The ADLIFE Project has received funding from the European Union under the Horizon 2020 Programme, grant reference number 875209.

Horizon 2020
European Union Funding
for Research & Innovation

D9.1 ADLIFE Intermediate progress report

Deliverable No.	D9.1	**Due Date**	30/06/2023
Description	This deliverable presents the work that has been conducted by WP9 on the evaluation of the ADLIFE intervention and the risk prediction models.		
Type	Report	**Dissemination Level**	Public
Work Package No.	WP9	**Work Package Title**	Evaluation
Version	1.0	**Status**	Final

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History

Date	Version	Change
16/05/2023	0.1	Draft template prepared by lead authors
06/06/2023	0.2	Draft version including co-authors contribution
09/06/2023	0.3	Initial version after lead authors review, shared with internal reviewers
27/06/2023	0.4	Incorporated feedback and comments from reviewers
29/06/2023	0.5	Pre-final revision
30/06/2023	1.0	Final deliverable

Key data

Keywords	Evaluation, mixed-methods approach, effectiveness, socio-economic impact, technology acceptance, implementation, performance metrics, explainability, model retraining
Lead Editor	Ania Gorostiza
Internal Reviewer(s)	Dr Juan de la Torre, Dr Lisa McCann

Executive Summary

ADLIFE aims to develop innovative digital health solutions to support the healthcare planning and care delivery for patients over 55 years old with advanced (severe) long-term conditions such as chronic obstructive pulmonary disease (COPD) and/or chronic heart failure (HF). The ADLIFE study is designed to provide robust scientific evidence on the assessment of the effectiveness, implementation, technology acceptance and socio-economic aspects of the ADLIFE intervention compared to the current standard of care (SoC) when applied in real-life settings of pilot sites across different countries.

WP9 is responsible for the evaluation of the ADLIFE intervention as well as the evaluation of the risk prediction models developed by WP5 for continuous risk assessment of potentially preventable situations (PPSs). The purpose of this deliverable is to report on the work that has been conducted by WP9 from the submission of the deliverable D11.1 “Requirement No.1: Study protocol” in M20 until M41 regarding the two previous targets.

The evaluation framework, data gathering process and analysis plan are available in the project’s research protocol, which has been further developed from its version v0.21 (17/03/2021), the basis of deliverable D11. The adaptations have responded to the needs of the ADLIFE intervention, the subsequent design of the evaluation and specific pilot sites’ needs and to a better understanding of the research protocol. On the one hand, four data collection guidelines have been designed and developed in order to conduct the data collection of each of the four assessments comprising the ADLIFE evaluation. On the other hand, the ADLIFE project has undergone modifications in the DoA concerning the number of pilot sites deploying the intervention and the intervention starting time; therefore, the evaluation framework has been correspondingly redesigned. Also, the research protocol has been registered in *ClinicalTrials.gov* and adapted to paper-format and published in the International Journal of Environmental Research and Public Health (IF: 4.61; Q1). The general simulation models for the socio-economic impact assessment have been developed and validated. All previous materials are presented through this deliverable D9.1 and are available in the appendixes. Regarding the evaluation of the risk prediction models, deliverable D9.1 reports results on: a) the evaluation of the properties of each of the proposed PPSs by measuring their ability and capacity to correctly classify; b) the analysis of the unobserved values in the created models; c) the interpretability of the PPSs; and d) the retraining of the PPSs in the AMCA database.

As next steps, WP9 will evaluate the intervention for all pilot sites in terms of effectiveness, implementation, technology acceptance and adoption and socio-economic impact, as specified in the research protocol. Particularly, since GWMK will not run the ADLIFE pilot as an interventional study in Germany, an observational study will be designed and conducted. Evaluation results will be reported in deliverable D9.2 Final evaluation report in M54. A final evaluation of the prediction models is also planned after the intervention, where the performance of the implemented models will be evaluated.

Statement of originality

This deliverable contains original unpublished work except where clearly indicated otherwise. Acknowledgement of previously published material and of the work of others has been made through appropriate citation, quotation or both.

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1 Acronyms

Abbreviation/Acronym	Defintion
A&E	Accident and Emergency
ACC	Accuracy
ACD	Advanced Chronic Disease
AI	Artificial Intelligence
AIC	Akaike Information Criteria
AMCA	Assuta Ashdod Hospital - Maccabi Healthcare Services Southern Region
AUC	Area Under Curve
COPD	Chronic Obstructive Pulmonary Disease
CPM	Clinical prediction models
D9.1	Deliverable 9.1
DCG	Data Collection Guide
DES	Discrete Event Simulation
DMIDS	Deutsche Medizinprodukte Informations System
DoA	Description of Action
E&D	Emergency Department
EC-LKHE	Ethics Commission of the Hesse State Medical Association (Landesärztkammer Hessen)
EHR	Electronic Health Records
F1	F1 score
FHIR	Fast Healthcare Interoperability Resources
FN	False negative
FP	False positive
GP	General Practitioner
GWMK	Gesunder Werra-Meißner Kreis
HF	Heart Failure
HR	Hazard Ratio
M	Month
MDR	European Medical Devices Regulation

ML	Machine Learning
MS	Milestone
NHS Lanarkshire	National Health Service Lanarkshire
NPV	Negative Predictive Value
OUH	Odense University Hospital
PC	Primary Care
PI	Principal Investigator
PPS	Potentially Preventable Situations
PPV	Positive Predictive Value
PREC	Precision
REC	Recall
RJH	Region Jämtland Härjedalen
SHAP	Shapley Additive exPlanations
SoC	Standard of Care
SPEC	Specificity
TCPP	Target Control Patient Population
TN	True negative
TP	True positive
TPR	True Positive Rate
UHCW	University Hospitals Coventry And Warwickshire National Health Service Trust
UoB	University of Birmingham
UTAUT	Unified Theory of Acceptance and Use of Technology
WP	Work Package

2 Context, purpose and approach of the deliverable

The work which supports the production of this deliverable 9.1 (D9.1) has been completed within Task 9.1 “Develop the evaluation framework and planning”, Task 9.2 “Evaluate outcomes at different time-points”, Task 9.3 “Evaluation of the clinical predictive rules” and Task 9.4 “Estimate the economic impact and long term prediction”, led by Kronikgune as described in the Description of the Action (DoA) in the framework of Work Package (WP) 9 “Evaluation” also led by Kronikgune.

Kronikgune has been responsible for the development of the effectiveness and socio-economic impact assessments. OptiMedis has been responsible for the development of the implementation assessment. University of Birmingham (UoB) has been responsible for development the technology acceptance assessment. Kronikgune and NTT Data have been responsible for the evaluation of the risk prediction models.

2.1 Context of the deliverable

ADLIFE aims to develop innovative digital health solutions to support the healthcare planning and care delivery for patients over 55 years old with advanced (severe) long-term conditions such as chronic obstructive pulmonary disease (COPD) and/or chronic heart failure (HF).

ADLIFE is divided into 11 different Work Packages, three transversal (WP1, WP2, WP10) and seven technical ones. WP7, along with WP6, are devoted to change the care model and empowering patients, while WP3, WP4, WP5 are devoted to the technical development of the ADLIFE toolbox. These five WPs will allow completing the Phase 1 (“Organizational issues and Information and Communications Technology [ICT] platforms implementation”) and lead to obtaining the ADLIFE toolbox and model that will be implemented in Phase 2 (WP8) and evaluated in different health systems (WP9) in Phase 3.

WP9 is responsible for the evaluation of whether the ADLIFE intervention, when applied in real-life settings, is able to deliver appropriate targeted and timely care for patients living with advanced chronic diseases (ACDs); as well as the evaluation of the risk prediction models developed in the context of WP5. Specifically, the main objectives of the WP9 are: 1) to coordinate the evaluation process; 2) to develop an evaluation strategy, framework and planning; 3) to ensure data collection across all pilot sites; 4) to evaluate the effectiveness, implementation, technology acceptance and socio-economic impact of the ADLIFE intervention compared to the Standard of Care (SoC); and 5) to evaluate the clinical predictive rules of the ADLIFE model. To address these objectives, WP9 is divided into 4 tasks: Task 9.1, responsible for the development of the evaluation framework and planning; Task 9.2, responsible for the evaluation of outcomes at different time-points; Task 9.3, responsible for the evaluation of the clinical predictive rules; and Task 9.4, responsible for the estimation of the economic impact and long-term prediction.

All issues dealt with in this deliverable are aligned with WP9 on the ADLIFE evaluation. Moreover, the clinical predictive models allowing the predictive and continuous risk assessment of potentially preventable situations (PPS) have been developed within WP5; and WP9 has closely worked with WP5 in the evaluation of the risk prediction rules. WP9 has also worked with WP10 in the definition of the main outcomes to be assessed by means of the qualitative methodology, as the interviews that will be performed at the end of the intervention will cover both WP perspectives.

2.2 Purpose of the deliverable

The purpose of this deliverable is to report on the work that has been conducted by WP9 from the submission of the deliverable D11.1 “Requirement No.1: Study protocol” in M20 until M41 regarding the two following targets: a) the evaluation of whether the ADLIFE intervention, when applied in real-life settings, is able to deliver appropriate targeted and timely care for patients living with ACDs, providing robust scientific evidence on the effectiveness, socio-economic, implementation, and technology acceptance assessment of the ADLIFE intervention compared to the SoC; and b) the evaluation of the risk prediction models developed in the context of WP5.

Work performed in Task 9.1 until month 20 (M20) was reported in the deliverable D11.1 “Requirement No.1: Study protocol”. However, after M20 the ADLIFE project has undergone modifications in the DoA concerning the number of pilot sites deploying the intervention and the intervention starting time. Given that the intervention has not yet started, deliverable D9.1 will not serve as a means of verification of Milestone MS12 “Baseline data for evaluation”, as stated in de DoA. Instead, it will report how the evaluation framework has been adapted to the modifications in the project and present the materials developed to carry out the evaluation.

2.3 Approach of the deliverable

This D9.1 is structured as follows: first, the evaluation of the ADLIFE intervention and second, the evaluation of the risk predictions models are presented. The evaluation of the ADLIFE intervention contains a brief description of the proposed evaluation framework; the main updates undergone in the research protocol, including a description of the modifications in the DoA and the alternative evaluation designed to overcome their impact; the development of the Data Collection Guides; and finally, the current status and the next steps of the ADLIFE evaluation. The evaluation of the risk prediction models contains the model evaluation procedures, the retrained models, the federated learning and a discussion. At the end of the deliverable, final conclusions and principal next steps are pointed out. I

In addition, this document describes the Proof of Concept on Federated Learning developed in the framework of WP5 by NTTData. By the time of the submission of WP5 Deliverables, this proof was not finalized. The consortium agreed to report the results of the test on this Deliverable, to share it with the European Commission.

3 ADLIFE Evaluation

The aim of the ADLIFE evaluation is to determine whether the ADLIFE intervention, when applied in real-life settings, is able to deliver appropriate targeted and timely care for patients living with ACD.

As stated in the project's research protocol, the ADLIFE evaluation will provide robust scientific evidence on the effectiveness, implementation, technology acceptance and socio-economic assessments of the ADLIFE intervention compared to the SoC using a mixed-methods strategy. Figure 1 represents the fourfold approach and the methodologies to assess the ADLIFE intervention.

