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TELEHEALTH AND MEDICINE TODAY

ORIGINAL RESEARCH

A Systematic Review Identifying Adverse Health Outcomes and Mortality Rates Associated with Telehealth

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Abstract

Background: The literature supporting telehealth management is growing, accelerated by the COVID pandemic. We hypothesize that there are risks of adverse events associated with telehealth interventions.
Methods: A review of PubMed (including MEDLINE), Embase, ISI (Web of Science), VHL/GHL, Scopus, ScienceDirect, and PsycINFO (January 1, 1960 to March 1, 2021) was conducted for all adverse events associated with telehealth. This systematic review and meta-analyses were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.
Results: The systematic review included 78 studies, of which eight were included in the quantitative synthesis and two meta-analyses were conducted. Telehealth was associated with a 40% lower mortality risk among patients with heart failure compared to traditional care. Telemonitoring was also associated with a lower mortality risk compared to usual care, with a pooled relative risk of 0.60 (95% confidence interval [CI]: 0.43–0.84) in the random-effects meta-analysis. Among patients with heart implants, telemonitoring was associated with a 35% lower mortality risk compared to traditional care. Overall, telehealth was not associated with an increased number of adverse events compared to traditional healthcare methods in the randomized controlled trials included in the review. However, there remains a need for additional studies with consistent outcome assessments to complement the existing literature.
Conclusions: While randomized clinical trials (RCTs) of telehealth interventions demonstrate enhanced patient outcomes in several studies and pave the way to evidence-based practice, the heterogeneity of the research questions suggests an important need for more complementary studies with consistent outcome assessments.

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In 2020, those providing healthcare were compelled to adapt quickly when faced with a global pandemic crisis. Many countries shifted to widespread healthcare provision by utilizing telephone and video consults as in-person patient visits became limited and medical offices were forced to close to maintain social distancing.[1] Telehealth is defined as the delivery and facilitation of health and health-related services, including medical care, provider and patient education, health information services, and self-care via telecommunications and digital communication technologies.[2] Healthcare provision through telehealth includes telephone support, messaging, internet-based approaches, and remote monitoring.[3] It is important to distinguish telehealth and telemedicine as telemedicine is considered a subset of telehealth and strictly refers to the provision of clinical health care services using communication technology.[4] During 2020, there was a massively increased demand for telehealth services across 50 countries most affected by COVID-19, highlighting the need to scale up telehealth capabilities.[5]

Perle and colleagues recently reviewed the positive effects of telehealth interventions for treating patients

who cannot pursue mental health services.[6] Similarly, another systematic review reported improved clinical and medication use outcomes, high patient satisfaction, and cost savings mainly through averting travel and preventing drug-related adverse issues.[7] These findings suggest that telehealth has a neutral to positive effect on patient safety and outcomes.[8] However, these benefits do not come without challenges that can be hard to quantify. For healthcare providers, challenges to adopting telehealth systems are a combination of operational, patient, and state-level insurance policy, privacy, and data security factors. From a patient's perspective, the barriers to telehealth adoption include data quality, reimbursement issues with insurance providers, privacy concerns, as well as patient technology barriers.[9] On the other hand, the literature reports significant risks of telehealth utilization and potential abuse issues that could compromise the safety and trust of patients.

Therefore, the aim of this study was to systematically review telehealth interventions that were tested in randomized clinical trials and aimed to improve patient care while evaluating the overall effects of these interventions across different health conditions.

Methods

Data sources

We searched for English-language studies (January 1, 1960 and March 1, 2021) in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines published using the following full-text databases: PubMed (including MEDLINE), Embase, ISI (Web of Science), VHL/GHL, Scopus, ScienceDirect, and PsycINFO. Search terms included "telehealth" and "telemedicine." However, throughout this paper, only the term telehealth will be used. The protocol for the systematic review was registered in the PROSPERO database under the registration number CRD42021253656. Table 1 provides a detailed listing of search terms and the strategy utilized.

Study Selection

The search strategy aimed to define the generic exposure (using keywords referring to telehealth techniques) and the outcome of interest (using keywords referring to either pre-defined adverse events [AE] or other events that are considered adverse *per se*). Two experienced and trained reviewers (AP and YA) independently assessed the inclusion eligibility of the retrieved studies. Studies were included if they were a randomized controlled trial (RCT) investigating telehealth use, reporting adverse events associated with telehealth usage, and were written in English (Table 2). After retrieving the articles from the electronic databases and after removing duplicates, titles and abstracts were reviewed by two reviewers independently (AP and YA). Additionally, a third reviewer (FC) was consulted to resolve conflicts and make a final decision. After this step, the full-text screening was performed by AP and YA, in a similar manner. Finally, to identify potentially missed but relevant publications, we manually screened the reference lists of all included studies.

We identified a total of 5,144 citations—1,189 were in PubMed, 487 in Embase, 912 in World of Science, 814 in Scopus, 1,003 in ScienceDirect, and 739 were in PsycINFO. After removing duplicates (3,760), a total of 1,384 articles were screened for their title and abstract. There were 1,071 articles excluded for either topic irrelevancy (n = 1,037) or lack of availability of full-text articles (n = 34), leaving 313 articles for a full-text scan. Of those, 83 were deemed ineligible due to study design (not a RCT), 124 articles assessed no outcomes of interest, five were written in a language other than English, 31 used a tool not classified as telehealth (those based on telephone calls or telephone triage), 18 used protocols or sole descriptions of the study project/intervention tool, 10 were literature reviews, nine were either secondary research or had only abstracts available and one did not report the outcomes in both groups. Additionally, 354 articles were identified by manual review, out of which 46 studies were included in the qualitative synthesis (Figure 1). Thus, the final set consisted of 78 published studies that underwent a full text abstraction including the qualitative synthesis. Out of them, eight were included in the quantitative synthesis as well, resulting in two meta-analyses.

Table 1. Detailed journal databases keyword search strategy of the electronic database

Search Keywords
1) Generic Exposure of Interest
(Telecare [mh] **OR** telehealth [mh] **OR** telemed* [mh] **OR** tele-homecare[tiab] **OR** telenursing [tiab] **OR** (health **AND** videophone[tiab]) **OR** (health **AND** video visit [tiab]) **OR** (health AND virtual visit[tiab]) **OR**(health AND televise* [tiab]) **OR** (telecommunication **AND** health [tiab]) **OR** eHealth [tiab] **OR** telerehab* [tiab] **OR** teleradiology [tiab] **OR** telepath* [tiab])
2) Outcome of Interest
(patient risk [tiab] **OR** patient safety [tiab] **OR** patient harm [tiab] **OR** medical error [tiab] **OR** medical liability [tiab] **OR** medical hazard [tiab] **OR** medical risk [tiab] **OR** adverse event [tiab] **OR** adverse incident [tiab])

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Table 2. Inclusion and exclusion criteria

	Include	Exclude
Patient population	Any patient population	None
Intervention & comparator	Telehealth usage in any medical discipline for patient management	No usage of any telehealth tool in some capacity for the experimental group
Outcomes	Studies reporting adverse events associated with telehealth usage in any medical discipline	No report of any adverse events
Study design	Randomized Control Trials (RCTs)	Any other design that is not an RCT
Limits	English language only	
Timespan	From 1960 until March 2021	

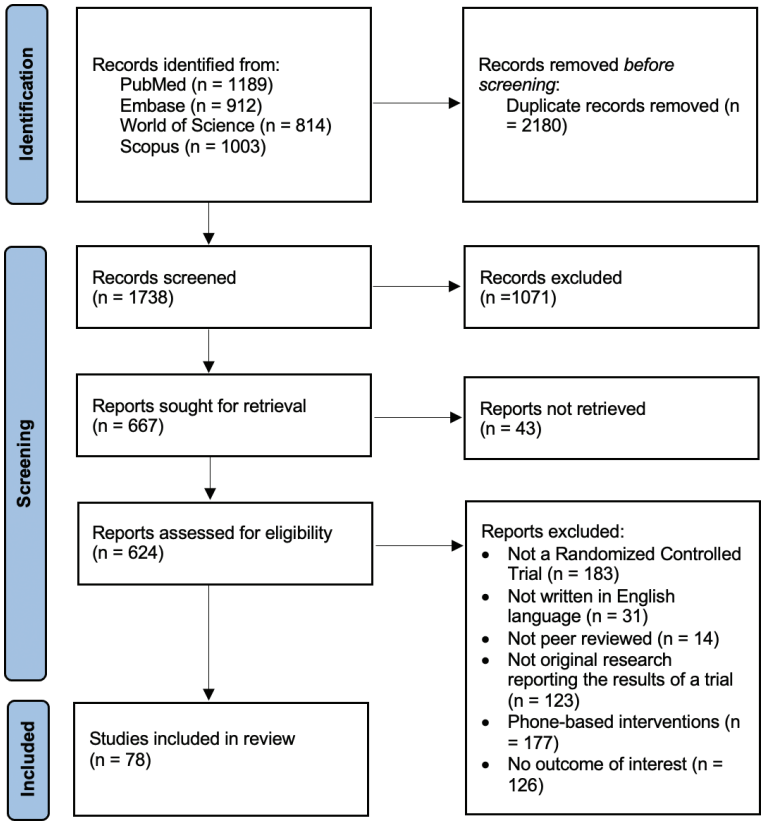

Fig. 1. Identification of studies via databases and registers.

Quality Assessment of Studies

The quality of the included studies was assessed by using the revised Risk of Bias 2 tool (RoB2) developed by the Cochrane Collaboration and modified to ensure standardized scoring.[10] The methodological quality was assessed by searching for selection bias, performance bias, attrition bias, and detection bias evidence. Methodological quality assessed regarding the blinding of participants in the studies was not included as a quality criterion because it was not possible to adequately blind participants in the context of telehealth interventions. We considered the scoring points relating to the blinding of the participants/personnel to be at low risk of bias for the reported outcomes that were based on objective measurements. In addition, some studies reported only the rates of AEs, without performing additional statistical tests, and thus the points attributed to the appropriateness of the statistical analysis were graded as being "positive" or at low risk of bias. The decision about whether the criteria were fulfilled was resolved by the discussion of two independent reviewers (AP and YA), and any disagreement was resolved by a decision with a third senior investigator (FC).

Quality of the Included Studies

The overall methodological quality of the studies was moderate. The overall risk of bias in the included studies is presented in Figure 1. This review included 78 RCTs, of which 70 were parallel designed, three were crossover

RCTs, and five were cluster RCTs. Among parallel-designed RCTs, 38 studies were evaluated as having an overall low risk of bias, 17 as posing some concerns, and the remaining 15 as having a high risk of bias.

Among crossover RCTs, two were judged as having an overall low risk of bias, and one as having a high risk. Finally, of the five cluster RCTs, three were evaluated as having an overall high risk of bias, while one was judged to have a low risk for bias and one RCT had serious concerns.

