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Research paper

A multicenter randomized clinical trial to evaluate the efficacy of telemonitoring in patients with advanced heart and lung chronic failure. Study protocol for the ATLAN_TIC project

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ABSTRACT

Background: Using technologies of information and communication (TICs) is emerging in medical assistance. TICs application for medical assistance is promising. Its applicability in advanced heart and/or respiratory failure is still controversial because studies have shown methodological weakness which could put in danger their conclusions. Our objective is to evaluate efficacy of the application of home monitoring biological parameters in a multi-level model of coordinated clinical care for patients with chronic diseases with advanced heart (HF) and/or respiratory failure (RF) in comparison with conventional clinical care.

Method: /Design: Multicentric, phase III, randomized, parallel groups, controlled clinical trial. Patients with advanced HF and/or RF were eligible to participate. Patients received medical assistance by a multi-level model of coordinated clinical care with or without home monitoring. Follow up was performed until 180 days after inclusion. Primary efficacy outcome was defined as the percentage of patients with hospitalization/emergency room visits. Secondary efficacy outcomes were hospital admissions, admissions to hospital emergencies and Primary Care Emergencies, number of days of hospital stay, total cost per patient in euros, mortality, change in functional status, quality of life, assistance and technology devices. Intention to treat, as well as per protocol, and incremental cost-effectiveness analysis will be performed. The number of recruits patients per arm is set at 255, a total of 510 patients.

Discussion: This trial could provide some knowledge about the real impact of home monitoring for patients with advanced HF and/or RF within a multi-level model of integrated care.

1. Background

The development of computers and technologies of information and communication (TICs) has notably revolutionized clinical practice in the last years. Mobile telephone systems and professional corporate networks have been developed allowing better intercommunication among professionals and patients [1]; and encrypted image transfer systems have allowed rapid access to diagnostic techniques such as dermatology, radiology and pathology [2,3].

Home monitoring is a non-invasive way of remote patient monitoring, that has gained attention as a promising strategy to improve care of chronic diseases. Home monitoring involves the use of electronic

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devices and TICs for the digital transmission of physiological and other disease related data from the patient's home to health care center providing care and clinical feedback. Its use has already demonstrated positive results in chronic diseases such as hypertension [4] and diabetes mellitus [5] in young patients who cannot assist with their conventional revisions due to work issues and in patients with chronic diseases in remote areas where access to health services is difficult [6].

Regarding home telemonitoring of patients with chronic organ failures, results have been more controversial. Telehealth technology, including mobile health and remote patient monitoring technologies, potentially provides more cost-effective solutions to the problems of financial viability and home visit acceptability by totally or partially substituting in-person interactions. However, its effectiveness until now has been ambiguous. In the last 20 years, there has been a progressive increase in the development of studies evaluating home-monitoring effect in chronic diseases, mainly in heart failure (HF), and to a lesser extent in chronic obstructive pulmonary disease (COPD) and asthma [7]. There are more than 200 studies and 58 reviews/meta-analyses in HF and they have shown a reduction in mortality and in the number of hospitalizations, but with low-moderate evidence, which concludes that further studies are still necessary [8]. There are around 70 studies in COPD and asthma with 12 reviews in which there seems to be an improvement in the quality of life and a reduction in the number of hospitalizations, all of them with a low level of evidence concluding that more studies are also still needed [9,10]. Moreover, some of these studies and reviews have shown methodological weaknesses which could put in danger their conclusions [11].

Therefore, with the current scientific data, there is no definitive evidence of the benefits of the application of home telemonitoring in patients with chronic advanced heart and/or respiratory failure. Given this state of the art, we have proposed the development of a multicenter randomized clinical trial in order to evaluate the efficacy of the application of physiological and biological parameters home motorization in a multi-level model of coordinated clinical care for patients with chronic advanced heart and/or respiratory failure with respect to best conventional multi-level and coordinated clinical care.

1.1. Patients and methods

We have designed a randomized multicenter clinical trial with parallel groups in adult patients with advanced heart and/or pulmonary failure. The recruitment is being performed in five centers from Spain (two tertiary teaching, two secondary general, and one basic hospital). All center belongs to the *Andalusian Public Health System* (SSPA).

Eligible population has been defined as patients with heart and/or respiratory failure in advanced stages, that are followed up in specialized care out-patient clinic or after hospital admission. Inclusion and exclusion criteria in the study are detailed in Table 1.

2. Inclusion and randomization

Inclusion of eligible patients who meet criteria and agree to participate in the trial was performed at hospital discharge in case of being recruited during a hospital admission, or at any of the clinical visits in the case of being recruited as outpatient. Once the patient was eligible, met inclusion criteria, did not meet any criteria for exclusion and signed the informed consent to participate in the clinical trial, randomization into one of the two allocation arms was performed.

Randomization was performed stratifying patients by centers, establishing a list of randomization for each center.