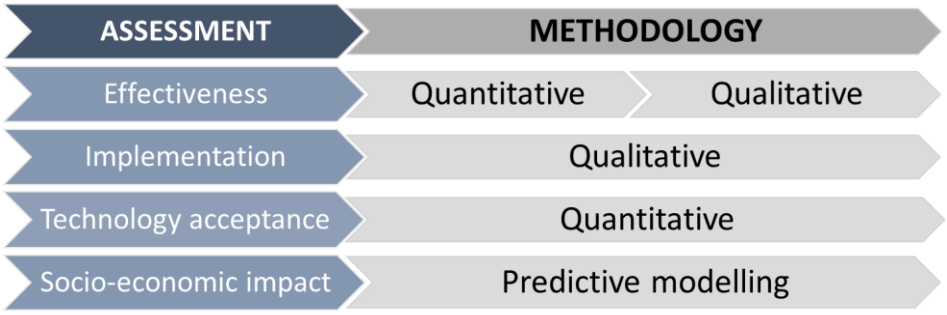


Figure 1 - ADLIFE evaluation framework

This section is structured as follows: first, the main updates undergone in the research protocol are presented. Second, the Data Collection Guides developed to collect data for the different evaluation approaches are presented. Finally, the current status and the next steps of the ADLIFE evaluation are analysed.

3.1 Research protocol

A research protocol providing the evaluation framework, the data gathering process and the analysis plan was developed and described in deliverable D11.1 "Requirement No.1: Study protocol", submitted on 30th April 2021. It has been registered in *ClinicalTrials.gov*, accessed on October 2022 with the identification number NCT05575336. The research protocol was also adapted to paper-format and published in the International Journal of Environmental Research and Public Health (IF: 4.61; Q1) on 10th February 2023[1].

After the submission of deliverable D11.1 the research protocol has evolved and various elements have been further developed. The new elements lie on the development in detail of the pseudonymization and anonymization process of data from intervention and control participants, respectively; the data collection; the methodology of technology acceptance and socio-economic assessments; and the alternative evaluation designed to minimize the impact

[1] García-Lorenzo B, Gorostiza A, González N, et al. Assessment of the Effectiveness, Socio-Economic Impact and Implementation of a Digital Solution for Patients with Advanced Chronic Diseases: The ADLIFE Study Protocol. *Int J Environ Res Public Health*. 2023;20(4):3152. Published 2023 Feb 10. doi:10.3390/ijerph20043152

of the deviations from the DoA undergone in the ADLIFE intervention. The alternative evaluation design includes the adaptation of the statistical analysis plan to measure the quantitative effectiveness under the new scenario, as well as the recalculation of the required sample size. Both the deviations from the DoA and the alternative evaluation plan are described in detail in the following sections. Moreover, as reflected in AMD-875209-9, University Hospitals Coventry And Warwickshire National Health Service Trust (UHCW) replaced FALKIEWICZ as pilot site in the project. Pilot sites have requested amendments to their ethics committees in accordance with previous modifications.

The updated version of the research protocol (v31) is under review and version 30 is attached in Appendix A, including a history log from its version v22.

3.1.1 Deviations from de DoA

The ADLIFE project has undergone modifications in the DoA concerning the number of pilot sites deploying the intervention and the intervention starting time, which affect the ADLIFE intervention and its evaluation.

3.1.1.1 Number of pilot sites

The number of pilot sites participating in the project has decreased from seven to five pilots since neither Region Jämtland Härjedalen (RJH) nor Gesunder Werra-Meißner Kreis (GWMK) will conduct the pilot as initially planned.

In the summer of 2022, RJH faced difficulties preparing its ADLIFE pilot. The provisioning of servers, the starting point of the preparation phase, still needed to be solved. This delay compromised the other tasks necessary for the deployment. The Coordinator and WP3 Leader closely monitored the status of this pilot. At the end of the year 2022, delays in the provision and achievement of the initial MS defined as key by the technical partners in RJH according to the deployment plan agreed upon at the 5th Plenary Meeting of the project were registered as a risk level of 25 (maximum score in likelihood and impact for the project). Then, it was decided to not jeopardize the development of the rest of the pilots in ADLIFE project and the best agreed on solution was to reduce the number of pilots from seven to six.

Afterwards, it should be noted that the European medical device regulation was implemented during the course of the ADLIFE project, once it had already started, so it was impossible to take into account the effect of this regulation on the contingency plan in the project proposal. Initially, in the first year of the project, GWMK submitted the ADLIFE study to the local ethics commission (ethics commission of Göttingen) as a "study in accordance with the professional code", obtaining the approval of the committee. Subsequently, by mid-2021, the European Medical Devices Regulation 2017/745 (MDR) came into force across Europe. When in December 2022, GWMK submitted to the ethics commission the necessary amendment to update the study protocol, as well as relevant information for patients and professionals (e.g. study guidelines), the MDR directly affected the project. The ethics commission of Göttingen required, due to MPR / MPDG demand, to hand in the study as MDR (MPDG) compliant study over the Deutsche Medizinprodukte Informations System (DMIDS) and name ethics commission of the Hesse State Medical Association (Landesärztkammer Hessen) (EC-LKHE). EC-LKHE required that several major issues needed to be resolved in order to obtain a positive response to start the intervention study. Some of the issues were as follows: each test site must name two humans as testing personnel; this testing personnel at test centers must be physicians and must be listed as practicing at the Hesse State Medical Association; the MDR / MPDG qualification of the testing staff was insufficient for all project doctors as well as for the PI (MDR / MPDG qualification was to be obtained through an 8-hour course); and a Risk management and signed insurance of basic safety & performance requirements were

requested by a legal person responsible for the manufacturing of the ADLIFE system. After assessing different alternatives, the German ADLIFE pilot site due to regulatory demands was not able to run the ADLIFE pilot as an interventional study in Germany as described in the ADLIFE study protocol v0.31. This situation has caused the number of pilots to be reduced from six to five.

3.1.1.2 Intervention time

Pilot sites using the ADLIFE platforms – Osakidetza, National Health Service Lanarkshire (NHS Lanarkshire) and University Hospitals Coventry And Warwickshire National Health Service Trust (UHCW) – have not started the ADLIFE intervention due to an extension of the deployment of the pilot application phases. For this reason, the patient follow-up has been shortened in pilot sites using the ADLIFE platform from nine/twelve to four months.

Meanwhile, two pilot sites – Odense University Hospital (OUH) and Assuta Ashdod Hospital-Maccabi Healthcare Services Southern Region (AMCA) – have started their intervention before the rest of pilot sites as they are using their own platforms.

3.1.2 Alternative evaluation plan

This section shows in detail the contingency plan designed to minimize the impact of the undergone modifications on the ADLIFE intervention described in previous section. The proposed measures have been included in the updated v31 of the research protocol.

3.1.2.1 Number of pilot sites

a) Original scenario

As defined in DoA, the total number of sites was seven, and the patients to be recruited were 846, 126 in six sites and 90 at one site. With this scenario, the evaluation was designed to measure the effect of the intervention by assessing by multilevel model[2] for longitudinal data, considering the clustered structure of the data. The pilot site of the patient was going to be included as a random effect to control the variability introduced by the differences between sites and to obtain generalizable results. All models were going to be adjusted by different time of follow-up of each participant, i.e., the time of follow up was planned to be included in the models as an extra covariable.

[2] Leyland AH, Groenewegen PP. *Multilevel Modelling for Public Health and Health Services Research: Health in Context*. Cham (CH): Springer; 2020.

b) Current scenario

As stated in previous section, the number of sites has decreased from seven to five. In this context, the multilevel models become prohibitive (i.e., the available number of clusters is insufficient, irrespectively their size), when:

$$k < N_1 \rho \qquad (1)$$

where k = number of clusters, N_1 = total sample size required under individual randomization, ρ = intraclass correlation[3].

Therefore, in this case the multilevel models that consider the site as a level (random effect) cannot be applied because equation (1) is not satisfied.

c) Alternative evaluation

Generalized mixed models will be used, including participants as a random effect. All models will be adjusted for site and other potentially confounding factors and variables of interest, i.e., the time of follow-up.

In addition, a stratified analysis can be performed to evaluate the intervention at each site. In the stratified analyses, sufficient statistical power can only be ensured in pilot sites recruiting at least 148 patients.

Sample size calculation: Accepting an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test, 148 subjects are necessary in the intervention group, and 148 in the control group, to recognize as statistically significant a difference greater than or equal to 0.6 units. The common standard deviation is assumed to be 1.2 and the correlation coefficient between the initial and final measurement as 0.06. It has been anticipated a drop-out rate of 20%.

3.1.2.2 Intervention time

a) Original scenario

As stated in the DoA, the estimated duration of the patients' follow-up was nine to twelve months (allowing for a time window to start from M36 to M38, ending on M47).

b) Current scenario

The extension in the deployment and integration tasks of the ADLIFE solutions in sites (Osakidetza, NHS Lanarkshire, UHCW) has caused a reduction in the patients' follow-up to four months (M45-M48). This shortening of the patient follow-up might imply a potential lack of statistically significant effect of the ADLIFE intervention. Evidence showing a statistically significant effect of advanced chronic diseases (heart failure) management programs on Emergency Department (E&D) visits in patients with severe conditions (heart failure NYHA III – IV) followed between 3 and 6 months has been found in a published meta-analysis in the literature[4]. This evidence might justify a remaining finding of an ADLIFE intervention

[3] Hemming, K., & Taljaard, M. (2016). Sample size calculations for stepped wedge and cluster randomised trials: a unified approach. Journal of clinical epidemiology, 69, 137–146. https://doi.org/10.1016/j.jclinepi.2015.08.015

[4] Oyanguren, J., García, P. M. L., Laguna, J. T., Goya, I. L., Martín, S. R., Lafuente, E. M., & Grandes, G. (2016). Efectividad y determinantes del éxito de los programas de atención a pacientes con insuficiencia cardiaca: revisión sistemática y metanálisis. Revista Española de Cardiología, 69(10), 900-914

statistically significant effect despite of its shorter patient follow-up after delaying the intervention start.

c) Alternative evaluation

The alternative evaluation design to overcome a potential lack of statistical significance of the ADLIFE intervention over a follow-up period of four months is addressed on the measurement of the primary outcome.

Following the DoA, the number of the E&D visits over the follow-up period - a quantitative variable -was defined as main primary outcome, and the effect of the intervention was intended to be assessed by generalized mixed models.

In the case of found a lack of statistical significance of the ADLIFE intervention in a follow-up period of eight months, two alternative measurements of the primary outcome will be considered consecutively to overcome this issue:

- The use of the E&D will be measured as a categorical binary variable equal to 0 when "patient has no E&D visits" and equal to 1 when "patient has at least 1 E&D visit" during the follow-up period. Using logistic regression models will allow estimating the ADLIFE effect on the probability of visit the E&D.
- Second, the use of the E&D will be measured as a time-to-event variable equal to the time in days elapsed from the baseline date to the first E&D visit that occurs. Using survival models, this approach of measurement will allow estimating the ADLIFE effect on the time to the first E&D visit that occurs.

3.2 Data collection guidelines

Four data collection guidelines have been designed and developed in order to conduct the data collection of each of the four assessments that comprise the ADLIFE evaluation.

3.2.1 Effectiveness assessment

In order to conduct the data collection for quantitative effectiveness assessment, three data collection templates and a data collection guide (DCG) have been developed and included as supplementary material in the research protocol.