Data Extraction

The data from the eligible studies were independently extracted by two reviewers (AP and YA) using a standardized tabulated form containing the following columns: (1) name of the first author, (2) geographical context, (3) study aim, (4) duration of the intervention/follow-up, (5) type of the telehealth tool applied, (6) number and description of study arms, (7) description of the study population, (8) the number of patients according to the study group based on the randomization and completion of the study, (9) outcomes specifically for the intervention and the control group (the rate of AEs, hospitalization, re-admission, and similar), and (10) significance of the test reported or the comments on the observed results.

Data Synthesis and Analysis

A meta-analysis of sufficiently homogenous studies was conducted. Homogenous studies were defined as those that measured the same outcomes at the same follow-up point in both intervention and control groups and included the same patient population. Two groups of studies were identified, one group of studies assessed how telemonitoring affected mortality rates in patients with heart failure (n = 4), and the other group focused on patients who underwent insertion of an implant (n = 4). For the purposes of the meta-analysis, we extracted the total number of patients randomized to the intervention and the control group, and the number of deaths per study group, in order to pool the relative risks across the studies and estimate the overall effect sizes. We pooled the estimates by conducting a meta-analysis of the raw data with the *metabin* function included in the *meta* package[10] in R software (R studio Version 1.2.1335). We assessed the between-study heterogeneity with Cochrane's Q and I2 tests,[11] where I2 > 50% and $p < 0.05$ indicates significant heterogeneity. In case of significant heterogeneity between the studies, a random effect model was used, and *vice versa*.

Graphical Presentation

The risk of bias assessment in the included studies was visualized with a summary plot. As the number of crossover and cluster trials was substantially lower than the parallel trials (trial numbers 3 and 5, respectively), the evaluation of these trials was not included in the graphical presentation. The plot was generated by utilizing the *robvis* package.[12] Forest plots were generated by using the package *meta.* Both visualizations were carried out using the R studio (R studio Version 1.2.1335).

Ethical approval for this specific systematic review is not applicable since the data utilized were collected from previously published research in the literature. All studies included in this review received ethical approval prior to data collection by the study investigators. In addition, it was not necessary or required to involve patients or the public in the design, conduct, or reporting of our research.

Results: Included Studies

Theme I. Telemonitoring

A total of 38 studies assessed telemonitoring in various patient populations (Supplementary Table 3). Of the nine studies that assessed mortality rate of any cause in heart failure patients, three observed a statistically a significant difference in mortality rates between the study groups, in favor of the telehealth group.[13–15] Four studies reported 6-month mortality rates in both groups in this population, and all were evaluated as having low risk of bias. Since there was a significant heterogeneity (I^2 = 65%, p = 0.03) between these studies, we used a random-effects model. This meta-analysis demonstrated a non-significant pooled relative risk of mortality of 0.60 (95% confidence interval [CI]: 0.0999–3.5478), p = 0.42 (Fig. 2).

The definitions of outcomes related to hospitalization rates varied between the studies; thus, it was not possible to make straightforward comparisons between the studies. However, three of the nine studies observed that the telemonitoring patient groups experienced significantly

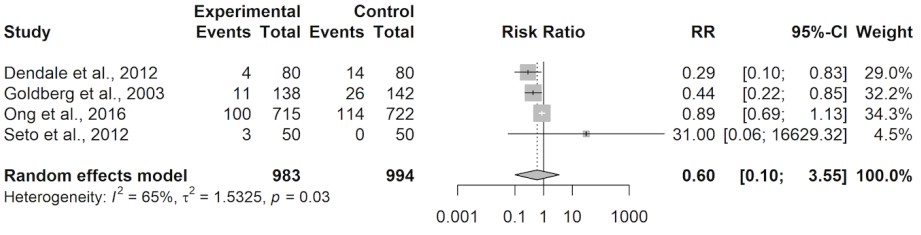

Fig. 2. Relative risks of mortality in patients with heart failure.

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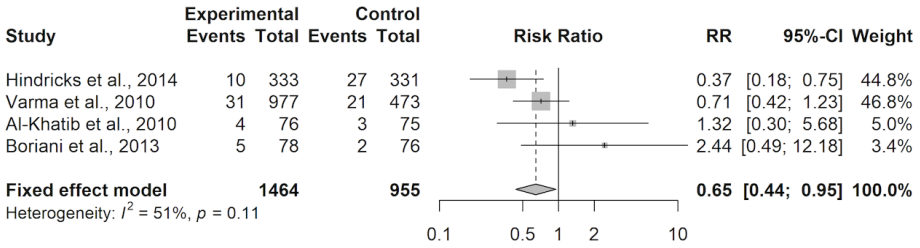

Fig. 3. Relative risks of mortality in patients with implants.

fewer hospital admissions as compared with the control groups.[14,16,17]

Eleven articles reported data from studies conducted on patients who had implants inserted (i.e., pacemakers, dual-chamber implantable cardioverter defibrillators or cardiac resynchronization therapy defibrillator implantation). The mortality data were reported by seven studies, and none of them reported a significant difference between the intervention and the control arms, except the study performed by Hindricks et al.,[18] who observed the control group had a significantly higher estimate of 1-year all-cause mortality. In this subgroup of studies, we identified four studies that were conducted in patients who received the insertion of implantable cardioverter defibrillators and cardiac resynchronization therapy defibrillators and reported 12-month mortality rates in both groups. All studies except one[18] were evaluated as having a low risk of bias. As the heterogeneity was not significant between the studies (I^2 = 50.5%, p = 0.108), we employed the fixed-effect model to carry out the meta-analysis. The pooled relative risk of mortality was significant—0.65 (95% CI: 0.4389–0.9541), p = 0.028 (Figure 3).

The hospitalization rates between the experimental and control arms were reported in four studies, and all studies confirmed the non-inferiority of the telehealth tool as compared with the usual care.

Studies that assessed the utilization of telehealth in patients without optimal blood pressure reported a variety of AEs that occurred during the study period; thus, it was not feasible to compare them. Only two studies reported deaths that occurred during the study period, without relating them to the study intervention.[19,20]

In patients with diabetes (n = 6), there were either no AEs during the study period[21,22] or equally distributed AEs between the study arms when remote monitoring was utilized.

Finally, only two of six studies found a statistically significant difference in the rate of AEs between the intervention and the usual care arm in favor of the telemonitoring group in a variety of patient populations.[21,23]

Theme II. Telerehabilitation

A total of 14 studies investigated the safety of telerehabilitation in different populations, and six of the studies included patients with heart failure (Appendix 1). The largest study was the only one that reported mortality and hospitalization rates during the telerehabilitation period without confirming a significant difference of AE rates when compared with the control group.[24] The rest of the studies either report no serious AEs during the study periods or no statistically significant difference in AEs between the study groups.

Among the studies conducted in cardiac risk patients (n = 3), there were no serious AEs that could be attributed to the use of telerehabilitation.[25,26]

Telerehabilitation investigated in a variety of patient populations (n = 6) resulted in either no AEs or injuries during the study period (in patients with gliomas or in patients with HIV) or in comparable rates between the study groups (in patients with a total knee arthroplasty, with post-stroke upper-limb impairment who underwent lumbar spinal surgery and in multiple sclerosis patients).

Theme III. Telehealth

Twenty-five studies investigated the safety of telehealth tools (e.g., without defining a specific domain within telehealth similar to the previous two categories) in the management of different patient populations (Appendix 2). Two studies revealed significantly lower mortality rates in the telehealth group compared with the control group (in patients with diabetes, chronic obstructive pulmonary disease (COPD), or heart failure and in older in-hospital patients with higher risks for hospital readmission). Studies done on telehealth and hospitalization rates mainly report no difference between the intervention and control (usual care) arm, except in a study conducted on patients with diabetes, COPD, or heart failure.[27] Data from studies that assessed the safety of cognitive behavior telehealth therapy indicate that telehealth tools are not likely to pose safety issues, as observed in patients with chronic fatigue syndrome. The studies either reported no AEs during the course of the study or a few events that could be associated with the intervention, however, without implying increased risks associated with online therapies or without confirming a significant difference between the groups.

Online psychotherapy services for people with depression also appear to be safe. There were no increased risks associated with their utilization as observed in a study conducted in people with depression[3] or in veterans diagnosed with a major depressive disorder.[28]

Finally, of the remaining 10 studies that assessed the safety of different telehealth tools, only one study[29] reported increased rates of AEs (defined as experience of intimate partner violence) when women who had undergone menstrual regulation used mHealth (a service sending automated interactive voice messages promoting contraceptive use).

Discussion

In summary, there are several key takeaway points from this study for the reader.

- Monitoring patients using telehealth techniques is associated with 40% lower mortality risks among patients suffering from heart failure compared to those who received traditional care.
- Patients who underwent telemonitoring had a lower mortality risk compared with the patients that underwent usual care.
- Among patients with heart implants, patients who received telemonitoring had a 35% lower mortality risk compared to patients receiving traditional care.
- Overall, telehealth was not shown to be associated with an increased number of adverse events when compared to traditional healthcare methods in RCTs in the literature.
- There remains an important need for more complementary studies with consistent outcome assessments.

Our systematic review of the literature found that telehealth is effective and can be considered safe for a wide variety of patient populations and interventions. We found 78 unique RCT studies reporting AEs when using a telehealth-related intervention. To the best of our knowledge, this is the first systematic review to investigate the relationship between telehealth and mortality rates specifically in the context of the COVID-19 pandemic. This is an important area of inquiry, given the rapid shift toward virtual care that occurred during the pandemic, and the potential implications of telehealth for patient outcomes. Our study includes both a quantitative and qualitative synthesis of the literature and provides and expands our understanding of the morbidity related to telehealth utilization. Most studies in the literature demonstrated comparable safety when it comes to telehealth usage in comparison to traditional healthcare provision. This stood true among all specialties in medicine, using a variety of telehealth techniques, including those designed for patient management purposes, rehabilitation, and counseling. Finally, in our pooled analysis, the results of the meta-analysis suggest that monitoring patients using telehealth techniques is associated with a 35% lower mortality risk in patients with cardiac implants as compared to those who received traditional care.

Telehealth applications aimed at managing different health conditions (e.g., COPD, diabetes, and cancer) either resulted in lower or comparable mortality rates when compared with conventional healthcare services. Moreover, this comparison also held true when looking at hospitalization and/or hospital readmission rates for patients with different chronic illnesses. Studies that investigated cognitive behavioral and online psychotherapy also confirmed that telehealth tools can be applied in treating a variety of patient conditions (chronic fatigue syndrome, depression, etc.), without posing safety risks. The only study that reported significantly higher AE rates in the intervention group, and is included in this systematic review, is the study that assessed the safety of a mHealth application that sent automated interactive voice messages promoting contraceptive use, where women who had undergone menstrual regulation using telehealth experienced more frequently intimate partner violence.[30] However, it should be noted that this type of telehealth tool is very specific and unique among included RCTs, and deserves further exploration for potentially confounding variables such as the social context and cultural backgrounds of the study's subjects.