3. Integrated care model for high complex patient of Andalusian health system

Patients with advanced cardiac and respiratory diseases are highly complex patients, due to the established organ failure and high prevalence of multimorbidity. They are placed on the top of the pyramid of the Kaiser Permanente model, so they involve a small percentage of patients with a high demand and consumption of resources [23]. The SSPA establishes that the care of these patients should be managed through an integrated health care model oriented towards the patient's needs, which is shared between primary care and hospital care and when it is necessary, with social services support [24]. The special medical needs of this population can be addressed through rapid access to medical co-management, complex diagnostics and programmed hospital admissions. This integrated care model is based on collaboration programs between internal medicine and primary care professionals, including physicians and nurses. The purpose of this model is improving health education with the promotion of self-care, optimization of hyper-specialized resources, placing them in strategic locations and offering to peripheral centers service by video-conference or electronic

Table 1
Inclusion and exclusion criteria for ATLAN_TIC study.

Inclusion criteria
1 Age≥18 years.
2 Suffering one of more of the following chronic non-reversible organ failure at advanced stages:
A) Heart failure with basal dyspnea grade ≥ III of $NYHA_a$.
B) Chronic respiratory failure with basal dyspnea ≥ III of MRC_b and/or oxigen saturation hemoglobin <90% and/or home oxygen therapy.
C) A + B or Heart Failure and/or Respiratory failure with basal dyspnea ≤ III (according to NYHA and MRC respectively) with 2 or more hospital admissions in previous year.
3 $PALIAR\ Index_c$ scoring among 0–7 points.
4 Present one of the following assistance situations: hospital admission, Palliative Care Teams or outpatient follow-up.
5 Patient or caregiver can speak, understand, read and write Spanish
6 Patient or caregiver are available of the using of mobile and tablet computer applications.
This knowledge will be confirmed by personal interview, with proof of the apparatus
7 Signing consent for participation
Exclusion criteria
1 Suffering of active malignant cancer disease except localized prostate adenocarcinoma undergoing hormonal treatment, and/or cutaneous basocellular-squamous cell carcinoma.
2 Possibility of substitute therapies in case of chronic renal disease (dialysis or transplantation).
3 Possibility of liver transplantation. In case of chronic liver disease
4 Chronic neurological disease with established cognitive impairment (Pfeiffer $questionnaire_c$ with 7 or more errors and/or MEC_d with ≤18 points).
5 Agony
6 Surprise question ("Would you be surprised if your patient died in the next 6 months?") with "I would not be surprised" result and PALIAR Score Score ≥7.5 points
7 Participate in another telehealth initiative.
8 Simultaneously attend at private health service and/or be institutionalized.

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messaging avoiding administrative inquiries [25,26]. The primary care and internal medicine professionals participate in a greater or lesser degree in the different actions of the model; identification of patients of high complexity, realization of a comprehensive assessment, a plan for continued care, home care, hospital care and care for the caregiver (Fig. 2).

4. Description of control (PAC), and intervention (TELEPAC) arm

PAC arm: All patients in this arm were given the optimal standard of care promulgated by the *Patient with Chronic Diseases plan* of the SSPA, based on a comprehensive clinical assistance shared between Primary and Hospital care. This arm also promotes self-care, the figure of the caregiver and frequent self-checks and registration on the patient's health paper notebook. The patient was advised to collect its biological parameters according to each patient needs and according to the patient's own devices. Clinical questionnaires were provided to recognize the onset of exacerbation symptoms. A call-center was also available, this being "reactive" to the patient's call, when he/she consider it necessary. This call center was constituted by the SSPA's Call Service named *Salud Responde* (SR), and it conducted a structured clinical interview to assess the severity of the alarm. According to severity gradation, SR fed-back patient's call with a dietary and/or therapeutic recommendation agreeing an appointment with the Primary care physician/Internist or sent emergency home care devices.

TELEPAC arm: All patients in this arm were given the same care protocol as PAC arm adding constant monitoring equipment for biological parameters and medical-related data. Devices are detailed at Additional information section. This home monitoring equipment automatically recorded data to the virtual health notebook that was available in real time for the care team by internet transfer. The home-monitoring system incorporated alarm routines according to a predetermined range of the physiological data, transferring it to the call center according to a designed protocol. Call Center performed the same structured clinical interview and response as in the PAC arm. If the patient did not include the home-monitoring data, the Agency of Social Services and Dependency of Andalusia (ASSDA) was activated to identify the motive and promote adherence, making and immediate 24 h phone call.

Trial intervention was administered, regardless of the arm, as soon as possible after the inclusion of the patient and when the patient or his/her legal representative have signed the informed consent, beginning the learning phase that is established in 15 days.

All patients received the best usual treatment based on existing protocols in hospitals and the best criteria of the internist and general practitioner.