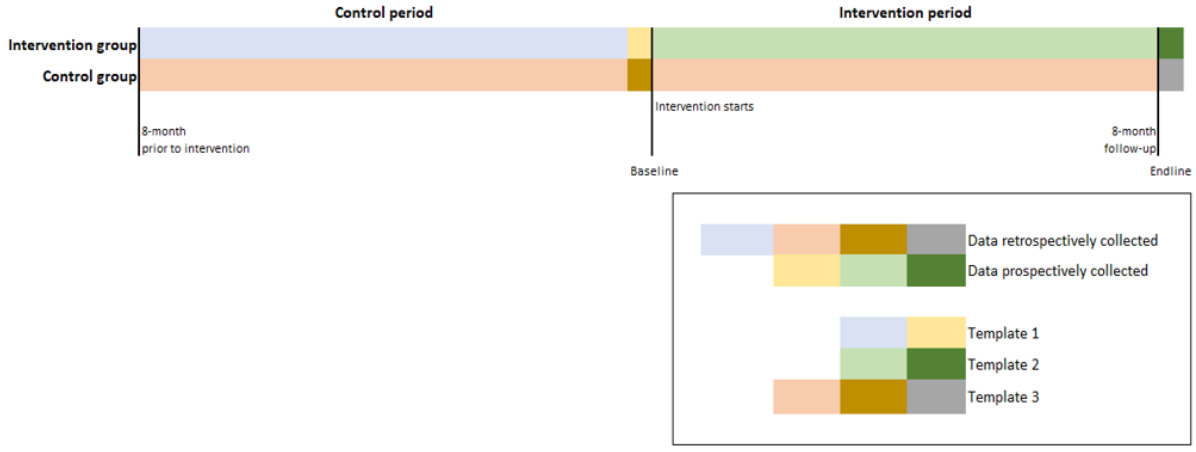


Figure 2 - ADLIFE evaluation approach

Three different data collection templates have been created to collect data from all pilot sites in the same format, following the study design and data collection flow described in Figure 2.

- Template 1 will be used to collect baseline and control period data from intervention group participants. Sites will be requested to share this information within the first four months after the beginning of the intervention and this data will be useful for preliminary assessments.
- Template 2 will be used to collect endline and intervention period data from intervention group participants at the end of the intervention.
- As the control individuals in this project do not sign informed consent and follow the SoC, all their data will be collected retrospectively. Moreover, some of the variables collected for the intervention patients will not be collected for them. Therefore, a specific data template (Template 3) has been designed to collect all data from the target control patient population at the end of the intervention.

For each pilot site, a folder with restricted access to the data manager and the evaluation team has been created in the project's SharePoint to upload the fulfilled data collection templates.

A DCG has been developed in order to guide pilot sites in the whole data collection and sharing process. It contains a detailed list of tasks (see Table 1) to be performed on the data collection process, together with a gantt-chart in which deadlines for each task are specified. All tasks in Table 1 are described in detail in the DCG and the Gantt-chart is complemented with the study design in Figure 2 for better comprehension.

Table 1: Tasks required to pilot sites in data collection process for effectiveness assessment

Task n.	Task
1	Identification of tentative target patient population
2	Identification of final target patient population
3	Intervention patients sign up on ADLIFE platform
4	Saving intervention participants
5	Identification of target control patient population (TCPP)
6	Baseline and control period of intervention participants data collection
7	Preliminary data cleaning process
8	Share data collected on task 6 with evaluation coordinator
9	Fulfil and share recruitment flowchart with evaluation coordinator
10	Endline and intervention period of intervention participants data collection
11	Control period and baseline + intervention period and endline of TCPP data collection
12	Data cleaning process
13	Anonymization of TCPP data (Template 3)
14	Health-related outcome log and Potentially Preventable Situations (PPSs) log data collection
15	Share data collected on tasks 10, 11 and 14 with evaluation coordinator

The codebook is also included in the DCG. The codebook contains the definition of the variables collected through the templates. It also contains information on the coding of the variables and on the data source from which to extract each data (FHIR repository or electronic health records (EHR)).

The DCG seeks to be self-contained and includes instructions to facilitate data managers the process of sharing data for ADLIFE's quantitative effectiveness assessment. DCG and data collection templates for quantitative effectiveness assessment are both available in Appendix B and Appendix C.

As the qualitative evaluation will take place at the end of the project, the DCG has not been developed yet. The main activity done over this period has been the identification and the definition of the main outcomes to be assessed by means of the qualitative methodology. This work has been worked together with WP10, as the interviews that will be performed at the end of the intervention will cover both perspectives.

3.2.2 Implementation assessment

A DCG has been developed for the qualitative implementation assessment. The aim of the DCG is to collect all questions for the qualitative implementation assessment to have a global vision of questions to be asked (pre and post assessment).

The DCG is structured as follows:

- Framework dimension (dimensions of the framework for implementation research: Intervention, Process, Organization, Technology, Human, Outer-setting, Net Benefits, Working conditions, ADLIFE) and the respective subcategories.
- Objective of the implementation assessment (exploitation, usability and technology acceptance, evaluation)
- Outcomes designed for the pre-implementation assessment of contextual factors (e.g., technological, human and organizational factors).
- Based on the framework, a semi-structured interview guideline was developed to be applied in pre-implementation interviews at the pilot sites to identify the contextual factors that can be relevant for the translation of the innovation action into practice.

The DCG is currently already used for the pre-interviews of contextual factors. The assessment takes place before the implementation of the ADLIFE toolbox within the context of Task 10.2. Following this assessment, the DCG will be reviewed again to check if still all questions included are needed for the post assessment, aiming to reduce the number of questions and thus the burden for the participants. The current version of the DCG for implementation assessment is available in 133Appendix D.

3.2.3 Technology acceptance and adoption assessment

A DCG has been developed for the pilot site administrators, who are responsible for communicating to the study participants for the completion of the evaluation questionnaire (Unified Theory of Acceptance and Use of Technology - UTAUT) at the required time during the intervention. Two groups of participants are involved: healthcare professionals, who will use the ADLIFE platform for collaborative care planning; and patients and their informal caregivers, who will use the ADLIFE platform for self-management according to their care plan. The evaluation takes into account two groups of pilot sites: 1) pilot sites deploying the ADLIFE Toolbox where participants will be asked to complete the UTAUT questionnaire at two time points, a quarter and three-quarters of the way into the intervention, and 2) pilot sites using their own systems where participants will be asked to complete the UTAUT questionnaire halfway through the intervention. DCG for technology acceptance and adoption is available in Appendix F.

3.2.4 Socio-economic impact assessment

In order to conduct the data collection for socioeconomic assessment, three data collection templates and a DCG have been developed and included as supplementary material in the

research protocol. This DCG was designed and shared with the pilot sites and it is intended to collect information on unit cost and drug prescription cost to adapt the general simulation model for all pilot sites. The DCG contains comprehensive information of the tasks, data collection templates content and deadlines. In Table 2 there is a summary and timeline of the main activities.

Table 2: Tasks and timeline for the socio-economic data collection process

Task n.	Task	Jan-24 (M48)
1	Collect and send unit cost data to evaluation coordinator	
2	Collect and send intervention patients drug prescription cost data to evaluation coordinator	
3	Collect and send control patients drug prescription cost data co evaluation coordinator	

Three data collection templates have been created to collect data from pilot sites. The templates will allow the information to be collected in a homogeneous way. In this sense, the DCG includes also a codebook, which contains an exact definition of the variables collected through the templates, as well as the coding and type of those variables. The information that each template will collect and when is detailed below:

- Unit cost: the information requested in this template regards the unit costs that works in each pilot site. Unit cost information about primary care doctor, primary care nurse, outpatient services, emergency room and hospitalisation will be collected. This information is necessary to adapt the general simulation model to each pilot site. This data collection will start on M47 and official health service sources will be used.
- Control patient drug prescription cost: this template contains the requested information regarding the control patient's drug prescription cost. The total drug prescription cost that each control patient has during the trial will be collected. This data collection will take place the end of the project and EHR will be used.
- Intervention patient drug prescription: this template shows the requested information regarding the intervention patient's drug prescription cost. The total drug prescription cost that each intervention patient has during the trial will be collected. This data collection will take place the end of the project and EHR will be used.

DCG and templates for socioeconomic assessment are available in Appendix G.

3.3 Current status

3.3.1 Effectiveness assessment

Regarding the effectiveness quantitative evaluation, DCG and templates were shared with pilot sites for internal discussion and planning a data collection workflow.

Two pilot sites, OUH and AMCA, started their intervention in M39 and have already started their data collection, nevertheless they are not expected to share baseline and control period data from their intervention participants until M45. Their recruitment period will take place either until they reach their required sample size or the recruitment period of the rest of sites is reached. OUH and AMCA have so far recruited 35 and 68 patients, respectively.

Regarding tasks listed in Table 1, pilot sites have already identified their tentative patient population in their EHR (Task 1). Only health professionals in OUH and AMCA have conducted the whole checking process to identify their final target patient population (Task 2), as this task has been postponed until the months strictly before the beginning of the intervention in most pilot sites. Tasks 3 and 4 are partially performed in AMCA and OUH, as they have started their recruitment. The status of previous tasks is summarised and monitored in Table 3.

Table 3: Status of tasks defined in DCG for quantitative effectiveness assessment in each pilot site

Task n.	Task	Osakidetza	NHS Lanarshire	UHCW	OUH	AMCA
1	Identification of tentative target patient population	Done	Done	Done	Done	Done
2	Identification of final target patient population				Done	Done
3	Intervention patients sign up on ADLIFE platform				In progress	In progress
4	Saving intervention participants				In progress	In progress

Regarding the effectiveness qualitative evaluation, the work carried on during these months has been focused on the identification and description of the outcomes to be qualitatively assessed. The outcomes for the qualitative effectiveness evaluation have been defined as follows: satisfaction with the platforms / usefulness, quality of care (integrating process, structure and outcome related variables), barriers and facilitators of the implementation, communication, satisfaction with accessibility, security and coordination. Then, they were shared with the rest of the partners for internal discussion and agreement. Once the outcomes were defined, questions to be formulated to the stakeholders were drafted. As both effectiveness and implementation assessments are considered in this WP9, most of the work have been done in collaboration with WP10.

3.3.2 Implementation assessment

The aim of the DCG that has been developed for the implementation assessment is to have a global vision of the methodology to be followed and the questions to be asked. After having collected all questions, as it has been described in the previous section, they were reconciled to reduce the number of questions and thus the burden for respondents. The following participants will be involved in the implementation assessment: patients, caregivers, healthcare professionals, managers and IT staff.

After having designed the DCG, the pre-implementation interviews were performed. The main aim for the implementation assessment was to define the requirements of implementation for further exploitation to later scaling-up and to identify organizational, technological, and human factors that influence the implementation of the ADLIFE toolbox are relevant for the translation of the innovation action into practice. For this, a qualitative assessment of contextual factors

at all pilot site has been conducted, as part of the implementation assessment (related to T10.2). As of M40, pilot sites completed the interviews and the analysis (Denmark, Germany, Israel, Spain, Sweden). Hence, data from 52 persons is available. Due to additional ethical requirements to conduct interviews, the two pilot sites from the UK are still outstanding to complete this task.

Initial feedback from the pilot sites showed that the analysis of local technical, organizational and human factors was very useful and provided a good insight on possible technical challenges, the need for change management processes and the requirement to involve service providers at all levels and to integrate new processes into everyday work.

3.3.3 Technology acceptance and adoption assessment

The evaluation framework and planning have been developed in this period. The DCG has also been developed and shared with the pilot site administrators. As the UoB team is leading this evaluation, the ethical considerations have been assessed by the UoB research ethics committee, with agreement to use the local pilot site ethical approvals.

The UTAUT questionnaires have been prepared and shared with the pilot sites for review. Translations have also been completed by pilot sites from English to Danish, German, Hebrew, Russian and Spanish. The questionnaires with the relevant translations have been developed on the Qualtrics software for the online administration. Pilot sites have reviewed the draft online questionnaires and feedback is currently being addressed.

3.3.4 Socio-economic impact assessment

To develop a common general simulation model for all pilot sites and then adapt it for each pilot site situation the steps described in Table 4 are to be followed. During this period, the first three steps have been addressed.

Table 4: Main steps and timeline of the Task 9.4.