Our findings are consistent with previous reviews conducted on this topic. For instance, Ekeland et al., conducted a review of systematic reviews over a decade ago showing that telehealth had similar or better outcomes for patients.[31] Similarly, other recent systematic reviews demonstrated the clinical effectiveness of telehealth continued to increase over the past decade.[32,33] Snoswell et al., conducted a systematic review of meta-analysis presented in the literature in 2020, and found that across five overarching medical disciplines (e.g., cardiovascular, neurology, pulmonary, obstetrics and intensive care), telehealth did not increase mortality rates.[34] It is important to note that previous studies examining the impact of telehealth on mortality rates have often focused on specific medical domains or conditions, such as cardiology, nephrology, or chronic obstructive pulmonary disease. In contrast, our study takes a broader view by examining the effects of telehealth tools that can be applied across a range of healthcare settings and disciplines, including telemonitoring and telerehabilitation. This approach allows us to identify common themes and trends across diverse patient populations, and to provide insights that may be relevant for a wider range of healthcare providers and policymakers.

Strengths and Lmitations

One of the strengths of our study is its comprehensive approach to identifying and synthesizing relevant research. We conducted a rigorous search of multiple databases, employed broad search criteria, and included all types of telehealth interventions to ensure the adequate

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breadth of our study. Since previous systematic reviews on the topic raised concerns that the quality of evidence was inconsistent and limited, we opted to include only well-designed RCT studies and conducted a thorough bias assessment using the revised RoB2tool to minimize our bias and provide a high level of quality evidence. Our findings thus provide a robust overview of the current state of knowledge on the topic and can inform clinical practice and policy decisions.

However, this study is not without limitations. First, inherent to the nature of systematic reviews, a methodological limitation is the rapid pace of technological change related to telehealth. Upon conducting analyses and publication, some of the technological methods included by the studies may be outdated or modified, making it hard to draw decisive conclusions. However, we attempted to minimize this limitation by including the most up-to-date published RCTs. Second, many telehealth study interventions had diffused aims and lacked sufficient and clear descriptions of the interventions. Further, the majority of studies included in the synthesis did not define safety as their primary aim, which resulted in many studies either excluding the definition of AEs, or mentioning them in a vague manner. Third, many of the studies endeavored to assess a complex set of activities or tools that sought to improve patient outcomes and these multi-component aspects may hinder an appropriate and direct evaluation of the intervention's outcomes. Fourth, in relation to the nature of the studies included in this review, the rather short duration of interventions may have contributed to a failure in detecting longer-term AEs. While all AEs were reported during the treatment periods, monitoring patients for a longer period following the treatment can provide needed insights into the long-term safety and effectiveness of telehealth compared to control treatments. Fifth, volunteer bias must be acknowledged as a selection bias. Participants in the studies, who were willing to enroll in RCTs and receive telehealth treatment, may be systematically different from the general population of patients. They first need to have the minimum technology, which might imply that they were in a better economic situation (which could impact the overall quality of health of an individual). Finally, the representativeness of our study sample to the larger population of interest is an important consideration, particularly given the diverse range of populations included in our systematic review, such as geographically and age-diverse populations. While we made efforts to include studies that represented a wide range of populations, we recognize that there may be limitations to the generalizability of our findings. In cases where race or ethnicity data were not collected, we made efforts to explain why this information was not available.

Besides the demonstrated clinical safety of telehealth utilization, the findings of this review provide important implications for public health policymakers. While this review synthesized robust evidence regarding the safety of telehealth, policymakers should also refer to other literature on this specific topic as well as telehealth satisfaction, economic benefits, and technical feasibility.[35–37] When examining telehealth's effectiveness and safety, it is often challenging to provide generalizable conclusions about the safety given the broad range and context of uses for telehealth. To overcome these challenges, this review synthesized the evidence in both a quantitative and qualitative manner, in order to offer a complete and up-to-date assessment of the literature. Additionally, we presented discipline-specific evidence regarding the safety of telehealth.

Overall, this systematic review shows that telehealth can be considered a safe alternative to traditional medical procedures. Given the trends in technological advances in the past decades, it is likely that healthcare reliance on telehealth will continue to grow. The findings can be utilized to guide policymakers and service evaluation, especially with the forced increased reliance on telehealth in the short- and long-term future. The healthcare industry, in collaboration with other sectors, must work to ensure digital inclusion, security and sustainability. Although the results of this systematic review are encouraging and point to the general safety of telehealth applications, our review also outlines a rich area for several key research questions including the need to evaluate the risks of different telehealth patient care interventions, utilizing longitudinal and adaptive study designs and with heterogeneous, diverse and large sample sizes to follow up with participants. A longitudinal study design will allow researchers and health practitioners to ensure that the treatment options do not yield long-term unforeseen concerns. Assessment of risks is essential. Finally, studies with an increased number of participants are encouraged for the results to be more generalizable.

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Conflict Statements

The authors have no conflict of interest to declare.

Contributors

All authors contributed to revising the work for important intellectual content, gave the final approval of the version to be published, and agreed on all aspects of the work, especially concerning its accuracy and integrity.

Further specific activities have been distributed as follows: F.C. conceived the research hypothesis. F.C. and W.R. designed the study. A.P., Y.A-A., and F.C. performed the articles screening. A.P., Y.A-A. and G.F. performed the data extraction. A.P., Y.A-A. and A.M. performed the quality assessment. A.P., Y.A-A., G.F., and A.M. accessed the raw data. F.C., O.A-T., P.B. shaped the manuscript with input from the entire team (written contributions of single paragraphs).

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Appendix 1. The characteristics and main findings of the studies that investigated the safety of telemonitoring/remote monitoring in various patient populations (group of studies classified as a major topic no 1)

1st Author / country	Intervention (telehealth tool) and control group	Duration/Follow-up of the study	Patient population (*N*)	Patients randomized (*n*)	Patients completed the study (*n*)	Adverse events in the intervention group	Adverse events in the control group	Main findings
Patients with heart failure								
Koehler et al., 2018 / Germany[1]	Remote monitoring vs. Usual care	Minimum 365 and maximum follow-up 393 days. In between, patient visits were scheduled at 3, 6, and 9 months.	Patients had HF, who were in New York Heart Association class II or III, had been admitted to hospital for HF within 12 months before randomization	Intervention group: 796 Control group: 775	Intervention group: 671 Control group: 673	The percentage of days lost due to unplanned CVD hospital admissions and all-cause death was 4·88% (95% CI: 4.55–5.23); the all-cause death rate was 7·86 (95% CI: 6.14–10.10) per 100 person-years of follow-up; all-cause mortality 61 (8%) and weighted average was 7·86 (6.14–10.10), CVD mortality 39 (5%) weighted average was 5.04 (3.68–6.90).	The percentage of days lost due to unplanned CVD hospital admissions and all-cause death was 6.64% (6.19–7.13); the all-cause death rate was 11·34 (9.21–13.95) per 100 person-years of follow-up; all-cause mortality 89 (12%) and weighted average was 11.34 (9.21–13.95), CVD mortality 59 (8%) and weighted average was 7.51 (5.82–9.70).	The percentage of days lost due to unplanned CVD hospital admissions and all-cause death was (ratio 0.80, 95% CI: 0.65–1.00; $p = 0.0460$); the all-cause death rate (hazard ratio [HR] 0.70, 95% CI: 0.50–0.96; $p = 0·0280$). All cause mortality 0.70± (0.50–0.96, $p = 0.0280$). CVD mortality was not significantly different between the two groups (HR 0.671, 95% CI: 0.45–1.01; $p = 0.0560$).
Ong et al., 2016 / USA[2]	Remote monitoring vs. Usual care	180 days	Older adults hospitalized with HF	Intervention group: 715 Control group: 722	Intervention group: 409 Control group: 415	180 day readmission *N* (%): 363 (50.8). Mortality *N* (%): 100 (14.0).	180 day readmission *N* (%): 355 (49.2). Mortality *N* (%): 114 (15.8).	The adjusted hazard ratio for 180-day readmission with the intervention is 1.03 (95% CI: 0.88–1.20; $p = 0.74$). The adjusted hazard ratio for 180-day mortality with the intervention is 0.85 (95% CI: 0.64–1.13; $p = 0.26$).

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Appendix 1. The characteristics and main findings of the studies that investigated the safety of telemonitoring/remote monitoring in various patient populations (group of studies classified as a major topic no 1)

1st Author / country	Intervention (telehealth tool) and control group	Duration/Follow-up of the study	Patient population (*N*)	Patients randomized (*n*)	Patients completed the study (*n*)	Adverse events in the intervention group	Adverse events in the control group	Main findings
Koehler et al., 2011 / Germany[3]	Remote monitoring vs. Usual care	The median follow-up was 26 months (minimum 12)	Stable chronic HF patients in New York Heart Association functional class II or III with a left ventricular ejection fraction ≤35%	Intervention group: 354 Control group: 356	Intervention group: 296 Control group: 297	Death from any cause 54 (15.25%), CVD death 40 (11.3%). Hospitalization for HF or death due to CVD cause—total no of events 153, no. of patients with event incidence per 100 patient-years at risk—87 (14.70); Any hospitalization—total number of events 486, no. of patients with event incidence per 100 patient-years at risk—192 (44.09) Hospitalization for any CVD cause total number of events 290, no. of patients with event incidence per 100 patient-years at risk—141 (27.79) Hospitalization for HF total number of events 113, no. of patients with event incidence per 100 patient-years at risk—64 (10.81)	Death from any cause 55 (15.45%), CVD death 46 (12.65%). Hospitalization for HF or death due to CVD cause—total no of events 160, no. of patients with event incidence per 100 patient-years at risk—95 (16.51); Any hospitalization—total number of events 394, no. of patients with event incidence per 100 patient-years at risk—179 (39.19) Hospitalization for any CVD cause total number of events 248, no. of patients with event incidence per 100 patient-years at risk—132 (26.05) Hospitalization for HF total number of events 114, no. of patients with event incidence per 100 patient-years at risk—74 (12.86)	Compared with usual care, remote monitoring had no significant effect on all-cause mortality (hazard ratio, 0.97; 95% confidence interval, 0.67 to 1.41; P0.87) or on CVD death or HF hospitalization (hazard ratio, 0.89; 95% confidence interval, 0.67 to 1.19; P0.44).