5. Sample size calculation

Sample size calculation was performed in order to obtain statistical significance in the comparison between TELEPAC and PAC arm, for a 95% confidence level and 90% power with two tails and establishing a reduction in the efficacy variable (percentage of patients with hospitalization requirements and/or visits to emergency rooms), which is considered in the literature as clinically relevant. According to the data obtained in the PALIAR project [12] 45% of patients with a score $\leq$7 had required at least one hospital admission in the previous 12 months. In this way, it would be expected assuming the most rigorous hypothesis, that the percentage of patients who would need to meet the endpoints during the 6 months of follow-up the PAC arm will be 45% and in the TELEPAC arm 30% (a relative reduction of 33.3% hospitalization rate). Using the SISA calculator (http://www.quantitativeskills.com/sisa/calculations/samsize.htm), for the previous conditions, a total of 217 patients per arm is calculated. Taking into account a maximum loss rate for different reasons of 15% per arm, the total number of patients per arm is set at 217 x (1/1-0.15) = 255; meaning a total of 510 patients in the trial.

6. Development of the trial, follow-up and study visits

Clinical follow-up was carried out with both arms. It will be their usual clinical tracing with an addition of five regulated trial visits, at inclusion (V0) and 15 (V1)-45(V2)-90(V3)-180 (V4) days of it. Parameters evaluated in the different trial visits are shown in Fig. 1. Throughout the duration of the study, the use of the technology was continuously monitored by accounting in computerized records.

7. Deviation of protocol and withdrawal criteria

Relevant deviations of the protocol were defined as errors in the assumption to the intervention arm, poor compliance with the use of technology, missed monitoring and the existence of missing data.

Clinical trial withdrawal criteria have been defined as noncompliance with protocol requirements, presence of significant adverse events or by decision of the patient-legal representative or physician.

8. Outcome measures

The primary efficacy variable was defined as the percentage of patients with hospitalization and/or emergency room visits.

Secondary efficacy variables were defined as the number of hospital admissions, number of admissions to hospital emergencies, number of visits to Primary Care Emergencies, number of days of hospital stay, total cost per patient in euros, mortality, final Barthel index, quality of life (EUROQoL 5D questionnaire adapted for Spain) [13], perceived assistance (SERVPERF questionnaire) [14], perceived quality of technology devices (TSUQ questionnaire) [15], cost-effectiveness of intervention (incremental cost per unit of efficiency with respect to variety of primary and secondary efficacy), and the presence of technical problems of the devices.

The overall economic cost of the follow-up period will be calculated by adding the calculated cost of day-bed (including staff) and procedure use, home monitoring devices, possible additional requirements, and diagnostic and therapeutic procedures for possible added complications.

The incremental cost-utility ratio of home monitoring program incorporated into a shared comprehensive clinical care plan has been determined for patients with chronic diseases in advanced stages. Specifically, we will calculate the quality-adjusted life year and the costs of the telemonitoring program of physiological data according to their retail price, public prices and hospital accounting systems [16,17].

Independent variables were established as affiliation data (sex, age, inclusion date), caregiver data, inclusion criteria, relevant clinical data (multimorbidity, PROFUND index [18], NYHA [19] and/or mMRC [20] dyspnea severity, weight/height, Charlson Index [21], main symptoms and their severity, analytical data (albumin, (g/dl), creatinine (mg/dl) Sodium, Hemoglobin Total leukocytes, total lymphocytes), pharmacotherapy (number and type of drug, completion, existence of possible errors in the taking), basal functional data (Barthel's index [22]) and organizational-care data (number of admissions in the last year including index income (if included in hospitalization episode), number of admissions in last 6 months).

9. Statistical analysis

A modified intent-to-treat analysis will be performed including all patients who have agreed to enroll in the study, signed informed consent, and were randomized. Additionally, a per protocol analysis will be carried out on those patients who, after being randomized, will be provided with the technological equipment, and have completed the training. There will be a comparative analysis of the results of the primary efficacy and secondary efficacy, safety and cost variables between PAC and TELEPAC arm using the Chi square test, the Yates correction and, when necessary, the Fisher exact test for qualitative variables. The Student's T or Mann-Whitney *U* test will be used for quantitative ones

V0 Inclusion day	V1 Day 15	V2 Day 45	V3 Day 90	V4 Day 180
Both arms	Demographic Clinical Assistencial Functional status Phisical examination Analisis Medication Quality of life	Death Assistencial variables Phisical examination Decompensation and symptoms Medication changes	Death Assistencial variables Phisical examination Decompensation and symptoms Medication changes Quality of life Quality of medical assistance	Death Assistencial variables Phisical examination Decompensation and symptoms Medication changes	Death Assistencial variables Phisical examination Decompensation and symptoms Medication changes Functional status Quality of life Quality of medical assistance
TELEPAC		Technology use Biological data recolected Adverse events	Technology use Biological data recolected Adverse events Quality of technology use	Technology use Biological data recolected Adverse events	Technology use Biological data recolected Adverse events Quality of technology use

Fig. 1. Scheme of the clinical trial visits.