Steps	Period
1) Describe the natural history of the disease and the conceptual model of patients with ACD	M25-M30
2) Collect the necessary data and obtain simulation parameters to populate the model	M25-M30
3) Development and validation of the simulation model for the current epidemiological scenario using DES	M31-M48
4) Adapt the simulation model to each pilot site context	M47-M49
5) Estimation of the impact of the intervention using data gathered in the trial	M43-M54
6) Obtain the long-term economic results to assess the sustainability of the ADLIFE project in time	M43-M54

3.3.4.1 Natural history of the disease and conceptual model

The natural history of the disease was defined, with the help of experts, to clarify the different stages and resource use needs that patients with ACDs can have. The natural history is understood as the course of the natural evolution of the disease in the population under study, considering the long-term effects that exposure can cause. In the case of patients with ACD, which usually suffer from more than one chronic disease, the natural history of the disease is characterised by frequent transitions between stable and unstable states over time[5]. During the stable state, patients usually remain at home and are followed by primary care professionals. However, when they become decompensated require additional and more specialised attention, being typically referred to hospital care. Once patients are under hospital care, they are not discharged back to their residence until their conditions are re-stabilized. This is a process that is repeated until the end of the patient's life (see Figure 3).

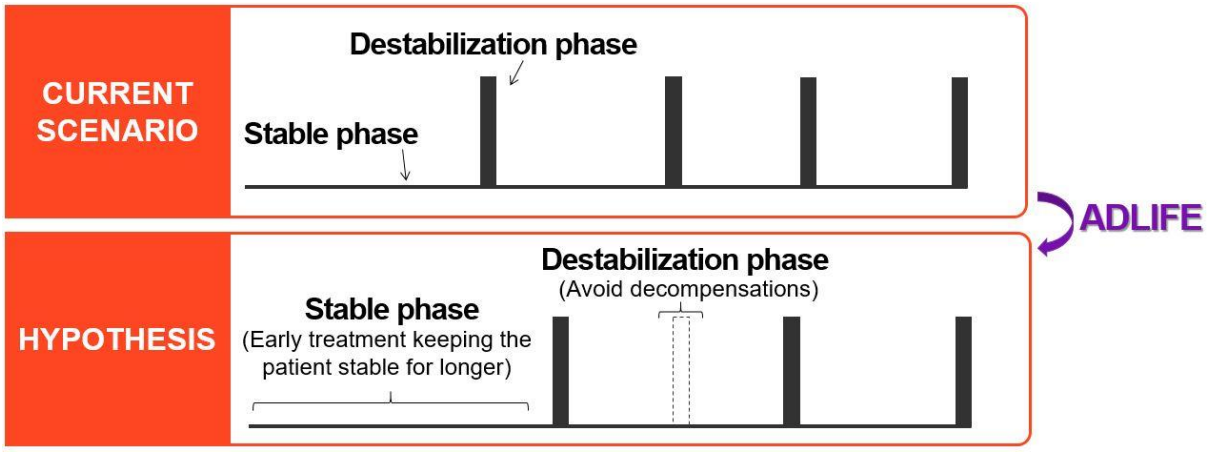


Figure 3 - Natural history of the disease of patients with ACDs

All this generates the need to organise the care around the patient and not around the disease[6,7]. Consequently, the clinical management of this type of patients is much more complex and time-consuming[8], where the poly-pharmacy induced is also an important factor that leads to a significant cost for the healthcare system. In this sense, the challenge face by ADLIFE is to support and improve the quality of life of patients with advanced chronic diseases by providing personalised dedicated integrated care. The hypothesis is that a patient-centred care base on early detection will control and reduce their destabilization phases, making a reduction in the use of most expensive hospital resources like ambulatory & emergency (A&E) services and/or hospitalisation.

On this basis, the conceptual model used for ADLIFE needs to represent the natural history of the disease as a dynamic process characterized by frequent transitions to decompensation

[5] Gill TM, Gahbauer EA, Allore HG, Han L. Transitions between frailty states among community-living older persons. Arch Intern Med. 2006;166:418-23

[6] Managing multi-morbidity in practice… what lessons can be learnt from the care of people with COPD and co-morbidities? Leicester: NHS Improvement; 2013

[7] Haque R. ARMOR: a tool to evaluate polypharmacy in elderly persons. Annals of Long-Term Care. 2009;17

[8] Tong B, Stevenson C. Comorbidity of cardiovascular disease, diabetes and chronic kidney disease in Australia. Canberra: Australian Institute of Health and Welfare; 2007 p. 80

states over time. Because of that, the natural history was divided into stable and destabilization states. Figure 4 shows the conceptual model that was defined, which includes all the possible pathways and contacts that patients can have. During the stable state phase patients are mainly cared by primary care (PC) professionals. In this state contacts with PC nurses and GPs at the health-care centre, at home or by telephone were counted. When patients become decompensated require additional attention, so they are referred to hospital care. During the destabilization phase, contacts with outpatient services, A&E services and hospitalisation were taken into account. Finally, patient's drug consumption and mortality was also taken into account throughout all the process.

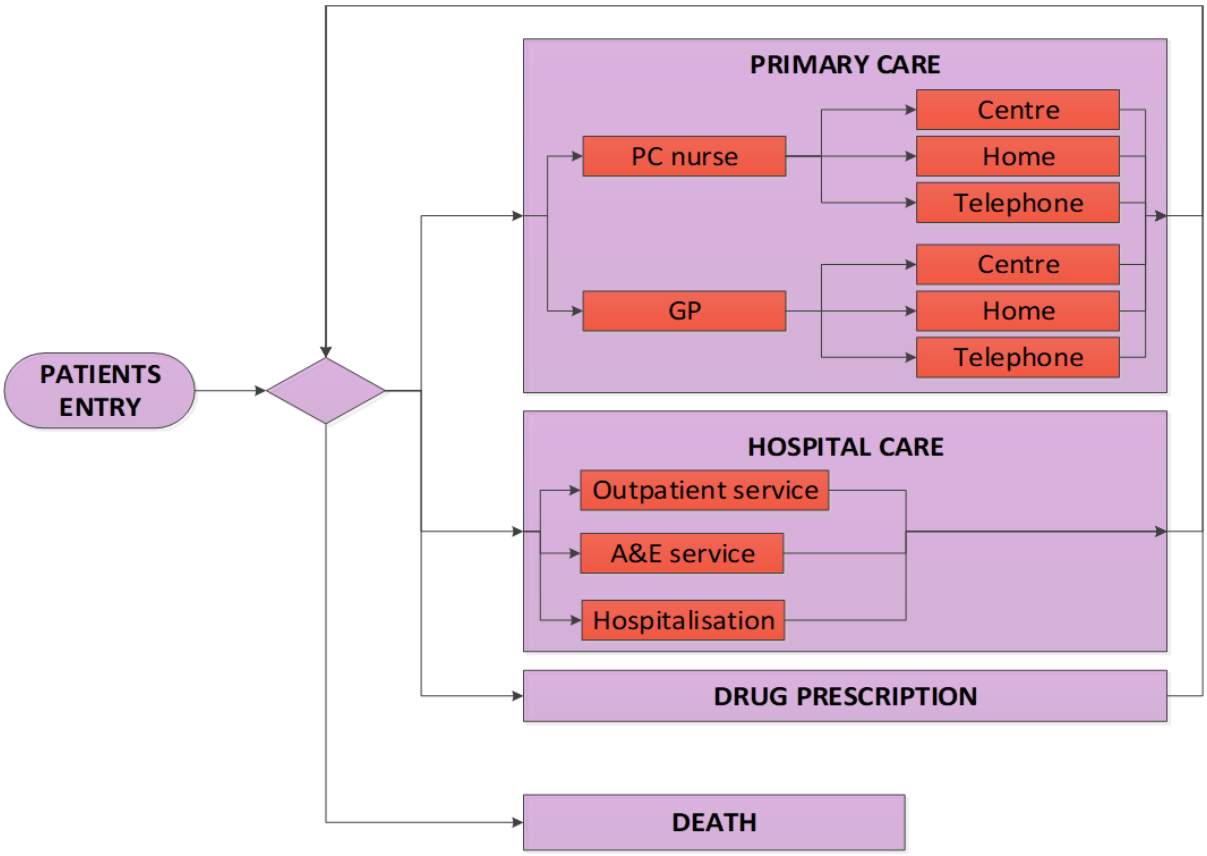


Figure 4 - Conceptual model of the disease of patients with ACDs.

3.3.4.2 Data collection

Accessible healthcare databases were employed to gather necessary data of the population under study, in order to calculate the mathematical functions and simulation parameters that allows to reproduce the natural history of the disease. In this case, the administrative and clinical databases of the Basque Health Service were used, because they were accessible and contain patient-level data in an anonymised way. The target population defined in ADLIFE project to identify patients with advanced chronic conditions followed the next inclusion criteria: patients over 55 years old, with HF (NYHA III-IV or ACCF/AHA C-D) and/or COPD (FEV1<50 or GOLD>2) and with or without comorbidities (diabetes, chronic renal failure, chronic hepatopathy, stroke and mild cognitive disorder). Presence of active malignant neoplastic disease and/or inclusion in the active list of transplantation were considered as exclusion criteria. In this sense, the population information that was obtained from Basque Health Service databases and used to develop the simulation model was in line with the specifications used to define the target population of ADLIFE project. To identify patients with HF and COPD, codes from ninth and tenth revision of the international classifications of diseases (ICD-9 and

ICD-10) were used. On one hand, for HF 428.*, 401, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93 ICD-9 and I50.*, I11.0, I13.0, I13.2, I13.9 ICD-10 codes were used. On the other hand, for COPD 492.* ICD-9 and J44.* ICD-10 codes were used.

The information to be extracted from the Basque Health Service databases included demographic, epidemiological and resource consumption data. Demographic patient-level data was composed by age, sex, vital status (alive/dead), Charlson index, date of birth, date of death, diagnoses and date of diagnoses. The resource consumption that was collected from EHR in primary care included contacts with PC nurses and general practitioners (GP) at healthcare centre, at home or by telephone. In hospital care, contacts with different specialities (cardiology, endocrinology, internal medicine, nephrology, neurology, psychiatry and respiratory) were taken into account. Besides, the contacts with outpatient services, contacts with A&E services and hospitalisations were also collected. The drugs prescribed to patients were considered too. The unit cost data of the different healthcare resources was obtained from the accounting system of Basque Health Service for the year 2019 in euros (EUR €) and is available in Appendix H.1. Finally, the population projections were obtained from the Basque Statistics Institute (EUSTAT).

Table 5: Descriptive analysis of the target population

Variable		N	%
Patients		104,500	
Sex	Women	49,510	47%
	Men	54,990	53%
Age	Mean	76.26 (11.19)	
	55-59 years	11,039	11%
	60-64 years	8,226	8%
	65-69 years	10,040	10%
	70-74 years	12,735	12%
	75-79 years	15,549	15%
	80-84 years	19,102	18%
	85-89 years	17,238	16%
	90-94 years	8,757	8%
	≥95 years	1,814	2%
Comorbidities	Heart failure	78,340	75%
	COPD	27,764	27%
Charlson index	Mean	2.97 (2.13)	
	1-2 comorbidities	55,839	53%
	3-4 comorbidities	30,779	29%
	≥5 comorbidities	17,882	17%

As can be seen in Table 5, from Basque Health Service databases 104,500 patients were identified from 2012 to 2019. The target population had on average around 76 years and 3 comorbidities. They were identified more patients with HF that meets the criteria than with COPD.

3.3.4.3 General simulation model development

In order to achieve a general simulation model that represents the evolution and care pathways of patients involved in ADLIFE project in a dynamic way, discrete event simulation (DES) technique was used. DES is a flexible modelling method that can represent complex behaviours and interactions between different individuals, levels and environments[9,10]. In the development process first the simulation parameters were obtained to later built up and validate the simulation model.