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Appendix 1. The characteristics and main findings of the studies that investigated the safety of telemonitoring/remote monitoring in various patient populations (group of studies classified as a major topic no 1)

1st Author / country	Intervention (telehealth tool) and control group	Duration/Follow-up of the study	Patient population (*N*)	Patients randomized (*n*)	Patients completed the study (*n*)	Adverse events in the intervention group	Adverse events in the control group	Main findings
Goldberg et al., 2003 / USA[4]	Telemonitoring (plus standard care) vs. Standard care	6 months	Patients hospitalized with New York Heart Association class III or IV HF, with a left ventricular ejection fraction < or =35%	Intervention group: 138 Control group: 142	Intervention group: NR specifically Control group: NR specifically	11 deaths (8%): sudden cardiac death 3, progressive HF 4, fatal myocardial infarction 0, arrhythmia 1, other vascular 1, non- CVD 1, cannot be determined 1. All rehospitalizations: 0.20 ± 0.30, CVD rehospitalizations 0.11 ± 0.26	26 deaths (18.4%): sudden cardiac death 6, progressive HF 8, fatal myocardial infarction 3, arrhythmia 2, other vascular 2, non—CVD 2, cannot be determined 2. All rehospitalizations: 0.19 ± 0.46, CVD rehospitalizations 0.08 ± 0.24	There was a 56.2% difference in mortality ($p < 0.003$). No differences in hospitalization rates were observed.
Dendale et al., 2012 / Belgium[5]	Telemonitoring vs. Usual care	6 months	Patients with chronic HF	Intervention group: 80 Control group: 80	Intervention group: not specified Control group: not specified	4 (5%) died. The number of HF—related readmissions/patient for HF 0.24 ± 0.51. The number of hospitalizations for all reasons was 0.80 ± 0.97.	14 (17.5%) died. The number of HF—related readmissions/patient for HF 0.24 ± 0.51. The number of hospitalizations for all reasons was 0.80 ± 0.97.	After 6 months of follow-up, all-cause mortality was significantly different between study groups: $p = 0.012$. The number of HF—related readmissions/patient for HF showed a trend of difference between study groups: $p = 0.056$. The number of hospitalizations for all reasons were not different between groups $p = 0.934$.
Frederix et al., 2018 / Belgium[6]	Telemonitoring vs. Usual care	6 months and 79 months	Patients with chronic HF	Intervention group: 80 Control group: 80	Intervention group: 80 were available for analysis (including mortality data) Control group: 80 were available for analysis (including mortality data)	57 (71%) deaths; the number of days lost due to HF readmissions—7.28 ± 12.55 days. The number of days lost due to all-cause readmissions—20.15 ± 21.99 days.	54 (68%) deaths; the number of days lost due to HF readmissions—11.81 ± 18.57 days. The number of days lost due to all-cause readmissions—25.75 ± 27.60 days.	Compared with usual care, the initial six-month telemonitoring programme had no significant effect on all-cause mortality (hazard ratio: 0.83; 95% confidence interval, 0.57 to 1.20; $p = 0.32$). The number of days lost due to HF readmissions was significantly lower in the TM group ($p = 0.04$).

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Appendix 1. The characteristics and main findings of the studies that investigated the safety of telemonitoring/remote monitoring in various patient populations (group of studies classified as a major topic no 1)

1st Author / country	Intervention (telehealth tool) and control group	Duration/Follow-up of the study	Patient population (*N*)	Patients randomized (*n*)	Patients completed the study (*n*)	Adverse events in the intervention group	Adverse events in the control group	Main findings
Seto et al., 2012 / Canada[7]	Telemonitoring vs. Usual care	6 months	Patients with HF	Intervention group: 50 Control group: 50	Intervention group: 44 Control group: 50	3 deaths (6%)	0 deaths	NA
Villani et al., 2014 / Italy[8]	Telemonitoring vs. Usual care	12 months	Patients with chronic HF	Intervention group: 40 Control group: 40	Intervention group: 40 Control group: 40	Major AEs: 5 deaths (12.5%), 12 hospitalizations, 17 composite end-point of mortality and hospitalizations. Minor Aes 41: unscheduled visits 35, emergency department visits (minor 6, serious 0).	Major Aes: 9 deaths (22.5%), 23 hospitalizations, 32 composite end-point of mortality and hospitalizations. Minor Aes 32: unscheduled visits 15, emergency department visits (minor 10, serious 7).	Deaths: no significant difference between the groups. Telemonitoring group: a significantly lower incidence of hospitalizations ($P < 0.03$), and a significant reduction in the composite end-point of mortality and hospitalizations ($P < 0.04$). Emergency Department admissions for worsening HF were more frequent in the Usual Care group ($P < 0.02$). In the Usual Care group, there was a lower incidence of minor adverse effects compared to the Integrated Management group ($P < 0.05$).
Spaeder et al., 2006 / USA[9]	TeleWatch—a telephone-based, automated, voice interactive, 2-way store and forward telemedicine system, to facilitate carvedilol titration in outpatients vs. Clinic only titration	3 months	Patients with New York Heart Association class II and III left ventricular systolic dysfunction	Intervention group: 25 Control group: 24	Intervention group: 23 Control group: 23	4 serious Aes	1 serious AE	None of the serious adverse events in the telemedicine group were deemed to be the result of the speed of the carvedilol titration.

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Appendix 1. The characteristics and main findings of the studies that investigated the safety of telemonitoring/remote monitoring in various patient populations (group of studies classified as a major topic no 1)

1st Author / country	Intervention (telehealth tool) and control group	Duration/Follow-up of the study	Patient population (*N*)	Patients randomized (*n*)	Patients completed the study (*n*)	Adverse events in the intervention group	Adverse events in the control group	Main findings
Patients with implants								
Crossley et al., 2011 / USA[10]	Remote monitoring vs. Standard in-office device follow-up	15 months	Patients who underwent insertion of an implantable cardioverter-defibrillator (ICD) (including cardiac resynchronization therapy devices (CRT-D)	Intervention group: 1014 Control group: 983	Intervention group: not specified Control group: not specified	NR	NR	Mortality rates between arms were compared using the log-rank test and were not significantly different for ICD patients ($P = 0.31$) or CRT-D patients ($P = 0.46$).
Varma et al., 2010 / USA[11]	Remote monitoring vs. Conventional care	3, 6, 9, 12, and 15 months after implantation of a cardioverter-defibrillator	Recipients of single- and dual-chamber ICDs with home monitoring implanted for class I/II indications who were not pacemaker dependent	Intervention group: 977 Control group: 473	Intervention group: 908 Control group: 431	10.4% Aes: death 31 (3.4%) at 12 months, stroke 3 (0.3%), surgical intervention 60 (6.6%)	10.4% Aes: death 21 (4.9%) at 12 months, stroke 5 (1.2%), surgical intervention 21 (4.9%)	No difference in safety was observed between the remote monitoring and conventional care groups.
Boriani et al., 2017 / Italy, France, Switzerland[12]	Remote monitoring (remote checks alternating with in-office follow-ups) vs. In-office follow-ups alone	The median follow-up was 24 months for both arms, with an interquartile range (IQR) of 15–25 months and 14–26 months in the Remote and Standard arm, respectively.	Patients with HF implanted with a biventricular defibrillator (CRT-D) with advanced diagnostics	Intervention group: 462 Control group: 455	Intervention group: 437 Control group: 428	55 Aes related to the implanted system	53 Aes related to the implanted system	No significant difference between groups. 2-year AE rates were 15.6 (95% CI: 11.9–20.3) and 15.2 (95% CI: 11.6–19.9) per 100 patients, respectively ($P = 0.92$) in the remote and standard arm, respectively.
Hindricks et al., 2014 / Australia, Europe, and Israel[13]	Remote monitoring vs. Standard care	12 months	Patients with chronic HF, NYHA class II-III symptoms, ejection fraction of no more than 35%, and a recent dual-chamber ICD or CRT-D implantation	Intervention group: 333 Control group: 331	Intervention group: 303 Control group: 279	63 had worsened composite score, 10 died (3%)	90 had worsened composite score, 27 died (8.15%)	The Kaplan-Meier estimate of 1-year all-cause mortality in the telemonitoring group was 3.4% vs. 8.7% in the control group (log-rank $P = 0.004$; HR 0.36, 95% CI: 0.17–0.74).

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Appendix 1. The characteristics and main findings of the studies that investigated the safety of telemonitoring/remote monitoring in various patient populations (group of studies classified as a major topic no 1)

1st Author / country	Intervention (telehealth tool) and control group	Duration/Follow-up of the study	Patient population (*N*)	Patients randomized (*n*)	Patients completed the study (*n*)	Adverse events in the intervention group	Adverse events in the control group	Main findings
Mabo et al., 2020 / France[14]	Remote monitoring vs. Standard care	The mean duration of follow-up was 18.3+3.3 months.	Patients with pacemakers	Intervention group: 269 Control group: 269	Intervention group: 248 Control group: 246	43 Aes: 18 deaths (6.7%)—3 HF and 15 from non-CVD causes; 29 hospitalizations of adverse CVD events; 1 hospitalization for complications related to the pacing system.	47 Aes: 13 deaths (4.83%)—4 from strokes and 9 from non-CVD reasons; 32 CVD hospitalizations; 7 hospitalizations for complications due to the pacing system.	Mortality—non significant difference (p = 0.37). Hospitalizations—non significant difference (p = 0.66).
Guédon-Moreau et al., 2013 / France[15]	Remote monitoring vs. Ambulatory follow-ups	24.2 months	Patients with ICDs	Intervention group: 239 Control group: 234	Intervention group: 211 Control group: 203	≥1 MAE—85 (40.3%) patients; The first or only MAE experienced by individual patients included 12 deaths (5.7%), 50 CVD (23.7%), 12 implant procedure-related (5.7%), and 11 device-related (5.2%) MAE	≥1 MAE—88 (43.3%) patients; The first or only MAE experienced by individual patients included 11 deaths (5.4%), 53 CVD (26.1%), 10 implant procedure-related (4.9%), and 14 device-related (6.9%) MAE in the control group.	HR 0.90; 95% CI: 0.67–1.21; P = 0.04 for non-inferiority
García-Fernández et al., 2019 / Spain[16]	Remote monitoring (home monitoring plus remote interrogations every 6 months) vs. home monitoring plus in-office evaluations every 6 months)	The mean duration of follow-up was 20.7 ± 7.1 months.	Patients with pacemakers and ICDs	Intervention group: 220 Control group: 225	Intervention group: 174 Control group: 186	≥1 major adverse cardiac event: 44 (20%); deaths 15 (6.8%), stroke 5 (2.2%). Hospitalizations due to cardiac implantable electronic devices or CVD reasons 53.	≥1 major adverse cardiac event: 44 (19.5%); deaths 15 (6.7%), stroke 4 (1.8%). Hospitalizations due to cardiac implantable electronic devices or CVD reasons 55.	P = 0.006 for non-inferiority