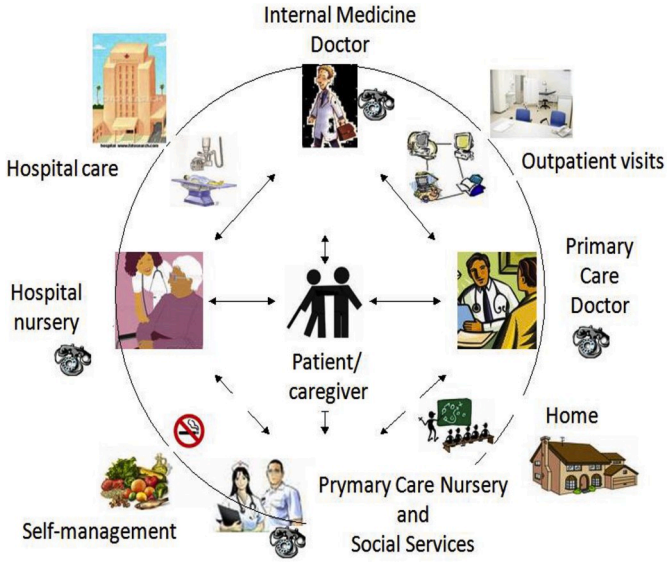

Fig. 2. Integrated care model for complex patients of the Andalusia Health Service.

accordingly to their normal or not-normal distribution. Differences between groups will be quantified using 95% confidence intervals.

The cost-effectiveness analysis will be performed using the incremental cost-effectiveness method, using as a primary efficacy unit each patient who has not developed the primary end point (hospital admission and/or emergency room visits), and as secondary efficacy units the number of hospital admissions, number of admissions to emergency rooms, mortality, final Barthel index and number of days of hospital stay. As cost unit, the sum of all previously collected costs of each patient will be counted. The formula to be used will be: Incremental cost-effectiveness (Euros per efficiency unit obtained) = NNT x (TELEPAC arm cost per patient/PAC arm cost per patient). All calculations will be performed using the SPSS 19.0 statistical package. A $p < .05$ will be considered statistically significant.

10. Interim analysis and stopping rules

An intermediate analysis of randomization and evaluation of the primary efficacy variable was carried out when 50% of the sample was reached in order to a) detect possible imbalances between the two test arms with respect to a predetermined list of independent secondary baseline variables, and b) assess whether the primary efficacy endpoint was obtained at this point in the trial. The list of independent secondary endpoints included the following: age, sex, type of inclusion criterion 2, type of inclusion criterion 3, median inclusion criteria 4, (see Table 1), mortality, and adverse clinical events. In the case of safety issues disbalances or if primary efficacy endpoint is obtained, the clinical trial will be stopped.

11. Adverse events and safety issues

Security variables were carried out in accordance with the Good Clinical Practice Standards and the current legislation. It was the investigator's responsibility to detect and document any event that meets the criteria and definitions of adverse event (AE) or serious adverse event (SAE). For this study that did not use medications, AE was defined as any untoward medical occurrence in a patient or clinical investigation participant administered an intervention, which does not necessarily have a causal relationship with the intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the study intervention, whether considered related to the study intervention. SAE was defined as any adverse event that causes the death of the patient, threatens the life of the patient, requires hospitalization or prolongation of the patient's hospitalization, causes disability or permanent disability.

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification was provided. The term "severe" is often

used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache).

Serious suspected adverse events that are medically important will be treated as serious, even if they do not meet the above criteria, including important medical events that require intervention to avoid any of the consequences described above.

The relationship of each AE to the technological devices will be determined by a medically qualified clinician according to the following definitions. Related, the adverse event follows a reasonable temporal sequence from technological devices use, and It cannot reasonably be attributed to any other cause. Not related, the adverse event is probably produced by the participant's clinical state.

Procedures for recording AE. All AEs occurring during the study/or until observed by the investigator or reported by the participant, whether or not attributed to technological devices, will be recorded on the case record form (CRF). The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to technological devices. Follow-up information should be provided as necessary.

Due to the characteristics of the technological devices of the clinical trial intervention, and to the low probability of the occurrence of AE related to them, except for specific technical problems that will not allow to transfer of biological data, there will not be an additional collection of safety data beyond those already defined in the study.

12. Quality control and regulatory considerations

To ensure investigators are following the protocol, complying with regulations and Good Clinical Practice (GCP) standards, and collecting and reporting quality data, sponsors of clinical trials monitored the progress of clinical trials performed by the investigators during the clinical trial. The core components of monitoring were to ensure patient protection and to validate the integrity of the data.

The quality control of the data was carried out throughout the study and of all the documents that are generated, as well as of each patient that was included during the study. The study data was transcribed onto CRF and only include a code assigned to each patient, to provide a patient identification code. In this quality control, the data recorded in CRF were checked per patient. This was responsible for a clinical trial monitor (CTM) that was not part of the investigators of the project. The CTM verified that the data have been faithfully transcribed from the patients' clinical records to these CRF, keeping patient confidentiality in accordance with the data protection law in force. Data quality control was scheduled with an initial visit to all centers, and after the inclusion of the first patient another intermediate visit when approximately half of the patients have been included and a final visit. If necessary, extraordinary visits was made to each center when they were accurate.