3.3.4.3.1 Simulation parameters

All the simulation parameters obtained to populate the model were calculated using the data collected from the Basque Health Service databases and all the statistical analyses were performed in Stata (version 14) or R (version 4.0.1).

From one hand, the prevalence and the incidence of patients with ACDs were obtained by sex and age group from 2012 to 2019. The cut-off was place in 2019 in order to avoid the COVID-19 effect in the resource use profile. Patients who were eligible to take part on ADLIFE before 2012 were considered as prevalent cohort and entered in the model from the start of the simulation. Patients who were eligible for ADLIFE in the years after, according to data observed from 2012 to 2019, constituted incident cohorts and were gradually introduced in the model. New patients who will become eligible for ADLIFE in the future were also gradually introduced in the model extrapolating the incidence from 2020 to 2030 according to the population forecast. All the input parameters are shown in Appendix H.2.

From the other hand, logistic regressions were used to obtain the simulation parameters needed to assign HF and/or COPD conditions to individuals according to sex and age group. As patients with ACDs can be subjected to mutually dependent chronic diseases, these conditions were taken into account in a consistent way[11]. Similarly, logistic regressions were used to obtain the simulation parameters needed to assign the Charlson group according to age, sex and diseases. The parameters of different logistic regressions used are shown in the Appendix H.3.

Finally, the mathematical functions that rule the simulation model, which define the times until different events occurrence or contacts with healthcare resources, were obtained developing a parametric survival analysis of the data. In the analysis different distributions were tested as

[9] Karnon J, Stahl J, Brennan A, Caro JJ, Mar J, Moller J. Modeling using discrete event simulation: a report of the ISPOR-SMDM modeling good research practices task force-4. Value Health. 2012;15:821-7

[10] Gunal MM. A guide for building hospital simulation models. Health Syst. 2012;1:17-25

[11] Hoogenveen RT, Boshuizen HC, Engelfriet PM, van Baal PHM. You only die once: accounting for multi-attributable mortality risks in multi-disease models for health-economic analyses. Med Decis Making. 2017;37:403-14

survival functions: exponential, generalized gamma, log-logistic, Weibull, Gompertz and lognormal. All functions were adjusted by independent variables (sex, age group, diseases and Charlson group). The type of function that best fit with the observed data was selected using the statistical Akaike Information Criteria (AIC)[12,13]. After that, the resultant mathematical functions were used to determine the time until the event occurrence according to the selected characteristics (sex, age group, diseases and Charlson group). The distributions used to obtain time until event functions and their parameters are shown in the Appendix H.4. As can be seen, Gompertz and Weibull distributions were selected to model time to event functions and can be expressed with the formulas below[14].

$$Time\ to\ event\ (Gompertz) = \frac{1}{\beta} * ln(1 - \frac{\beta}{HR\ *\ \alpha} * l\,n(1-u))$$

$$Time\ to\ event\ (Weibull) = (-\frac{1}{HR * \alpha} \times ln(1-u))^{\frac{1}{\beta}}$$

Where:

$$ln(\alpha) = x_0 + x_1 * sex + x_2 * age\ group + x_3 * hf + x_4 * copd + x_5 * Charlson\ group$$

The equations included a uniformly distributed random factor between 0 and 1 (u) and two parameters α and β that defined the characteristics of the distribution. The hazard ratio (HR) is used to incorporate intervention effect into the model, but this parameter will only be used in the model once the effect of ADLIFE intervention is calculated at the end of the trial.

3.3.4.3.2 Simulation model

A dynamic multi-cohort model was built using the software Arena®, a simulation tool property of Rockwell Automation[15,16]. The rate at which individuals entered into the simulation model was determined by the prevalence and the incidence numbers obtained for each year. When they first entered in the model their characteristics or personal attributes (sex, age group, diseases and Charlson group) were assigned, as well as uniformly distributed random factors between 0 and 1 that made each individual's life course different. These random numbers were the ones that generated different times for individuals with same characteristics in the process of assigning time until event.

As stated before, to develop the model DES technique was used. DES models require considering time in an explicit way. The rationale is that the natural history of the disease is converted into events that can occur in the life course of an individual and the time until those events is calculated. Subsequently, for all the competing risks presented in Figure 4, a list of

[12] Kleinbaum DG, Klein M. Survival Analysis: a self learning text. New York: Springer Science; 2012. 718 p

[13] Latimer NR. Survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data: inconsistencies, limitations, and a practical guide. Med Decis Making. 2013;33:743-54

[14] Román R, Comas M, Hoffmeister L, Castells X. Determining the lifetime density function using a continuous approach. J Epidemiol Community Health. 2007;61:923-5

[15] Hoyle M, Anderson R. Whose costs and benefits? Why economic evaluations should simulate both prevalent and all future incident patient cohorts. Med Decis Making. 2010;30:426-37

[16] Ethgen O, Standaert B. Population - Versus cohort-based modelling approaches. Pharmacoeconomics. 2012;30:171-81

future events that the individual will go through was generated according to different characteristics (sex, age group, diseases and Charlson index). The event that will occur first was determined according to which was the closest in time. After that, the time to event for that event was recalculated and the event that will occur next was determined again according to which was the closest in time. This process was repeated until the patient left the model by death or the time horizon of the simulation reached its end. Individuals alive or without an event at the end of the study period were categorized as survivors, i.e., as a censored data. According to competing risks presented in Figure 4, the list of future events that the individual will go through was the following:

- If the shortest time is time until death or the time horizon of the simulation reaches its end, the patient will left the model.
- If the shortest time is time until contact with PC nurse or GP at centre, at home or by telephone, the respective contact will be counted. After the contact occurrence, the time to event for the next contact with PC nurse or GP will be recalculated and assigned to patients according to their characteristics.
- If the shortest time is time until contact with outpatient services, the visit with the respective specialist will be counted. After the contact occurrence, the time to event for the next contact with outpatient services will be recalculated and assigned to patients according to their characteristics.
- If the shortest time is time until contact with A&E services, the respective contact will be counted. After the contact occurrence, the time to event for the next contact with A&E services will be recalculated and assigned to patients according to their characteristics.
- If the shortest time is time until contact with hospitalisation, the respective contact will be counted. After the contact occurrence, the time to event for the next contact with hospitalisation will be recalculated and assigned to patients according to their characteristics.

3.3.4.3.3 Validation

Once the model construction was finished, the validation process started. The validation is a set of methods used to measure with which accuracy a model makes predictions[17]. In this case, the model was validated comparing the simulated event rates with the observed ones from the year 2012 to 2019. The objective was to assure that the simulation model properly reproduced the current epidemiological scenario. For that purpose, a goodness of fit test was conducted with the following statistics[18]: the correlation coefficient (R), normalized mean square error (NMSE), fractional bias (FB), fractional variance (FV) and the fraction of predictions within a factor of two (FAC2). To validate a model, the correlation coefficient and the factor of two must be higher than 0.8, the normalized mean squared error must be lower

[17] Eddy DM, Hollingworth W, Caro JJ, Tsevat J, McDonald KM, Wong JB. Model transparency and validation: a report of the ISPOR-SMDM modeling good research practices task force-7. Med Decis Making. 2012;32:733-43

[18] Chang JC, Hanna SR. Technical Descriptions and User's Guide for the BOOT Statistical Model Evaluation Software Package, Version 2.0. Cairo: Hindawi Publishing Corporation; 2005

than 0.5 and the fractional bias and the fractional variance must be between -0.5 and 0.5. The goodness of fit test carried out is available in Appendix H.5 0.

3.4 Next steps

WP9 will evaluate the intervention for all pilot sites in terms of effectiveness, implementation, technology acceptance and adoption and socio-economic impact, as specified in the research protocol. Particularly, since GWMK will not run the ADLIFE pilot as an interventional study in Germany, then an observational study will be conducted, which is currently being designed. Once the intervention of this pilot site is fully defined, WP9 will design an appropriate evaluation plan for the German pilot site. Evaluation results will be reported in deliverable D9.2 Final evaluation report in M54. The next steps by assessment approach are detailed below.

3.4.1 Effectiveness assessment

Osakidetza, NHS Lanarkshire and UHCW will start their ADLIFE intervention in M45. Then, all pilot sites will conduct data collection for quantitative effectiveness assessment according to the steps detailed in Table 1 and more in detailed in the DCG.

Two new relevant aspects will be discussed and incorporated in the effectiveness evaluation: 1) the fact that two pilots (OUH and AMCA) use their own platforms instead of the ADLIFE platforms; and 2) the fact that these same pilots have started the intervention before the rest. To overcome the first issue, OUH and AMCA have been asked to fully describe their intervention to define similarities and differences between their intervention and ADLIFE intervention. Different approaches will be discussed in order to overcome both issues.

As for the qualitative effectiveness evaluation, the next steps will be: 1) to share, discuss and agree with all pilot sites the questions for the interviews; and 2) to develop a methodological framework to perform the interviews and analyse the subsequent results.

3.4.2 Implementation assessment

Once all pre-interviews have been completed and the data from the qualitative analysis is available, a cross-national analysis will be conducted to better understand the local technical, human and organizational contextual factors across the pilot sites and to identify factors that are relevant for a successful implementation of the ADLIFE toolbox.

Following the pre-assessment, a post-assessment on contextual factors will be conducted after completion of the pilot test in M48. For this, the already defined interview questions will be reviewed again, and amended if needed. The results will be compared with the results of the pre-assessment to get a complete picture on the contextual factors and recommendations for action for the further implementation of the toolbox will be derived.

3.4.3 Technology acceptance and adoption assessment

The questionnaires will be finalised and links to the questionnaires will be shared with the pilot site administrators in M42. Based on the data collection guideline schedule, requests for questionnaire completion will be sent to participants. Questionnaire responses will be collected and analysed to assess the future intention of participants to use ADLIFE, should such a platform be available to use in regular clinical practice.

UTAUT aims at explaining user intention towards the application of a new technology and the resulting user behaviour. UTAUT will be used to assess the likelihood of successful adoption and use of the ADLIFE tools. The main objectives are to determine factors of performance

expectancy, effort expectancy, social influence, cultural and language influence, adoption timeline and associated facilitating conditions on the intended adoption behaviour of the users of the ADLIFE technology. We will also look at gender, age, experience and usability aspects as modifying factors for technology acceptance.

Questionnaire data will be exported from Qualtrics to a statistical software package, such as STATA. Descriptive statistics will be used to summarise the participants' demographics and core set of constructs. To measure the reliability of the model's constructs and form correlations between then, data analysis will be done using technique such as structural equation modelling, a multivariate statistical analysis technique that is used to analyse structural relationships and tests the underlying factors and hypotheses. The questionnaire has an open-ended question at the end for participants to express their opinions, concerns or give suggestions. Depending on the quality of responses, some qualitative data analysis will be done to identify themes and related comments.

3.4.4 Socio-economic impact assessment

Although the first version of the DES model is complete and functional, there are still some issues to refine and improve. First, to estimate the simulation parameters to assign the pharmacy costs using a linear regression (M43-M48). Second, to share the templates to collect the information requested in the DCG in order to adapt the general simulation model to each pilot site (M47-M49). After refining the general simulation model, the next step will be to calculate the ADLIFE socioeconomic impact measured as the change in the resource use profile on patients (M43-M54). Finally, an assessment of the medium-long term ADLIFE socioeconomic impact will be estimated (M43-M54). The cost of the disease for current and ADLIFE scenario will be obtained multiplying the resource consumption by the unit costs obtained from each pilot sites. The resource consumption and costs of both scenarios will be then projected in time considering the previously obtained projections and aging population. Therefore, the burden of the disease will be determined under both scenarios and a budget impact analysis can be carried out.

