. Which modules of the telemedicine system are used differently since COVID-19?
            - *Possible answers: telemonitoring, education, self-care/self-management, heart failure community, other.*
        i. What do you think of this development?
    - No, there is no difference in the use of telemedicine before, during, and in the current COVID-19 period.

Time Investment in telemedicine vs. No telemedicine in Heart Failure Care (HTA)

40) How much time do you, on average, spend on an appointment at a heart failure outpatient clinic without telemedicine?
    ... minutes / hours

41) How much time do you, on average, spend on an appointment at a heart failure outpatient clinic with telemedicine?
    ... minutes / hours

42) How much time does it take to explain telemedicine to a heart failure patient (for the initial setup)?
    ... minutes / hours

43) How much time do you, on average, spend per week on providing telemedicine? (this includes monitoring digital statuses transmitted through the telemonitoring system, contacting the patient as needed, evaluating measurements, etc.)
    ... minutes / hours