The documents constituting the master file of the study included all the documents established in the Good Clinical Practice (CPMP/ICH/135/95).

13. Ethic, deontological and regulatory considerations

The Investigator ensured that this study was conducted in accordance with the principles of the Declaration of Helsinki, ICH Guidelines for Good Clinical Practice and in full conformity with relevant regulations.

The protocol, informed consent form, participant information sheet, any applicable documents and all substantial amendment of them was submitted to an appropriate Ethics Committee (EC) and Regulatory Authority for written approval.

The trial staff ensured that the participants' anonymity is maintained complying with Data Protection Legislation (according to Spanish Law 15/1999, on Protection of Personal Data, from the 13th of December). The participants were identified only by a participant ID number on the clinical record folder and electronic database. All documents were stored securely and only accessible by trial staff and authorized personnel.

Informed consent was necessary for this study, and the investigator was responsible for obtaining it once it is established that the patient meets the selection criteria for recruitment and before starting the study, after having provided appropriate information about objectives, methods, anticipated benefits and potential risks to the patient or his/her legal representative.

Additional information

13.1. Technological devices

Technology provider was TELEFONICA S.A.® through its "Chronic Management Platform". It is a modular remote management service for chronic patients, which facilitates its control and monitoring biological data that is housed in the cloud. It offers health care in remote to the patient, in a complementary or substitute way to face-to-face care. Patients received devices that allowed them an easily follow of their daily medical agenda, communicate, monitor and accurately send their physiological-data and symptoms by answering a series of questions about their health each day. The information was transmitted to a cloud platform accessible to health professionals and integrated with their work tools (Fig. 3). This communication was made through M2M mobile communications between the patient's gateway and the management platform for chronic patients. The equipment offered by the service consisted of a basic pack plus the specific pack for each patient's disease. The basic pack device was a tablet-pc with several models (Prestigio Multipad Visconte 2®, Samsumg ATIV TAB 5® or Acer Iconia W501®) equipped with a standard M2M Smart Vc Card or microsim. Specific devices include Onyx II 9650® pulxiometer, Omrom 708-BT® blood pressure monitor, OMROM BF206-BT® bascule, and a two-model glucometer (Abbott Freedom Lite®, USB Bayer Contour XT®) (Fig. 3). The chronic patient's gateway included, among other things, patient authentication, automatic reception and visualization of biological data and treatments, possibility of manual introduction of biological data, access to daily agenda and questionnaires, messenger system, educational content (videos) and access to the personal folder of health fully integrated with the health services of the SSPA.

13.2. Educational kits

All patients were provided with the same educational material. In the TELEPAC arm it will be loaded on the tablet-pc and in the PAC arm it will be given in paper format and DVD. This educational training was

Devices	Model	
Tablet-pc equipped with a standard M2M Smart Vc Card or microsim	Prestigio Multipad Visconte 2®, Samsumg ATIV TAB 5® Acer Iconia W501®	
Pulsioximeter	Onyx II 9650®	
Blood pressure monitor	Omrom 708-BT®	
Bascule	OMROM BF206-BT®	
Glucometer	Abbott Freedom Lite® USB Bayer Contour XT®	

Fig. 3. Technological devices.

performed by personal interview by specific nurse hired for this study with support of educational paper brochure and dvd. This same information was included in the tablet pc in TELEPAC arm in pdf and video. This material consisted of educational brochure and videos with specific information of the disease and its decompensation signs and symptoms. The information included changes in daily habits, exercise and knowledge of pharmacological treatment. This material was selected by the School of Patients of the Andalusian School of Public Health.

13.3. TELEPAC alarms algorithms

Two alarm types were defined, clinical alarms and biological alarms. Clinical alarms arose from the use of perceived health questionnaires to identify symptoms of exacerbation of chronic heart or respiratory failure (Tables 2a and 2b). In case of HF, the questionnaire was *How is your heart?* designed for the ICOR study [27], and in RF the questionnaire, *How are my lungs?* designed for CRONEX study [28]. Alarms for biological data arose from the alteration of the physiological data that could be measured in the study: heart rate, blood pressure, oxygen saturation, weight and capillary glycaemia according to the needs of each patient. The registry of the different clinical constants was carried out by the patient at the beginning daily and later it was regulated according to each patient's needs, establishing a minimum of once a week. Depending on the different values obtained, different alerts were activated. No alert (green color), the patient entered data with normal values. Alerts of absence (gray color), the patient did not enter the data in the system in two consecutive taking. Biological alert of low severity (yellow color), there was an alteration of the parameters of moderate severity that was maintained two takings followed with at least 24 h of difference. Biological alarm of high severity (red color), there was a severe alteration of the parameters. The electronic platform had default reference values adapted from the clinical practice guidelines of the corresponding diseases **(**Table 3**),** but due to this special characteristic population normal value ranges were individualized for each patient. An alteration of the physiological data triggered an alarm. In TELEPAC arm, patients were provided with all the devices they need to control for their diseases and they were connected with a tablet-pc that will transmit the results in real time to Telefónica's chronic management platform. Once an alert was generated in the system, the Call Center called patients and performed a structured interview (Table 4) by a designed algorithm in its software program. It analyzed alarm symptoms with biological data to perform a stratification of severity, generating a specific action: therapeutic recommendation and appointment with the family doctor in case of low severity, with an internist for intermediate severity or activation of emergency services for high severity.