4 Evaluation of risk prediction models

Clinical prediction models (CPM) are increasingly used to complement clinical reasoning and decision-making in modern medicine. To these ends, developed models first and foremost need to provide accurate and (internally and externally) validated estimates of probabilities of specific health conditions or outcomes in the targeted individuals. Subsequently, the adoption of such models by professionals must guide their decision-making, and improve patient outcomes and the cost-effectiveness of care.

Prediction modelling research may distinguish three major phases including: (1) developing and internally validating a prediction model; (2) testing in, and if necessary, adjusting or updating the model for other individuals (external validation); (3) assessing the model's impact on therapeutic management and patient outcomes. To show that a prediction model successfully predicts the outcome of interest in the development sample even when complemented with internal validation techniques, is not sufficient to confirm that a model is valuable. Indeed, when applied to new individuals, the performance of prediction models is generally lower than the performance observed in the population from which the model was developed. Therefore, performance of developed and internally validated prediction models should still be tested or validated in new individuals before they are implemented in guidelines or applied in practice.

CPMs are powerful tools which provide estimates of patient outcome data. A CPM can be constructed by means of a statistical method or a machine learning approach in a dataset containing information of a sample of eligible patients. They include a set of covariates (predictors) used to obtain the absolute probability or risk that a certain event is present or will occur within a specific time period. As previously noted, CPMs are developed to guide healthcare professionals in their decision-making process.

Under this setting, WP5 leaders have developed Artificial intelligence (AI) derived algorithms to prevent the following unwanted outcomes or Potentially Preventable Situations (PPSs): Dependency, Depression, Hypotension, Malnutrition, Readmission and Avoidable admission. All of them have been developed using data from Osakidetza EHR. In the previously submitted Deliverable 5.2, the section “6.3. Data description and quality assessment” contains the information about the data used to generalize the models.

After having developed the CPMs under the leadership of the WP5, their performances are evaluated and presented in this deliverable. The rest of the content of this section will be organized based on the following structure: first of all, theoretical explanations of the metrics used for AI model evaluation are given. After that, PPS evaluation results will be displayed, according to the aforementioned metrics, explainability and missingness regarding to the featured involved in the models. Then, findings about the retraining of the models in the AMCA data set will be reported. Finally, some aspects about Federated Learning will be described.

4.1 Model evaluation procedures and metrics

As all the assessed PPS risk models are considered binary classification problems, the relevant quantities for calculating the metrics for a binary classifier are the four entries in the confusion matrix (defined as a cross table composed of predicted classes and observed categories, see Table 6), which are the following:

- **True positive (TP):** The true positive denotes the number of correctly classified positive samples.
- **True negative (TN):** The true negative denotes the number of correctly classified negative samples.

- **False positive (FP):** The false positive denotes the number of samples incorrectly classified as positive.
- **False negative (FN):** The false negatives denote the number of samples incorrectly classified as negative.

Table 6: Contingency table

		Observed event	
		Positive	Negative
Prediction (PPS)	Positive	TP	FP
	Negative	FN	TN

Given these aforementioned variables, we will define the next metrics used to evaluate the PPS models:

Accuracy (ACC). The accuracy is the ratio between the correctly classified samples and the total number of samples in the evaluation dataset. This metric is among the most commonly used in applications of Machine Learning (ML) in medicine, but is also known for being misleading in the case of different class proportions since simply assigning all samples to the prevalent class is an easy way of achieving high accuracy. The accuracy is bounded to [0, 1], where 1 represents predicting all positive and negative samples correctly, and 0 represents predicting none of the positive or negative samples correctly. Its formula:

$$\mathrm{ACC} = \frac{\mathrm{TN} + \mathrm{TP}}{\mathrm{TN} + \mathrm{TP} + \mathrm{FP} + \mathrm{FN}}$$

Recall (REC). The recall, also known as the sensitivity or True Positive Rate (TPR), denotes the rate of positive samples correctly classified, and is calculated as the ratio between correctly classified positive samples and all samples assigned to the positive class. The recall is bounded to [0, 1], where 1 represents perfectly predicting the positive class, and 0 represents incorrect prediction of all positive class samples. This metric is also regarded as being among the most important for medical studies, since it is desired to miss as few positive instances as possible, which translates to a high recall. Mathematically:

$$\mathrm{Recall} = \frac{\mathrm{TP}}{\mathrm{TP} + \mathrm{FN}}$$

Specificity (SPEC): The specificity is the negative class version of the recall (sensitivity) and denotes the rate of negative samples correctly classified. It is calculated as the ratio between correctly classified negative samples and all samples classified as negative. The specificity is

bounded to [0, 1], where 1 represents perfectly predicting the negative class, and 0 represents incorrect prediction of all negative class samples.

$$\text{Specificity} = \frac{\text{TN}}{\text{TN} + \text{FP}}$$

Precision (PREC): The precision denotes the proportion of the retrieved samples which are relevant and is calculated as the ratio between correctly classified samples and all samples assigned to that class. The precision is bounded to [0, 1], where 1 represents all samples in the class correctly predicted, and 0 represents no correct predictions in the class.

$$\text{Precision} = \frac{\text{TC}}{\text{TC} + \text{FC}}$$

In this formula, C denotes “class”, and in binary classification models can be either positive (P) or negative (N). In this case, we will have two precision indicators: Precision positive value and precision negative value. The positive case of precision is often referred to as the Positive Predictive Value (PPV) and the negative case is often referred to as the Negative Predictive Value (NPV). Specifically, the PPV is the ratio between correctly classified positive samples and all samples classified as positive, and equals the precision for the positive class.

$$\text{PPV} = \frac{\text{TP}}{\text{TP} + \text{FP}}$$

$$\text{NPV} = \frac{\text{TN}}{\text{TN} + \text{FN}}$$

F1 score (F1): The F1 score is the harmonic mean of precision and recall, meaning that it penalizes extreme values of either. This metric is not symmetric between the classes, i.e., it depends on which class is defined as positive and negative. For example, in the case of a large positive class and a classifier biased towards this majority, the F1 score, being proportional to TP, would be high. Redefining the class labels so that the negative class is the majority and the classifier is biased towards the negative class would result in a low F1 score, although neither the data nor the relative class distribution has changed. The F1-score is bounded to [0, 1], where 1 represents maximum precision and recall values and 0 represents zero precision and/or recall.

$$\text{F1} = \frac{2 \times \text{TP}}{2 \times \text{TP} + \text{FP} + \text{FN}}$$

Area Under Curve (AUC): Area under Curve (AUC) or Receiver operating characteristic (ROC) curve is used to evaluate and compare the performance of binary classification model.

AUC is a plot of the proportion of true positives versus the proportion of false positives at different probability cut off points. Recall is on Y-axis and (1-Specificity) is on X-axis. Higher the AUC score, better the model.

4.2 PPS evaluation results

4.2.1 Performance metrics

Recurrent Neural Networks (RNN), more precisely Long-Short Term Memory (LSTM), have been applied for the PPS modelling. The results derived from the metrics used in each of the predictive models developed are reflected in Table 7.

Table 7: Performance metrics results of the potentially preventable situations (PPS) models

	AUC	Precision		Recall		F1-score		ACC
		Negative	Positive	Negative	Positive	Negative	Positive	
Dependency	0.68	0.61	0.65	0.7	0.56	0.65	0.6	0.63
Depression	0.96	0.94	0.86	0.85	0.95	0.89	0.9	0.9
Hypotension	0.67	0.62	0.61	0.58	0.65	0.6	0.63	0.62
Malnutrition	0.70	0.61	0.68	0.76	0.52	0.68	0.59	0.64
Readmission	0.69	0.85	0.33	1	0.01	0.92	0.02	0.85
Avoidable admission	0.65	0.6	0.63	0.68	0.54	0.64	0.58	0.61

Firstly, for the prediction of the positive class, it is observed that the PPV is around 0.65, with the exception of the risk model for depression (0.86) and readmission (0.33). As for sensitivity (recall), its values ranged from 0.31 (readmission) to 0.95 (depression).

Regarding negative prediction, negative PPV (i.e. NPV), all values were around 0.62 (hypotension, malnutrition, avoidable admission) while for depression the NPV was 0.95. As for negative recall, all were higher than 0.58.

The F1 score was higher in negative than in positive cases. Finally, the AUC ranged between 0.645 (avoidable admission) and depression (0.94).

4.2.2 Explainability

Interpretability in Machine Learning refers to the ability of a model to be understood, allowing people to comprehend the reasoning behind its predictions. This is where the concept of explainability is discussed.

Explainability involves using different methods to interpret the functioning of the model and understand how, given an input, the output is obtained. Explainability is not always a requirement when developing machine learning models, but it is advisable as it can provide information on how the model is acting and detect biases or decisions that are not being carried out correctly. Nevertheless, it is necessary in critical applications, such as in medicine, where decisions made can have major consequences and it is necessary to understand how they were reached.

Shapley Additive exPlanations (SHAP) was chosen for these analysis because it allows:

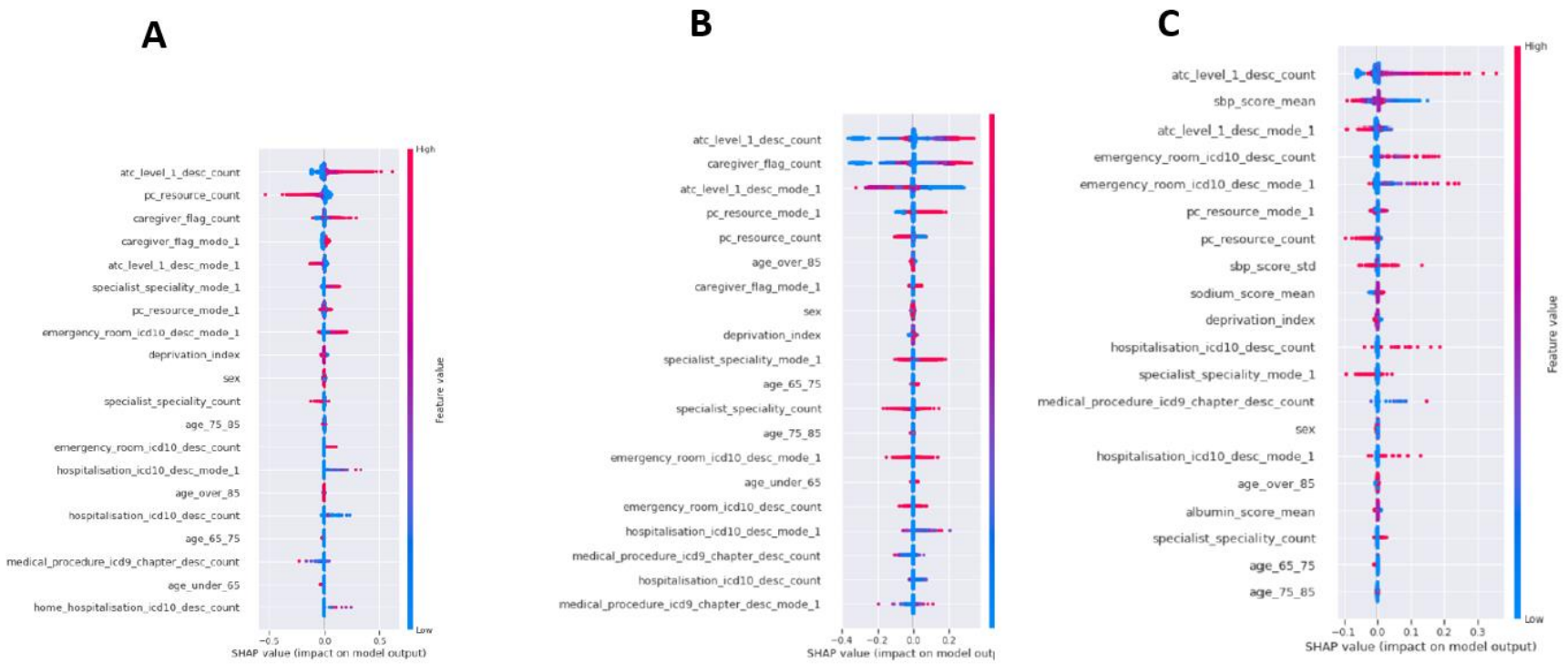
- global and local explainability;
- visual representation of which features contribute the most to the model's predictions;
- quantifying the contribution each feature has had on a specific prediction;
- graphical representation of how different values of each feature influence predictions;
- representation of the interaction between two features and their values on predictions.