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Appendix 1. The characteristics and main findings of the studies that investigated the safety of telemonitoring/remote monitoring in various patient populations (group of studies classified as a major topic no 1)

1st Author / country	Intervention (telehealth tool) and control group	Duration/Follow-up of the study	Patient population (*N*)	Patients randomized (*n*)	Patients completed the study (*n*)	Adverse events in the intervention group	Adverse events in the control group	Main findings
Landolina et al., 2012 / Italy[17]	Remote monitoring vs. "Remote transmission off" (standard arm).	4, 8, 12, 16 months	HF patients with implantable cardiovert-er-defibrillators (ICDs) or an ICD for resyn-chronization therapy	Intervention group: 99 Control group: 101	Intervention group: 89 Control group: 87	7 deaths (7.07%) at 16 months For the assessment of the incidence rate of study endpoints, there were 127 person-years in the remote arm	8 deaths (7.92%) at 16 months For the assessment of the incidence rate of study endpoints, 126 person-years in the standard arm.	NR
Boriani et al., 2013 / France, Hungary, Israel, Italy, Spain, and Switzerland[18]	Remote monitoring vs. Control group (with standard follow-up with-out alerts)	12 months	Patients in sinus rhythm with de novo implanta-tion of CRT-D for systolic HF with NYHA class III/IV (and a left ventricular ejection fraction <35%	Intervention group: 78 Control group: 76	Intervention group: 67 Control group: 66	5 deaths (6.41%)—HF 3, complications after aortic surgery 1, chronic kidney disease 1 19 hospitalizations for various causes (related to 18 patients)	2 deaths (2.63%)—HF 1, stroke 1 22 hospitalizations (related to 16 patients)	The annual rate of all-cause hospitalizations per patient did not differ between the two groups ($p = 0.65$).
Al-Khatib et al., 2010 / USA[19]	Remote monitoring vs. Quarterly device interrogations in clinic	12 months (every 3 months)	Patients with ICDs	Intervention group: 76 Control group: 75	Intervention group: 69 Control group: 70	Deaths—4 (5%); Hospitalizations—23%	Deaths—3 (4%); Hospitalizations—24%	No significant differ-ence between groups.
López-Liria et al., 2019 / Norway[20]	Remote monitoring vs. Standard outpa-tient visits	12 months	Patients with pacemakers	Intervention group: 25 Control group: 25	Intervention group: 23 Control group: 23	8% of patients had at least one CVD AE, 28% had at least one hospitalization	4% of patients had at least one CVD AE, 32% had at least one hospitalization	CVD AE—no significant differ-ence $p = 0.39$. Hospitalization—no significant difference $p = 0.53$.
Patients with blood pressure problems								
McManus et al., 2018 / UK[21]	Telemonitoring combined with telemonitoring vs. Usual care	12 months	Hypertensive patients older than 35 years	Intervention group: 395 Control group: 394	Intervention group: 330 Control group: 350	11 CVD events (new atrial fibrillation, angina, myocardial infarction, coronary artery bypass graft or angioplasty, stroke, peripheral vascu-lar disease, or HF)	9 CVD events (new atrial fibrillation, angina, myocardial infarction, coronary artery bypass graft or angioplasty, stroke, peripheral vascular disease, or HF)	Reported potential side-effects (pain, stiffness, etc.) were similar between the groups. There was no difference in anxiety between any of the groups.

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1st Author / country	Intervention (telehealth tool) and control group	Duration/Follow-up of the study	Patient population (*N*)	Patients randomized (*n*)	Patients completed the study (*n*)	Adverse events in the intervention group	Adverse events in the control group	Main findings
McManus et al., 2010 / UK[22]	Telemonitoring (self-monitoring of BPand self-titration of antihypertensive drugs, combined with telemonitoring of home BP measurements) vs. Usual care	6 and 12 months	Patients who had BP more than 140/90 mm Hg despite antihypertensive treatment	Intervention group: 263 Control group: 264	Intervention group: 234 Control group: 246	Stiff joints 95 (41%), pain 89 (38%), fatigue 84 (36%), swelling of legs 74 (32%), sleep difficulties 72 (31%), dry mouth 68 (29%), feeling flushed 61 (26%), cough 61 (26%), breathlessness 53 (23%), sore eyes 48 (21%)	Stiff joints 104 (42%), pain 84 (34%), fatigue 78 (32%), swelling of legs 55 (22%), sleep difficulties 80 (33%), dry mouth 59 (24%), feeling flushed 57 (23%), cough 60 (24%), breathlessness 59 (24%), sore eyes 58 (24%)	Frequency of most side-effects did not differ between groups, apart from leg swelling (self-management, 74 patients [32%]; control, 55 patients [22%]; $p = 0.022$).
Green et al., 2008 / USA[23]	Remote monitoring (BPM-Web group—home BP monitoring and secure patient Website training only vs. BPM-Web-Pharm group—home BP monitoring and secure patient Web site training plus pharmacist care management delivered through Web communications) vs. Usual care	12 months	Participants aged 25 to 75 years with uncontrolled essential hypertension	Intervention group 1 (BPM-Web group): 259 Intervention group 2 (BPM-Web-Pharm group): 261 Control group: 258	Intervention group 1 (BPM-Web group): 246 Intervention group 2 (BPM-Web-Pharm group): 237 Control group: 237	BPM-Web group: 2 deaths from cancer-related complications, 4 non-fatal CVD events BPM-Web-Pharm group: 1 death from a cardiac arrest, 3 non-fatal CVD events	2 non-fatal CVD events	The investigators attributed none of the deaths, CVD events, or other hospitalizations to study participation.

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1st Author / country	Intervention (telehealth tool) and control group	Duration/Follow-up of the study	Patient population (*N*)	Patients randomized (*n*)	Patients completed the study (*n*)	Adverse events in the intervention group	Adverse events in the control group	Main findings
Margolis et al., 2013 / USA[24]	Telemonitoring vs. Usual care	12 months of intervention and 6 months of post intervention follow-up	Adults with uncontrolled BP	Intervention group: 228 Control group: 222	Intervention group: 194 Control group: 186	49 AEs—6 hypotension, dizziness, or loss of consciousness, 4 hypertension, 2 strokes, 1 atrial fibrillation, 1 angina	60 AEs—2 allergic reactions attributed to BP medicine, dizziness 1, hypertension 1, strokes 5, 3 transient ischemic attacks, 1 atrial fibrillation, 1 myocardial infarction, 2 cardiac bypass surgeries	NR
McKinstry et al., 2013 / UK[25]	Telemonitoring vs. Usual practice	6 months	People aged 29–95 years with uncontrolled BP	Intervention group: 200 Control group: 201	Intervention group: 195 Control group: 188	1 death, 3 patients became anxious due to self-monitoring	2 deaths	In total, 43 adverse events were recorded (included a variety of events, no difference between the study groups reported).
Kim et al., 2015 / Korea[26]	Remote monitoring and office follow-up vs. remote monitoring without physician office care using the remote monitoring device vs. Usual care with home BP monitoring	Every 8 weeks for 24 weeks	Hypertensive patients over 20 years of age	Intervention group 1 (RM and office follow up): 124 Intervention group 2 (RM without physician office care): 126 Control group: 124	Intervention group1 (RM and office follow up): 111 Intervention group 2 (remote monitoring without physician office care): 105 Control group: 115	At least 1 AE: 34/124 (intervention group 1) and 29/126 (intervention group 2)	At least 1 AE: 28/124	There were no differences in the number of adverse events among the three study groups. The nature of AEs included dizziness, chest pain, insomnia, etc.

Continued

Appendix 1. The characteristics and main findings of the studies that investigated the safety of telemonitoring/remote monitoring in various patient populations (group of studies classified as a major topic no 1)

1st Author / country	Intervention (telehealth tool) and control group	Duration/Follow-up of the study	Patient population (*N*)	Patients randomized (*n*)	Patients completed the study (*n*)	Adverse events in the intervention group	Adverse events in the control group	Main findings
Patients with diabetes								
Shea et al., 2009[27]	Home telemedicine unit vs. Usual care	5 years	Medicare recipients with T2DM, aged ≥ 55 years	Intervention group: 844 Control group: 821	Intervention group: not specified Control group: not specified *Note*: approximately 1,431–1,445 out of 1,665 subjects (or 86–87%) were included in all analyses	176 deaths	169 deaths	The mortality rate was similar between the groups. There were no serious adverse events related to the intervention.
Wild et al., 2016 / UK[28]	Telemonitoring vs. Usual care	9 months	People with poorly controlled T2DM	Intervention group: 160 Control group: 161	Intervention group: 146 Control group: 131	2 hypoglycaemic episodes, 1 hypotensive episode, 1 peripheral angioplasty, 1 myocardial infarction, 1 admission to hospital with HF, 1 cerebral infarction with hemorrhagic transformation	2 hypoglycaemic episodes, 1 abscess in the presence of uncontrolled glycaemia, 1 ischaemic stroke, 1 coronary angioplasty, 1 hospital admission with a urinary tract infection and hyperglycemia	There were few adverse events that could be attributed to T2DM or BP control and these were equally distributed between the intervention and control groups
Nicolucci et al., 2015 / Italy[29]	Telemonitoring vs. Usual practice	12 months	Patients with T2DM	Intervention group: 152 Control group: 149	Intervention group: 114 Control group: 135	None	None	No safety problems were detected during the study. In particular, no episode of severe hypoglycemia was recorded.

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Appendix 1. The characteristics and main findings of the studies that investigated the safety of telemonitoring/remote monitoring in various patient populations (group of studies classified as a major topic no 1)

1st Author / country	Intervention (telehealth tool) and control group	Duration/Follow-up of the study	Patient population (*N*)	Patients randomized (*n*)	Patients completed the study (*n*)	Adverse events in the intervention group	Adverse events in the control group	Main findings
Jeong et al., 2018 / Republic of Korea[30]	Telemonitoring vs. Telemedicine vs. Conventional care	24 weeks	Patients with T2DM	Intervention group (Telemonitoring): 113 Intervention group (Telemedicine): 112 Control group: 113	Intervention group (Telemonitoring): 99 Intervention group (Telemedicine): 99 Control group: 101	30 AEs (26.55%) in telemonitoring and 23 AEs (20.54%) in telemedicine; AEs related complications in T2DM: 7 (6.19%) in telemonitoring and 3 (2.68%) in telemedicine group: Serious AEs: one patient each with a malignant hepatic neoplasm and skin ulcer in the telemonitoring group; and one patient with hematuria in the telemedicine group	33 AEs (29.2%); AEs related with T2DM complications: 7 (6.19%); Serious AEs: one patient each with angina pectoris and rotator cuff syndrome in the control group	Not calculated.
Lee et al., 2020 / Malaysia[31]	Remote telemonitoring with team-based management vs. Usual care and blood glucose monitoring as required using a glucometer	52 weeks	Patients with T2DM	Intervention group: 120 Control group: 120	Intervention group: 104 Control group: 104	NR	NR	No adverse events or serious adverse events were reported during the intervention which were adjudicated to be study related.
Quinn et al., 2011 / USA[32]	Telemonitoring (3 arms) vs. Usual care	12 months	Patients with T2DM	Intervention groups: Group 1: 38 Group 2: 33 Group 3: 80 Control group: 62	Intervention groups: Group 1: 23 Group 2: 22 Group 3: 62 Control group: 56	One patient from one intervention group was hospitalized twice for reasons not reported to the study.	NR	Hypoglycemic events, hospitalizations, and emergency-room visits were infrequent in all groups. The Data and Safety Monitoring Board determined that there were no direct study-related adverse events found. No patients died during the 12 months of this study.