In the PAC arm, patients collected data from the devices they have at home and the questionnaires in paper format. They were taught about their individualized normal value ranges and that in case of alteration they could contact call center for assistance. The call center performed same structured interview and response.

As shown, physiological data taking and response of the system was the same in both arms, being the only difference how information reached the healthcare staff, proactively in the case of patients of the PAC arm, and automatically in the TELEPAC arm (Fig. 4).

Table 2a
Decompensation symptoms questionnaire for Heart failure.

How is my heart?		Answer	
1.	I have more swollen feet than usual	Yes	No
2.	I feel more tired or suffocated than usual	Yes	No
3.	I had a bad night because of suffocation	Yes	No
4.	I have had to add more pillows to breathe better at night	Yes	No
5.	I had to sleep sitting because of the suffocation	Yes	No
6.	I have felt more dizzy or weak than usual	Yes	No
7.	I have had more chest pain than usual	Yes	No
8.	I feel worse than yesterday	Yes	No

2 or more "yes" answers mean a clinical alarm.

Table 2b
Decompensation symptoms questionnaire for respiratory failure.

How are my lungs?		Answer	
1.	I have more suffocation than usual	Yes	No
2.	My sputum has changed color (or is darker)	Yes	No
3.	My sputum has increased	Yes	No
4.	I have cold symptoms	Yes	No
5.	I have been increased the wheezing in the chest	Yes	No
6.	I have a sore throat	Yes	No
7.	I have cough increased	Yes	No
8.	I have a fever	Yes	No

Answer "Yes" to the first three questions scores 2 and the rest questions score 1.
Answer "No" scores 0.
Score $\geq$4 means a clinical alarm.

14. Discussion

Tele-health initiatives and home-monitoring initiatives represent a promising future option in medical care. Its benefits have been proven in different chronic diseases such as hypertension [29] and diabetes [30]. But there is no robust scientific evidence that such a benefit appears in patients with advanced heart and/or respiratory failure.

Regarding the type of patients included in previous studies, these were mainly patients with heart failure with NYHA II and III baseline dyspnea and of moderate and high severity in the case of COPD, which excludes patients in a more severe stage. Those stages are the ones that more care resources demand and theoretically are the ones that should most benefit from closer monitoring. In our study, we want to evaluate the application of home-monitoring devices in patients with advanced heart and/or respiratory failure within an already integrated care model. Therefore, a special care circuit has not been created for a clinical trial; this circuit is based on a real care model using the existing care resources where home monitoring devices will be added. This real care resources will try to solve some of the problems found in home monitoring reviews. We are going to recruit a mixed population of patients with advanced heart and/or respiratory failure with low-intermediate and high resources consumption by recruiting patients during chronic follow up (low-intermediate needs) and after admission (high risk). This point will allow us to evaluate the optimal situation for home monitoring in this population.

When considering small studies (less than 300 patients) the health benefits always reached statistically significant differences, but when the size of the studies increases, there were no statistically significant differences. It is even possible to find how the same authors showed that their pilot study found statistically significant differences, but in the multicentre project no statistically significant differences were met [31]. Possibly this is because in few patient trials we face with a more controlled environment and the staff involved in the intervention is usually more motivated. To avoid this, we have chosen a fully integrated call center in our health care system that will provide the study a real and homogeneous intervention (a "real life experiment", or "living laboratory").

The call center in our study will be *Salud Responde* that currently carries out a wide activity. On one hand, it has an administrative activity, facilitating the process of citation in different levels of assistance and information about any subject related to the SSPA. On the other hand it also has active programs of exclusive sanitary content such as health advice, follow-up of hospital discharge during the weekends of patients with special needs, management of health campaigns by SMS messages to mobiles, linguistic translation service, information on tobacco, coordination of telephone support to Community Nursing Link, access to the Registry of Advanced Care Directives of Andalusia, follow-up of patients assisted by emergency dispositive and staying at home, tele-continuity of palliative care and diabetic patients, information on

Table 3
Biological parameters values range for the triggering of alarms.