SHAP is a method that is based on cooperative game theory and is used to enhance transparency and interpretability of machine learning models. The main objective of this method is to assign an importance to each input feature of the model, so that it can be understood how each feature has contributed to the output.

The most important concept in this method are Shapley values, which are calculated as the average marginal contribution of one feature value across all possible coalitions of feature values. These values represent the contribution/influence that a feature has had on the final prediction of the model. Thanks to these Shapley values, it is possible to know which features have been most important in the predictions.

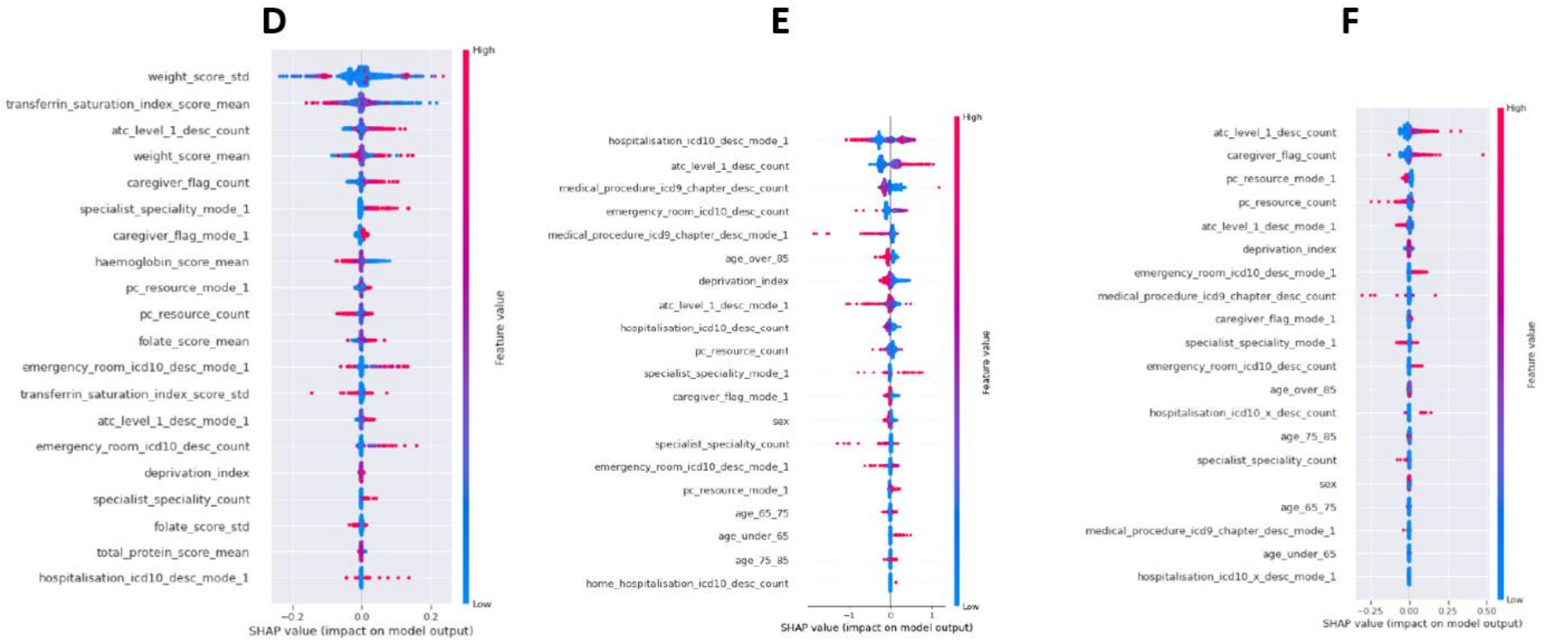
Figure 5 and Figure 6 display the SHAP values of the six developed PPS as follows: Dependency (Figure 5, A panel), Depression (Figure 5, B panel), Hypotension (Figure 5, C panel), Malnutrition (Figure 6, D panel), Readmission (Figure 6, E panel) and Avoidable admission (Figure 6, F panel).

The features are ranked according to the sum of absolute SHAP values for all samples. Plots are coloured from blue to red, with blue dots representing the lowest values. On each panel corresponding to a specific PPS, a positive SHAP value indicates an increase in the risk of the presence of the studied event. As for the top input variables that showed relevant impact on each of the evaluated events through all the six PPS, drug prescription was found to be the one that reflected the highest and direct relationship in four of the developed models (dependency, depression, hypotension and avoidable admission). Furthermore, it should be pointed out that the fact of having caregiver revealed also a positive association with having an event of depression or dependency as well as malnutrition. Variables related to medical procedures such as hospitalisation or use of resources (visits to emergency room, primary care, etc.) were the ones that most contributed for predicting readmission or avoidable admission.



Dependency *summary plot* Depression *summary plot* Hypotension *summary plot*

Figure 5 - SHAP values summary plot for Dependency (A), Depression (B) and Hypotension (C)



Malnutrition summary plot Readmission *summary plot* Avoidable admission *summary plot*

Figure 6 - SHAP values summary plot for Malnutrition (D), Readmission (E) and Avoidable admission (F)

4.2.3 Missing data report

One of the important aspects of the development of PPS models is the quality of the information with which they work. The lack of information on the variables involved in the algorithms developed can lead to a possible bias in the results obtained. For this reason, the quality of the information on the variables involved in the predictive model has been evaluated in each of the PPS models developed.

In the following paragraphs we will explain in more detail the issues encountered in the PPSs developed.

4.2.3.1 Dependency

From the initial set of 76,227 patients, a positive sample of 9,833 patients is obtained with a slightly symmetrical distribution of sequences at the level of missing data and an average of approximately 56% missing data for the entire set (Figure 7).

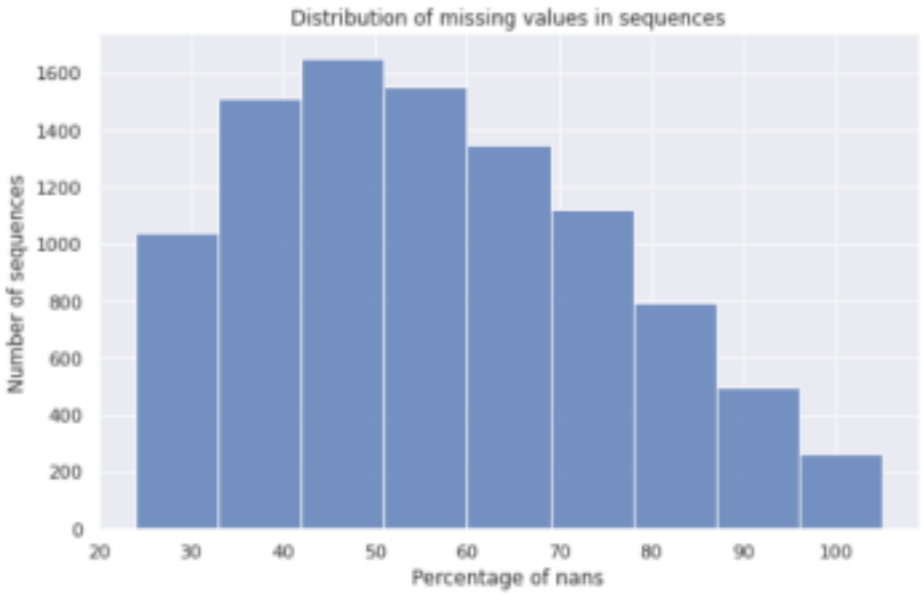


Figure 7 - Distribution of missing values in sequences in dependency outcome.

Thus, when a threshold of 60% of the quantity of information per sequence is exceeded, 74% of patients are lost, which is a significant loss.

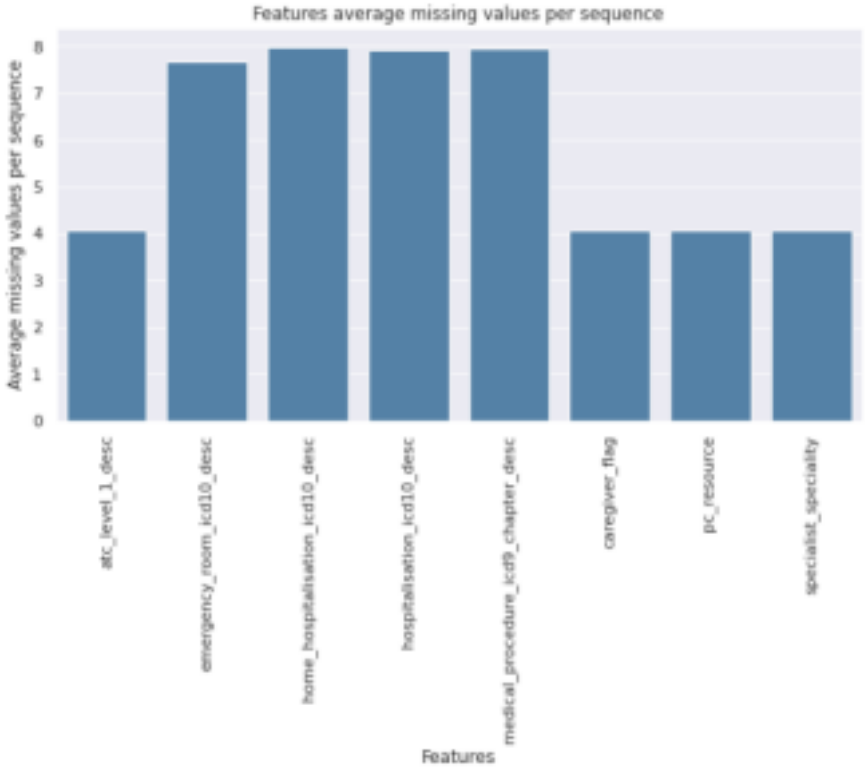


Figure 8 - Features average missing values per sequences in dependency outcome.

It is also observed that, for the set of excluded patients, the lack of information in the variables of hospitalisations, medical procedures, and intensive care facilities is related, as their loss is uniform and they exceed fifty percent of the missing sequences.

4.2.3.2 Depression

Of the initial 76,227 patients, a total of 56,256 patients (26% loss) remain after the process of selection and annotation of positive cases, this being the case with the largest volume of patients.

Of the selected cohort of patients, 69% of the sample has a level of missing information of more than 65% in the sequences. The average loss of information in this group is fairly uniform among the variables, with the hospitalisations and health resources variables standing out again, so we have a sample with a high level of sparsity in the modelling as shown below (Figure 9).