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Appendix 1. The characteristics and main findings of the studies that investigated the safety of telemonitoring/remote monitoring in various patient populations (group of studies classified as a major topic no 1)

1st Author / country	Intervention (telehealth tool) and control group	Duration/Follow-up of the study	Patient population (*N*)	Patients randomized (*n*)	Patients completed the study (*n*)	Adverse events in the intervention group	Adverse events in the control group	Main findings
Patients with various health conditions								
Ryan and O'Shea 2009 / Ireland[33]	Remote monitoring (Supervise patients self-testing) vs. Usual care (patients attended the anticoagulation management service at least every 4–6 weeks and were dosed by the anticoagulation pharmacist or physician)	6 months	Patients who were on warfarin therapy for at least 2 months	Intervention group: 132 Control group: 132	Cross-over trial	There were two serious thrombotic complications during the supervised patient self-testing management period (deep vein thrombosis).	There were two serious adverse events during the anticoagulation management service arm of the study (gastrointestinal bleed, transient ischemic attack)	NR
Pinnock et al., 2013 / UK (Scotland)[34]	Telemonitoring vs. Conventional self-monitoring	12 months	Adults with at least one admission for COPD in the year before randomization.	Intervention group: 128 Control group: 128	Intervention group: 105 Control group: 100	16 deaths	21 deaths	The number of deaths did not differ significantly between the telemonitoring and control groups (adjusted odds ratio 0.66 (95% confidence interval 0.29 to 1.48), $p = 0.31$).
Teot et al., 2020 / France[35]	Home wound care from a local clinician guided by an off-site wound care expert via telemedicine vs. Control group who received wound care either at home or at site by a wound care physician	6 months	Patients with complex wounds	Intervention group: 110 Control group: 110	Intervention group: 89 Control group: 94	3 deaths	10 deaths	There was no significant difference between the groups.

Continued

Appendix 1. The characteristics and main findings of the studies that investigated the safety of telemonitoring/remote monitoring in various patient populations (group of studies classified as a major topic no 1)

1st Author / country	Intervention (telehealth tool) and control group	Duration/Follow-up of the study	Patient population (*N*)	Patients randomized (*n*)	Patients completed the study (*n*)	Adverse events in the intervention group	Adverse events in the control group	Main findings
Lee et al., 2019 / Malaysia[36]	Telemedicine-based home management program vs. Standard provider-centered care model	30 and 90 days	Patients after liver transplantation	Intervention group: 51 Control group: 51	Intervention group: 50 Control group: 50	28% of readmissions after discharge, the complications included: GI issues 2, acute kidney injury 2, anemia 1, biliary 3, cardiac 0, dehydration 1, elevated liver function tests 0, fever/sepsis 1, hyperglycemia 1, pulmonary 0, seizures 0, wound 3	58% of readmissions after discharge, the complications included: GI issues 5, acute kidney injury 2, anemia 2, biliary 4, cardiac 1, dehydration 2, elevated liver function tests 1, fever/sepsis 3, hyperglycemia 4, pulmonary 1, seizures 1, wound 3	The intervention arm showed a lower rate of readmissions after discharge at 28% compared to 58% with control (P = 0.004).
Kim et al., 2020 / Republic of Korea and Canada[37]	Remote monitoring vs. Control (who also received the device for remote monitoring, but without behavioral intensification, telephone contacts, breakthrough visit calls, and prescription algorithm)	The first trial participant was enrolled on September 27, 2016 and the last participant completed the scheduled follow-up on December 7, 2017.	Ischemic stroke patients hospitalized in the three participating centers	Intervention group: 31 Control group: 29	Intervention group: 29 Control group: 28	4 (13%). Serious AEs: 3 (10%).	5 (17%). Serious AEs: 3 (10%).	No significant difference.

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Appendix 1. The characteristics and main findings of the studies that investigated the safety of telemonitoring/remote monitoring in various patient populations (group of studies classified as a major topic no 1)

1st Author / country	Intervention (telehealth tool) and control group	Duration/Follow-up of the study	Patient population (*N*)	Patients randomized (*n*)	Patients completed the study (*n*)	Adverse events in the intervention group	Adverse events in the control group	Main findings
Maiolo et al., 2003 / Italy[38]	Telemonitoring vs. Face to face medical visits	12 months	Patients on long-term oxygen therapy	Intervention group: 23 Control group: 30	NA—cross-over study; control phase was the 1st one, and the intervention the 2nd	Hospital admissions: COPD patients (n = 20) 1.23 (1.17), RD patients (n = 3) 0.00	Hospital admissions: COPD patients (n = 20) 2.15 (1.21), RD patients (n = 3) 1.33 (0.58)	The mean number of hospital admissions was significantly lower in the second phase of the study than in the first phase, for both COPD patients (mean difference 0.92, 95% CI: 0.26 to 1.58, P < 0.01) and RD patients (mean difference 1.33, 95% CI: 0.10 to 2.77, P < 0.05).

Abbreviations: AE, adverse event; BP, blood pressure; COPD, chronic obstructive pulmonary disease; CRT-D, cardiac resynchronization therapy devices; CVD, cardiovascular; HF, heart failure; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; MAE, major adverse event; NA, not applicable; NR, not reported; NYHA, New York Heart Association; RD, restrictive disease; T2DM, diabetes type 2.

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Appendix 2. The characteristics and main findings of the studies that investigated the safety of telerehabilitation in various patient populations (group of studies z as major topic no 2)

1st Author / country	Intervention (telehealth tool) and control group	Duration/ Follow-up of the study	Patient population (*N*)	Patients randomized (*n*)	Patients completed the study (*n*)	Adverse events in the intervention group	Adverse events in the control group	Main findings
Patients with heart failure								
Piotrowicz et al.,2020 / Poland[1]	Telerehabilitation vs. Usual care	9 weeks, 12 to 24 months of follow-up	Patients with heart failure up to 6 months after a cardiovascular hospitalization	Intervention group: 425 Control group: 425	Intervention group: 386 (425 with mortality data, 409 with hospitalization data) Control group: 395 (425 with mortality data, 409 with hospitalization data)	Two deaths occurred during the 9-week training period in the intervention arm, 1 of non—CVD causes and 1 because of a hemorrhagic stroke. Twenty-four months follow-up: all-cause mortality was 54 (12.7) 12.5%, CVD mortality was 36 (8.5) 8.3%, all-cause hospitalization was 232 (54.6) 58.1%, CVD hospitalization was 141 (33.2) 36.8%, HF hospitalization 104 (24.5) 26.8%.	Two patients died in the control arm during the 9-week observation period, 1 via sudden cardiac death and the other at home of an unknown cause. 24 months follow-up:: all-cause mortality was 52 (12.2) 12.4%, CVD mortality was 36 (8.5) 8.8%, all-cause hospitalization was 245 (57.6) 60.5%, CVD hospitalization was 161 (37.9) 40.7%, HF hospitalization 103 (24.2) 26.1%.	No significant value for adjusted hazard ratios.
Piotrowicz et al., 2010 / Poland[2]	Telerehabilitation vs. Outpatient-based standard cardiac rehabilitation	8 weeks	Patients with heart failure	Intervention group: 77 Control group: 75	Intervention group: 75 Control group: 56	Three episodes of paroxysmal atrial fibrillation, including one asymptomatic event diagnosed through electrocardiogram monitoring.	One episode of paroxysmal atrial fibrillation was noted. These arrhythmias were not related to intervention and occurred during routine daily activities.	NA
Piotrowiczet al.,2015 / Poland[3]	Telerehabilitation—home-based tele monitored nordic walking vs. Usual care	8 weeks	Patients with HF, including those with CVD implantable electronic devices	Intervention group: 77 Control group: 34	Intervention group: 75 Control group: 32	There were few minor events related to telerehabilitation, though 5.3% patients reported minor skin reactions due to the electrodes.	NR	Neither death nor other major events including the need for hospitalisation due to HF exacerbation occurred as a result of participating in the home-based tele monitored nordic walking training.

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Appendix 2. The characteristics and main findings of the studies that investigated the safety of telerehabilitation in various patient populations (group of studies z as major topic no 2)

1st Author / country	Intervention (telehealth tool) and control group	Duration/ Follow-up of the study	Patient population (*N*)	Patients randomized (*n*)	Patients completed the study (*n*)	Adverse events in the intervention group	Adverse events in the control group	Main findings
Peng et al., 2018 / China[4]	Telerehabilitation vs. Usual care	8 weeks duration, 2 and 6 months after discharge follow up	Patients with HF	Intervention group: 49 Control group: 49	Intervention group: 42 Control group: 41	None	None	No patients experienced any significant complications or adverse outcomes during the program.
Hwang et al., 2017 / Australia[5]	Telerehabilitation vs. Traditional hospital outpatient-based program of the same duration and frequency	12 weeks intervention and after 12 weeks a follow up	Patients with stable chronic HF (including HF with reduced or preserved ejection fraction)	Intervention group: 24 Control group: 29	Intervention group: 23 Control group: 26	6 AEs: angina x 3, diaphoresis x 1, palpitations x 2	2 AEs (diaphoresis)	No significant difference was found in the number of AEs between the two groups.
Cardiac risk patients								
Skobel et al., 2016 / Great Britain, Spain, Germany[6]	Telerehabilitation vs. Cardiac rehabilitation delivered by conventional means	6 months	Patients with presence of coronary arterial disease after acute myocardial infarction or elective coronary intervention, EF ≥30 %,	Intervention group: 55 Control group: 63	Intervention group: 12 Control group: 42	6 AEs (31%). More specifically, 2 patients complained of chest pain based on chest infection after coronary artery bypass grafting, 2 patients were admitted to hospital with consecutive angiography due to new onset of angina pectoris which was not related to training and 2 patients contacted the study center because of chest pain before training and were sent to hospital for further investigation resulting in coronary artery bypass grafting because of progression of disease.	3 AEs (8%). Reasons for AEs were new onset of atrial fibrillation (n = 1), new angina at rest (n = 1), which resulted in angiography without intervention and pseudo-aneurysm of the right femoral arteries after percutaneous coronary intervention (n = 1) with surgery intervention.	However, there was no complication directly associated with cardiac rehabilitation.