	Green	Yellow	Red
Weight (kg)	Basal line	Increase >= 1 kg/day	Increase >= 3 kg in 2 days
Heart beat (bpm): Tachycardia	60- 100 If HF: 55-75	101-130 If HF: 76-100	> 130 If HF: >100
Heart beat (bpm): Bradycardia	60- 100 If HF: 55-75	40-59 If HF: 40-54	< 40 If HF: <40
Blood pressure (mm Hg): Hypertension	SBP 100-150 DBP 60-95	SBP 151-200 DBP 96-110	SBP > 200 DBP >110
Blood pressure (mm Hg): Hypotension	SBP 100-150 DBP 60-95	SBP 90-99 DBP 40-59	SBP <90 DBP < 40
Oxigen saturation (%)	Fall <3% basal line	Fall 3-5% basal line	Fall > 5% basal line.
Fasting capillary glucose level (mg/dl): Hyperglycemia	90-180	181-300	> 300
Fasting capillary glucose level (mg/dl): Hypoglycemia	90-180	60-89	< 60
Pre-prandial and before bedtime capillary glucose level (mg/dl): Hyperglycemia	80-200	201-450	> 450
Pre-prandial and before bedtime capillary glucose level (mg/dl): Hypoglycemia	80-200	60-79	< 60

Green color = normal values.
Yellow color = moderate alteration of the parameters maintained two takings followed with at least 24 h of difference.
Red color = severe alteration of the parameters.
Bpm = beats per minute. HF = Heart failure. SBP Systolic blood pressure. DBP = Diastolic blood pressure.
*Adapted from Clinical guidelines for Heart Failure [42] and Chronic Obstructive Pulmonary Disease [43].

Table 4
Call center Structured interview.

Alert symptoms
Unbearable dyspnea at rest
Ortopnea with four or more pillows
Marked increase in peripheral edema
Angina pectoris
Incapacitating cough
Appearance of fever higher than 38 °C with affectation of general state or level of consciousness
Other symptoms with affectation of general state

the vaccination campaign against influenza and chickenpox. This extensive experience in the telephone assistance makes Salud Responde the ideal call center for the response to clinical alterations and physiological data in this high complexity population [32].

One of the major problems encountered in home telemonitoring studies with a high number of patients is adherence to the use of home-monitoring devices. Adherence issue is also influenced by study size. So in the small studies, technology adherence observed is around 80–90% [33], but it drops to 50% as the number of patients increases [34]. The inclusion of social services in our study will help to control adherence of patients to the use of technological devices by doing a positive reinforcement. Currently the Agency of Social Services and Dependency of Andalusia (ASSDA) already carries out telehealth activities such as telecare programs. Telecare program is an essential service to facilitate that people with dependence could permanence in the environment in which they develop their life, in some cases as a sufficient instrument to maintain their personal autonomy, and in others as a complementary service to others means. It consists of direct and personalized attention to situations of emergency, insecurity, loneliness or isolation, through specialized professionals who provide the necessary support to be able