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Appendix 2. The characteristics and main findings of the studies that investigated the safety of telerehabilitation in various patient populations (group of studies z as major topic no 2)

1st Author / country	Intervention (telehealth tool) and control group	Duration/ Follow-up of the study	Patient population (*N*)	Patients randomized (*n*)	Patients completed the study (*n*)	Adverse events in the intervention group	Adverse events in the control group	Main findings
Kraal et al., 2017 / The Netherlands[7]	Telerehabilitation vs. home-based training with center-based training	3 months intervention duration, assessments done at 2, 6 and 12 months follow up	Low-to-moderate cardiac risk patients entering cardiac rehabilitation	Intervention group: 45 Control group: 45	Intervention group: 41 Control group: 37	None	None	No serious AEs were recorded during center-based and home-based training.
Batalik et al., 2020[8]	Telerehabilitation vs. Regular outpatient training group	12 weeks	Cardiac rehabilitation patients	Intervention group: 28 Control group: 28	Intervention group: 25 Control group: 26	1 patient was admitted to the hospital due to cardiac symptoms during the 12-week intervention. After a short observation in the university hospital , he was released without any required medical treatment.	1 patient was admitted to the hospital due to cardiac symptoms during the 12-week intervention. After a short observation in the university hospital, he was released without any required medical treatment.	No serious AEs were recorded.
Patients with various health conditions								
Moffet et al., 2015 / Canada[9]	Telerehabilitation vs. Face-to-face home visit approach (standard care)	2 and 4 months	Patients who had a total knee arthroplasty	Intervention group: 100 Control group: 98	Intervention group: 98 Control group: 84	14 (13%) patients with AEs, 12 patients (12%) with serious AEs	16 (16%) patients with AEs, 9 (9%) patients with serious AEs	Not calculated. AEs involved pain, bruising, swelling and similar, while serious AEs were defined as death, hospitalization and other events.
Hou et al., 2019 / China[10]	Telerehabilitation vs. Usual care treatment	3, 6, 12, and 24 months	Patients who underwent lumbar spinal surgery	Intervention group: 84 Control group: 84	Intervention group: 60 Control group: 61	9 AEs, mostly mild, self-limited joint and back pain	6 AEs, mostly mild, self-limited joint and back pain	The rate of AEs did not differ significantly in frequency or severity of AEs in these 2 groups.

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Appendix 2. The characteristics and main findings of the studies that investigated the safety of telerehabilitation in various patient populations (group of studies z as major topic no 2)

1st Author / country	Intervention (telehealth tool) and control group	Duration/ Follow-up of the study	Patient population (*N*)	Patients randomized (*n*)	Patients completed the study (*n*)	Adverse events in the intervention group	Adverse events in the control group	Main findings
Lo et al., 2010 / [11]	Telerehabilitation (robot-assisted) vs. Intensive comparison therapy vs. Usual care	6, 12, 24 weeks and 36 weeks	Patients with moderate-to-severe upper-limb impairment 6 months or more after a stroke	Intervention group 1 (robot assisted): 49 Intervention group 2 (intensive comparison): 50 Control group: 28	Intervention group 1 (robot assisted): 47 Intervention group 2 (intensive comparison): 46 Control group: 27	AEs: therapy related AEs: robot group—12 (24%). intensive comparison: 9 (18%). Serious AEs: related to study therapy 0 in both groups. Robot group—any serious AE 11 (22%), death 0, hospitalization 19 (39%); intensive comparator—any serious AE 18 (36%), death 2 (4%), hospitalization 20 (40%)	Therapy related AEs: 0. Serious AEs: death 1 (4%), hospitalization 15 (54%), related to study therapy 0	NR
Paul et al., 2019 / UK[12]	Web-based physiotherapy—individualized, home exercise program vs. Active comparator (printed sheet of exercises, completing a paper-based exercise diary)	0, 3, 6 and 9 months	People with multiple sclerosis	Intervention group: 45 Control group: 45	Intervention group: 36 Control group: 36	27 AEs	33 AEs	NR. 42 of AEs were falls. Two participants had skin reactions due to the Tegaderm. None of the AEs were deemed to be related to the intervention.
Gehring et al., 2019 / The Netherlands[13]	Telerehabilitation vs. waiting-list control group	6 months	Patients with stable grade II and III gliomas.	Intervention group: 23 Control group: 11	Intervention group: 19 Control group: 9	NR	NR	No exercise-induced injuries, although one patient reported aggravation of pre-existing osteoarthritis-related knee pain at the sixth month of the exercise program.
Piraux et al., 2019 / Belgium[14]	Telerehabilitation vs. Control (patients without physical activity)	6 weeks	People living with HIV	Intervention group: 13 Control group: 12	Intervention group: 9 Control group: 8	NR	NR	No AEs related to the intervention recorded.

Abbreviations: AE, adverse event; HF, heart failure; CVD cardiovascular, NR, not reported; NYHA, New York Heart Association.

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Appendix 3. The characteristics and main findings of the studies that investigated the safety of various telehealth tools in various patient populations (group of studies classified as minor topics)

1st Author / Country	Intervention (telehealth tool) and control group	Duration / Follow-up of the study	Patient population (*N*)	Patients randomized (*n*)	Patients completed the study (*n*)	Adverse events in the intervention group	Adverse events in the control group	Main findings
Telehealth in patient management								
Steventon et al., 2012 / England[1]	Telehealth—screening/diagnosis and management vs. Usual care (range of services available in the trial sites, excluding telehealth)	12 months	People with diabetes, COPD, or heart failure	Intervention group: 1605 Control group: 1625	Intervention group: 1570 Control group: 1584	Death—4.6%. Hospitalization—42.9%.	Death—8.3. Hospitalization—48.2%.	Mortality—unadjusted odds ratio 0.54, 95% confidence interval 0.39 to 0.75, $P < 0.001$. Hospitalization—unadjusted odds ratio of 0.82 (95% confidence interval 0.70 to 0.97, $P = 0.017$).
Hiraniet al., 2013 / UK[2]	Telehealth management (general and disease specific health education, with non-immediate review by specialist nurses and other care providers) vs. Usual care (existing healthcare and social services, in line with local protocols	12 months	Patients with COPD, T2DM, or HF	Intervention group: 845 Control group: 728	Intervention group: 431 Control group: 328	No AEs or side effects related to any of the telehealth devices were reported in the intervention group throughout the trial.	NR	No AEs or side effects related to any of the telehealth devices were reported in the intervention group throughout the trial.
Salisbury et al., 2016[3]	Healthlines service / Telemonitoring and management (in addition to usual care) vs. Usual care alone	6 and 12 months	641 adults aged 40 to 74 years with a 10 year CVD disease risk of 20% or more	Intervention group: 325 Control group: 316	Intervention group: 295 Control group: 291	38 AEs: 22 serious and unexpected events. Only one serious event in the intervention arm was likely to be related: a participant was admitted to hospital with low blood pressure, which could have been due to antihypertensive drugs not being reduced after weight loss.	38 AEs: 24 serious and unexpected events	The rates of AEs were similar between groups.
Absolom et al., 2021 / UK[4]	Telehealth management—eRAPID (weekly online symptom reporting) with usual care vs. Usual care alone	6, 12 and 18 weeks	Patients with colorectal, breast, or gynecological cancers commencing chemotherapy	Intervention group: 256 Control group: 252	Intervention group: 181 Control group: 199	Total number of admissions—133. Number of patients who had an admission—86/256 (33.6). Number of patients with suspected sepsis—59/86 (68.8%)	Total number of admissions—121. Number of patients who had an admission—84/252 (33.3). Number of patients with suspected sepsis—44/84 (52.4%)	There was no significant difference between the groups in the total number of admissions (IRR = 1.14 95% CI 0.84 to 1.53), $p = 0.4003$.

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Appendix 3. The characteristics and main findings of the studies that investigated the safety of various telehealth tools in various patient populations (group of studies classified as minor topics)

1st Author / Country	Intervention (telehealth tool) and control group	Duration / Follow-up of the study	Patient population (*N*)	Patients randomized (*n*)	Patients completed the study (*n*)	Adverse events in the intervention group	Adverse events in the control group	Main findings
Cho et al., 2017 / Korea[5]	E-health—Internet-based integrated healthcare system for diabetes management and safety vs. Usual outpatient management	6 months	Patients with type 2 diabetes for more than 1 year	Intervention group: 244 Control group: 240	Intervention group: not specified Control group: not specified	17 AEs	15 AEs	There was no side effect associated with the intervention system and no significance between groups (p = 0.5127).
Vesterbyet al., 2017 / Denmark[6]	Telehealth support/ Telemonitoring and management—educational and video conferencing consultations vs. Standard fast-track plan	1 year after surgery	Patients who were planned to undergo first-time elective total hip replacement	Intervention group: 36 Control group: 37	Intervention group: 36 Control group: 36	1 telehealth patient with fever was admitted but no deep infection was found, and the patient was discharged with antibiotics after 3 days of observation.	No of re-admissions: 0	Mean re-admission events were similar in the 2 groups.
Jakobsen et al., 2015 / Denmark[7]	Home-based telehealth hospitalization vs. Standard treatment and care at the hospital	30, 90, and 180 days after discharge	Patients with severe COPD	Intervention group: 29 Control group: 28	Intervention group: 19 Control group: 21	3 deaths; readmission rates within 180 days 1.08 (0.39—1.77).	4 deaths; readmission rates within 180 days 2.39 (0.37—4.41).	Cox regression showed no significant difference between the readmission rates (hazard ratio = 2.01; 95% confidence interval, 0.71–5.71).
Kashem et al., 2006 / USA[8]	Telehealth management (Internet-based store-and-retrieval telehealth system) vs. Usual care	8 months	36 patients with HF with NYHA class 2 to 4 with hospitalization within past 6 months	Intervention group: 18 Control group: 18	Intervention group: 18 Control group: 18	NR	NR	The control group had a significantly higher number of hospitalizations and a significantly higher number of total hospital days compared to the telehealth group.
Jerant et al., 2001 / USA[9]	Telehealth management / Home telecare (home telecare delivered via a 2-way video-conference device with an integrated electronic stethoscope) vs. nurse telephone calls vs. Usual outpatient care	12 months	Patients 40 years of age and older with a primary hospital admission diagnosis of CHF	Home telecare nursing group: 13 Telephone home nursing group 12 Control group: 12	Home telecare nursing group: 13 Telephone home nursing group 11 Control group: 12	None reported.	None reported.	Two subjects, both randomized to the telephone group (which is not classified into telehealth in this SR), died during the study.

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Appendix 3. The characteristics and main findings of the studies that investigated the safety of various telehealth tools in various patient populations (group of studies classified as minor topics)

1st Author / Country	Intervention (telehealth tool) and control group	Duration / Follow-up of the study	Patient population (*N*)	Patients randomized (*n*)	Patients completed the study (*n*)	Adverse events in the intervention group	Adverse events in the control group	Main findings
Liang et al., 2021 / Taiwan[10]	Tele-homecare (after discharge) vs. Usual home care	3 and 6 months	Inpatients, older than 65 years, with high risk for readmission with a length of stay, acuity of admission, comorbidity, and visits to emergency department index of ≥7	Intervention group: 100 Control group: 100	Intervention group: 91 Control group: 76	The 6 month readmission rate—44%. Emergency department visits—12%. Death—8%.	The 6 month readmission rate—41%. Emergency department visits—26%. Death—19%.	The readmission rate—the difference was not significant (OR = 1.131, 95% CI = 0.645–1.981, *P* = 0.668). Emergency department visits—the difference was significant (OR = 0.388, 95% CI = 0.183–0.822, *P* = 0.013). Death—the difference was significant (OR = 0.371, 95% confidence interval [CI] = 0.154–0.892, *P* = 0.027).
Telehealth in cognitive behavior therapy								
Janse et al., 2018 / The Netherlands[11]	Internet-based cognitive behavioral treatment with protocol-driven therapist feedback vs. Internet-based cognitive behavioral treatment with therapist feedback on demand vs. Waiting list control	6 months	Patients with chronic fatigue syndrome	Intervention group 1 (with protocol-driven therapist feedback): 80 Intervention group 2 (with therapist feedback on demand): 80 Control group: 80	Intervention group 1 (with protocol-driven therapist feedback): 79 Intervention group 2 (with therapist feedback on demand): 79 Control group: 76	4 of 38 (11%) patients in the protocol-driven condition indicated AEs, 7 of 39 (18%) in the on-demand condition reported AEs. Patient-reported intervention side effects: Protocol-driven feedback group 3/37 (8.1%), Feedback on demand group 3/38 (7.9%)	12 of 46 (26%) indicated AEs	There were no significant differences for the three conditions in the proportion of patients reporting an exacerbation of symptoms and/or functional impairments.
Nijhof et al., 2012 / The Netherlands[12]	Internet-based cognitive behavioral treatment vs. Usual care	6 months	Adolescents aged 12–18 years with chronic fatigue syndrome	Intervention group: 68 Control group: 67	Intervention group: 67 Control group: 64	None	None	No serious AEs were reported.

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Appendix 3. The characteristics and main findings of the studies that investigated the safety of various telehealth tools in various patient populations (group of studies classified as minor topics)

1st Author / Country	Intervention (telehealth tool) and control group	Duration / Follow-up of the study	Patient population (*N*)	Patients randomized (*n*)	Patients completed the study (*n*)	Adverse events in the intervention group	Adverse events in the control group	Main findings
Andersson et al., 2012 / Sweden[13]	Online cognitive behavior therapy vs. Online non-directive supportive therapy	10 weeks, follow-up was post-treatment	Patients with OCD	Intervention group: 50 Control group: 51	Intervention group: 48 Control group: 51	At post-treatment, two participants in the intervention group reported AEs that could be associated with the treatment. One participant immediately stopped the treatment due to increased OCD symptoms and left the study. Another participant reported increased sleep disturbances, but these symptoms diminished after 5 weeks. At follow-up, one participant reported increased depressive symptoms a few weeks after the treatment ended: these symptoms were still prominent and impairing 4 months after receiving the intervention.	NR	NR
Anderson et al., 2020 / UK[14]	Internet-delivered therapy using video conferencing vs. A standard behavioral treatment offered within the specialist service and recommended by the National Institute for Health and Care Excellence (delivered via Skype)	12 months	Adolescents with CFS/ME	Intervention group: 44 Control group: 45	Intervention group: 39 Control group: 36	Only 1 AE was assessed as possibly related to the trial treatment, where a family felt that some CFS/ME symptoms worsened when following treatment recommendations. The family took a break from treatment and then returned to it.	NA	No serious AEs were reported by the 89 participants referred during the pilot phase of the trial.

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Appendix 3. The characteristics and main findings of the studies that investigated the safety of various telehealth tools in various patient populations (group of studies classified as minor topics)

1st Author / Country	Intervention (telehealth tool) and control group	Duration / Follow-up of the study	Patient population (*N*)	Patients randomized (*n*)	Patients completed the study (*n*)	Adverse events in the intervention group	Adverse events in the control group	Main findings
Telehealth in depression treatment								
Salisbury et al., 2016[15]	Healthlines Depression Service vs. Usual care.	4, 8 and 12 months	Patients with a confirmed diagnosis of depression	Intervention group: 307 Control group: 302	Intervention group: 255 Control group: 270	34 AEs—one was related to the intervention (increased anxiety from talking about depression) and was not serious	36 AEs—two patients died (one due to COPD and one due to throat cancer), both in the usual care group	Not calculated, but the rates of AEs were similar.
Egede et al., 2015 / USA[16]	Psychotherapy for depression via telehealth (video-conferencing) vs. Behavioral activation for depression in the same room	8 sessions	Veterans (aged ≥58 years) meeting criteria for major depressive disorder	Intervention group: 120 Control group: 121	Intervention group: 100 Control group: 104	None	None	No AEs were noted for any participant in the study.
Telehealthfor other illnesses/purposes								
Bohm et al., 2016 / Germany[17]	Fluid status telehealth alerts vs. Standard care (no alerts)	6, 12, 18 months	Patients recently implanted with an ICD with or without cardiac resynchronization therapy	Intervention group: 505 Control group: 497	Intervention group: 383 Control group: 369	59 deaths	63 deaths	All-cause death incidents at (18, 24) months were (6.3%, 11.0%) and (8.5%, 15.7%) respectively (HR, 0.89; 95% CI, 0.62–1.28; P = 0.52).
Reiss et al., 2019 / Bangladesh[18]	mHealth—automated interactive voice messages promoting contraceptive use vs. Control group (no voice messages)	4 months duration, follow up was 2 weeks and 4 months after the intervention	Women in Bangladesh who had undergone menstrual regulation (MR), a procedure to "regulate the menstrual cycle when menstruation is absent for a short duration.	Intervention group: 485 Control group: 484	Intervention group: 389 Control group: 383	43 AEs (defined as experience of intimate partner violence)	25 AEs (defined as experience of intimate partner violence)	The rate of AEs was higher in the intervention group: (aOR = 1.97; 95% CI = 1.12 to 3.46; *P* = 0.03) when measured using a closed question naming acts of violence.
Smith et al., 2015 / Cambodia[19]	m-Health (mobile phone-based intervention, which comprised six automated, interactive voice messages with counsellor phone support, as required) vs. Standard care	4 and 12 months after an abortion	Women seeking abortion	Intervention group: 249 Control group: 251	Intervention group: 169 Control group: 159	None	None	The intervention had no significant effect on the repeat pregnancy or abortion rate and there were no reports of adverse effects.

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Appendix 3. The characteristics and main findings of the studies that investigated the safety of various telehealth tools in various patient populations (group of studies classified as minor topics)

1st Author / Country	Intervention (telehealth tool) and control group	Duration / Follow-up of the study	Patient population (*N*)	Patients randomized (*n*)	Patients completed the study (*n*)	Adverse events in the intervention group	Adverse events in the control group	Main findings
Ellison et al., 2007 / USA[20]	Robotic Telerounding vs. Traditional bedside rounds		Adults undergoing a urologic procedure requiring a hospital stay of 24 to 72 hours	Intervention group: 134 Control group: 136	Intervention group: 134 Control group: 136	Postoperative patient morbidity: 18 (16.7%)	Postoperative patient morbidity: 18 (15.9%)	Morbidity rates were similar between the study arms (P = 0.64).
Schaub et al., 2015 / Switzerland[21]	Online self-help intervention with chat vs. Without chat vs. Waiting list control	3 months	Occasional marijuana users	Intervention group 1 (with chat): 114 Intervention group 2 (without chat): 101 Control group: 93	Intervention group 1 (with chat): 38 Intervention group 2 (without chat): 41 Control group: 38	None	None	None of the patients had to be treated as an emergency case or had to be referred to an inpatient treatment service. None of the involved counselors or researchers are aware of any adverse or serious adverse event related to this study that was reported by other addiction counseling services.
Meyer et al., 2009 / USA[22]	Tele-consultation vs. Telephone consultation	90 days	Participants with acute stroke symptoms	Intervention group: 110 Control group: 111	Intervention group: 104 Control group: 103	Mortality—19%	Mortality—13%	There was no mortality difference (OR 1.6; 95% CI: 0.8–3.4; p = 0.2690).
Demaerschalk et al., 2010 / USA[23]	Tele consultation vs. Telephone consultations	90 days	Patients with symptoms and signs consistent with an acute stroke syndrome	Intervention group: 27 Control group: 27	Intervention group: 22 Control group: 24	4% death, 4% intracerebral hemorrhage	11% death, 0% intracerebral hemorrhage	NR

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Appendix 3. The characteristics and main findings of the studies that investigated the safety of various telehealth tools in various patient populations (group of studies classified as minor topics)

1st Author / Country	Intervention (telehealth tool) and control group	Duration / Follow-up of the study	Patient population (*N*)	Patients randomized (*n*)	Patients completed the study (*n*)	Adverse events in the intervention group	Adverse events in the control group	Main findings
Paul et al., 2014 / UK[24]	Web-based physiotherapy vs. Usual care	12 weeks	Community dwelling adults moderately affected by multiple sclerosis (Expanded Disability Status Scale 5–6.5).	Intervention group: 15 Control group: 15	Intervention group: 15 Control group: 14	NR	NR	During the intervention there were three AEs (fractured elbow, hospital admission due to infection, breast cancer diagnosis). All were deemed to be unrelated to the intervention.
Sekimoto et al., 2019 / Japan[25]	Telehealth period check ups (regular visits every two months with intermediate video calls via an iPad mini) vs. Control period (regular visits every two months)	6 months	10 patients diagnosed with Parkinson's disease according to the British Brain Bank criteria, aged 20–75 years	Intervention group: 10 Control group: 10 Note: cross-over trial	Intervention group: 10 Control group: 10	NR	NR	There were no AEs or side effects.

Abbreviations: AE, adverse event; HF, heart failure; MAE, major adverse event; CVD, cardiovascular, NR, not reported; ICD, implantable cardioverter-defibrillator; COPD, chronic obstructive pulmonary disease; T2DM, diabetes type 2; NYHA, New York Heart Association; IRR, incidence risk ratio; OR, odds ratio; OCD, obsessive–compulsive disorder; CFS/ME, chronic fatigue syndrome/myalgic encephalomyelitis.

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