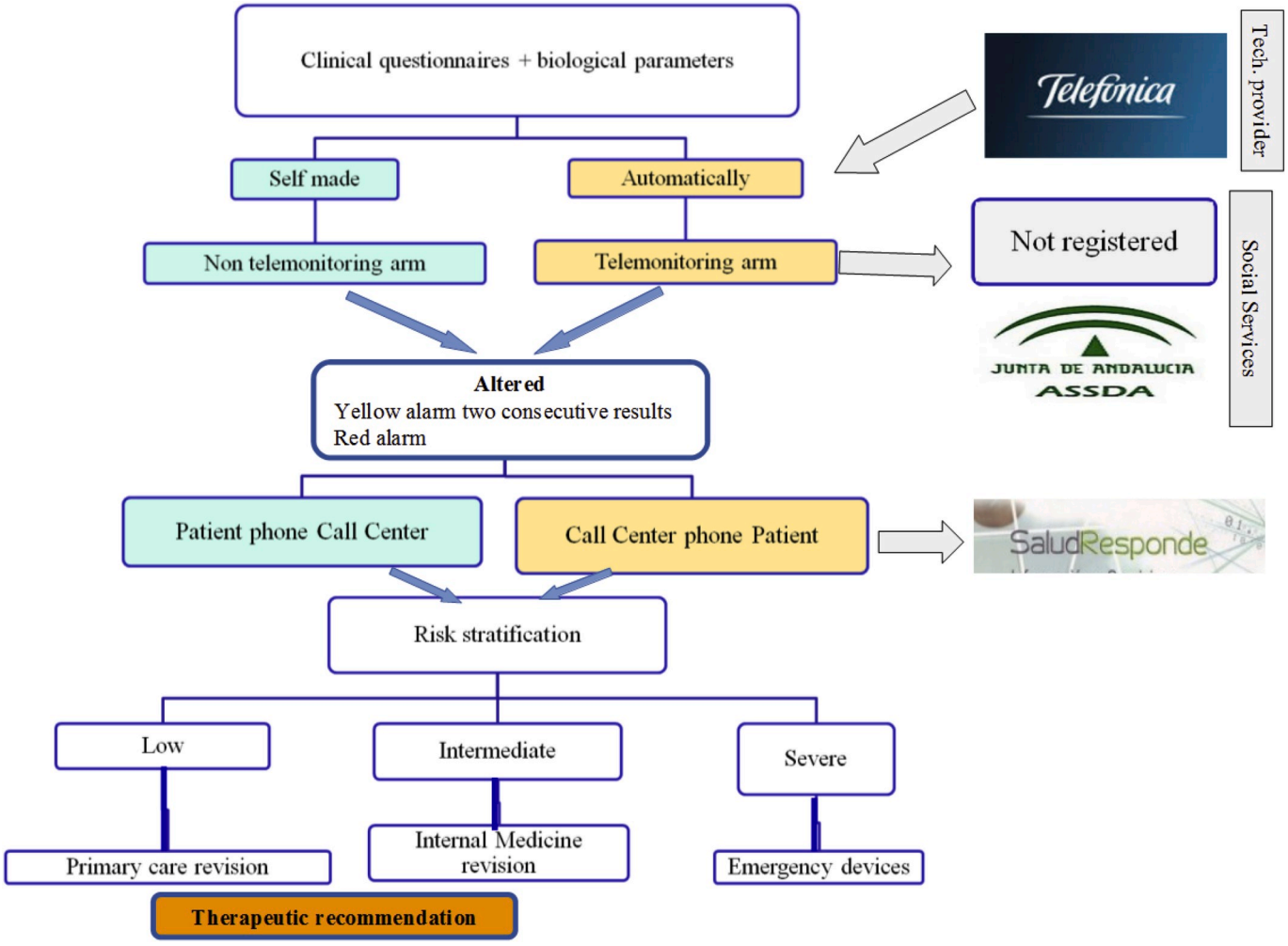

Fig. 4. Clinical protocol of ATLAN_TIC project.
* Technology: Web page, tablet pc, pulsioximeter, blood pressure monitor, bascule, glucometer.
ǂ Therapeutic recommendation: Lifestyle advice, medical assistance according to specialist reports.
ǂǂ Emergency devices: Emergency medical service or recommendation of attendance at primary care o hospital emergency room.

to solve diverse nature situations, mobilizing the most appropriate resources for each case. It is a special device connected to the telephone line that allows immediate contact with the service through a push-button (pendant or bracelet) from anywhere in the home [35]. Patients who benefit from this service usually fulfill the profile of high complexity patients that will be included in this study. Another important fact for adherence is the complexity of the telemedicine system. We have chosen for this study a very simple telemedicine system for the patient or caregiver and it had been applied in other studies [27], so only a few incidences are expected.

The technological devices that are carried out in different studies are very heterogeneous. From video-conferences with or without telemonitoring [36] to phone devices like tablet or smartphone or by web page [37]. Moreover, established interventions in response to biological data alterations are also very heterogeneous. They are described from phone calls/videoconference [38] to visits at the patient's home [39]. There are also different ways of data collection, synchronous or asynchronous in time, from once or twice a week to be attended only during office hours. Surprisingly, better outcomes have been reached with the reception of data telemonitoring at office hours [8]. Although these literature reports we have designed a real-time care protocol because we believe that this type of action facilitates quick identification of HF and Respiratory failure crisis and enable us early use of rescue medication to stop it. This type of response is not present in most of the studies described and, as we mentioned before, it will be provided by Salud Responde.

In cost studies, it is difficult to make an assessment in the meta-analyzes because of the inconsistency of the methods of cost analysis in the different studies for HF. Although there seems to be a tendency to show benefits, there is no significant differences and is highly variable depending on the context and the type of health system [40]. In the case of COPD, there are too few reports on the economic expenses so it is difficult to generalize results [41]. In designing our study by inserting telemonitoring technology into an already operational care model that includes its own call center, there is no increase in infrastructure costs. Therefore, we will be able to make a study of costs in which the expenditure of the use of the technological devices and of the patient care variables will be correctly valued.

Another strength of our study is that it is going to be carried out in different hospitals that serve urban and rural population so that a homogeneous and a representative sample of the target population will be obtained.

This study has some limitations. It is an open label trial where allocation to an intervention could not be masked. We have limited this study at six months. There is no evidence about the optimal duration of home telemonitoring, but in this population of high complexity patients there is a great mortality at twelve months [18] but we can estimate mortality at six months with high accuracy by PALIAR index [12].

If the use of home monitoring is effective, it can set the foundations for implementing these initiatives throughout the SSPA. If it is negative, the analysis of the reasons for failure may help to improve our integrated care model for advanced chronic patients.

15. Conclusions

The current benefit of the use of home-monitoring in patients with advanced heart and/or respiratory failure is controversial. Given that the high complexity of these patients requires integrated medical care systems, it is necessary to evaluate the efficacy of home-monitoring in these patients within an integrated care model. We think, that the ATLAN_TIC clinical trial will answer these issues.

Contribution of the authors

All authors have participated actively in the study.

Ethics committee

This study was approved by the ethics committee of Hospitales Universitarios Virgen del Rocio, Hopsitales Universitarios Virgen Macarena, Hospital de la Serrania de Ronda, Hospital Universitario Virgen de Valme, Complejo Hospitalario de Jaen.

ClinicalTrials.gov identifier

NCT03018717.

Declaration of competing interest

The authors have no conflict of interest.

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