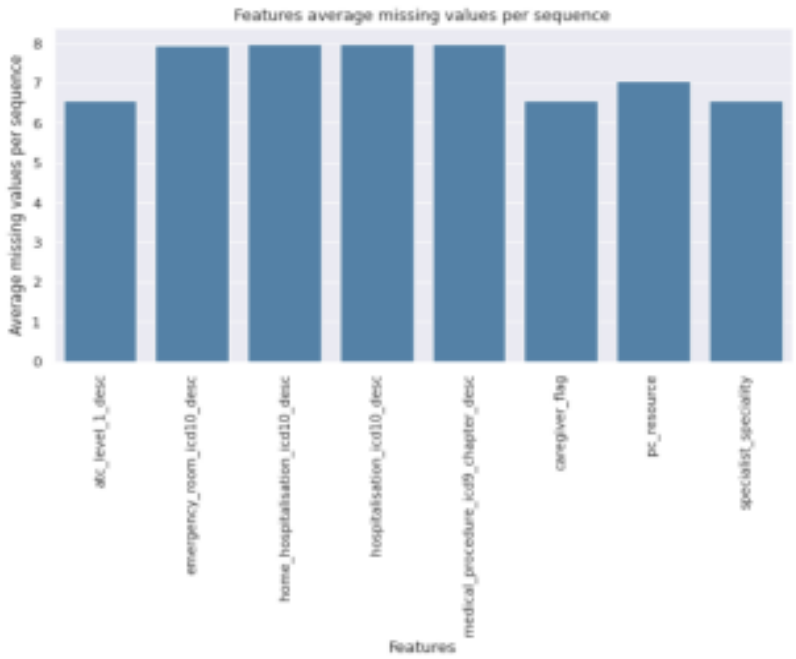


Figure 9 - Features average missing values per sequences in depression outcome.

4.2.3.3 Hypotension

This case demonstrates a substantial patient loss during the patient selection phase, resulting in a cohort of 2,801 patients, or a loss of 96% of the population (Figure 10).

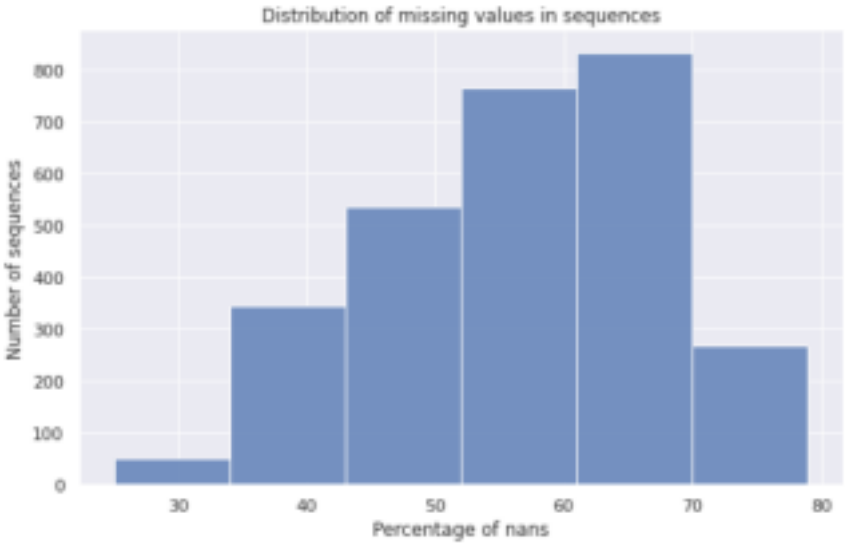


Figure 10 - Distribution of missing values in sequences in hypotension outcome.

The number of sequences with a high percentage of missing values is comparable to previous cases, but there are more sequences with between 50 and 70 percent of data lacking. It should be noted that there are no completely vacant sequences.

This indicates that if we desire sequences with a minimum of 60% information, we will lose 92%, or 2,578 patients, reducing the sample size to a point where it is nearly unsuitable for training.

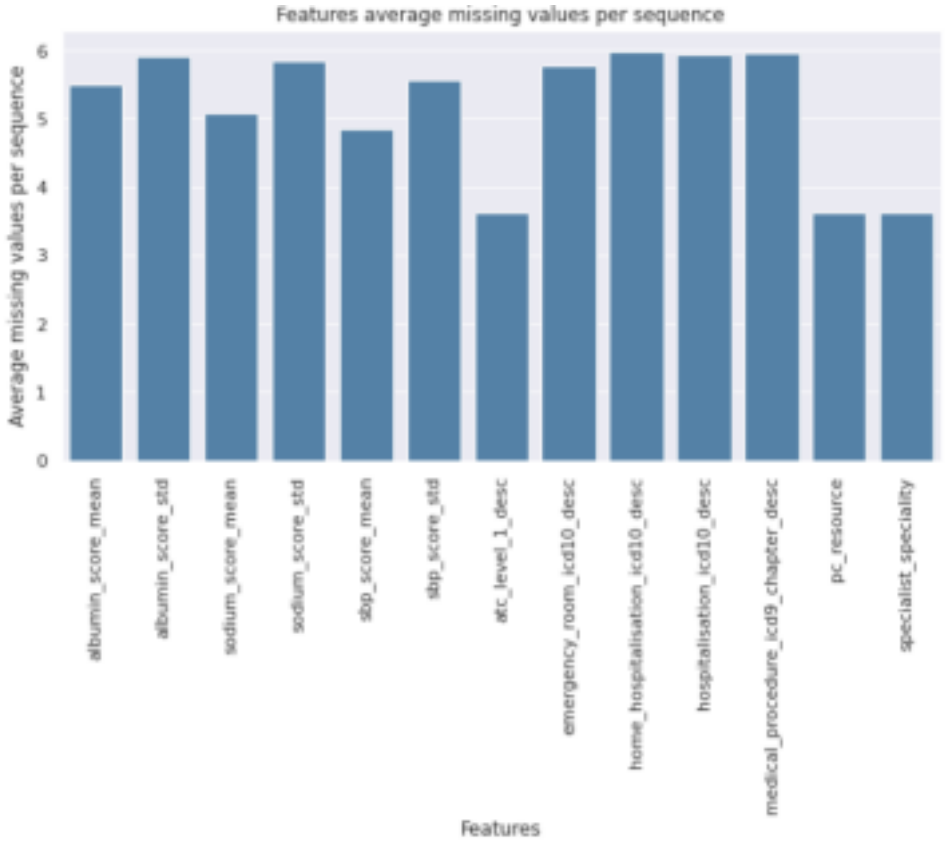


Figure 11 - Features average missing values per sequences in hypotension outcome.

The uniform nature of the lacking information makes this case extremely challenging to model. The median value of missing data per sequence for patients who did not satisfy the aforementioned criteria is depicted in the graph above. We cannot determine a specific reason why patients are discarded at the variable level, as the absent information in the sequences is located above the period's middle and is distributed in a quasi-continuous manner.

4.2.3.4 Malnutrition

The malnutrition case involves a cohort of 9912 positive patients, representing an 87% reduction from the initial sample of patients. With an average of approximately 66% missing data in the samples, the distribution of sequences at the level of missing data is symmetrical.

In addition, at least 21 percent of the samples are lacking, meaning we will never have complete samples (Figure 12).

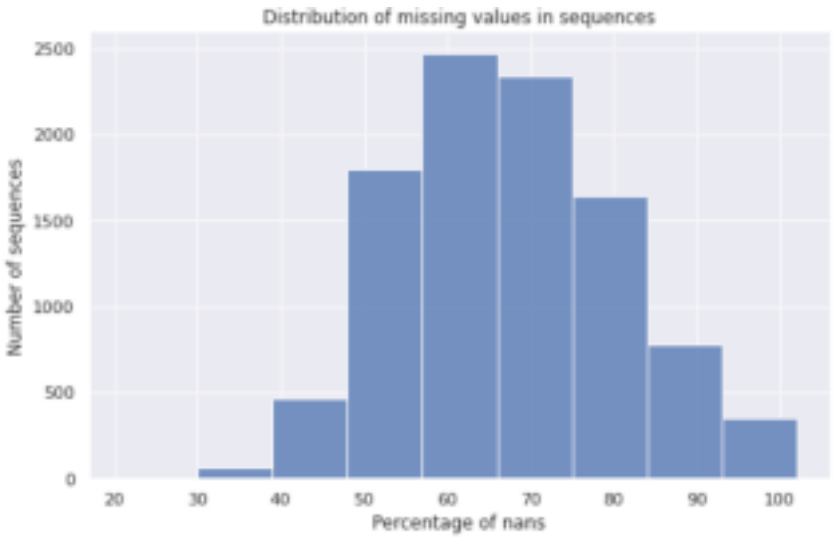


Figure 12 - Distribution of missing values in sequences in malnutrition outcome.

On the basis of the preceding assumptions, setting the minimum information threshold to 40% would result in a loss of 68% (6,744 patients). And the adjustment of this threshold is extremely sensitive to small changes, as from 60% onwards, 99.9% of patients are lost.

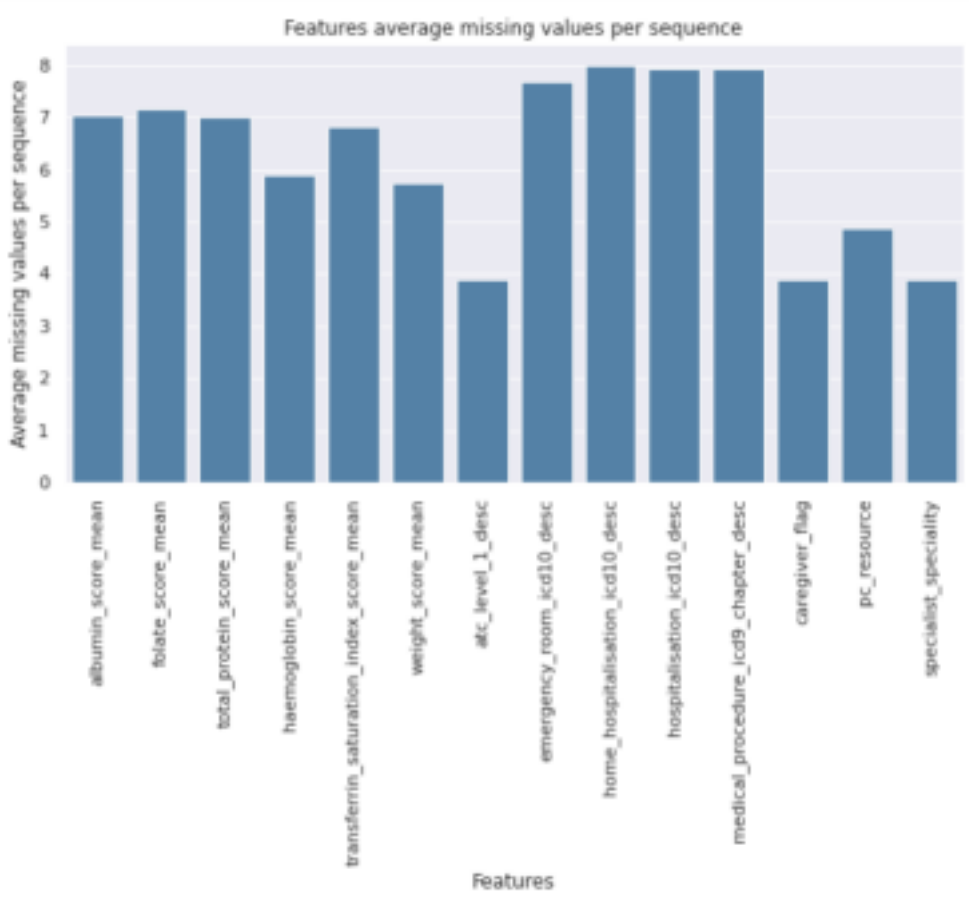


Figure 13 - Features average missing values per sequences in malnutrition outcome.

As there is still a lack of data above 5 values in almost all types for the time granularity of the PPS, it is evident how difficult it is to determine which variables could be taken into consideration during piloting.

4.2.3.5 Readmission

Given that we have not worked with sequences for this prediction model, we were unable to identify sequences at the level of missing data. This makes the case of readmission distinct from the other cases. When it comes to readmission, we have not identified patients based on whether or not they have certain data or conditions; rather, we have analysed readmission events in all of the patient records. This was done while processing the data and developing the models. A hospital discharge that is followed by a subsequent admission within a predetermined amount of time is regarded as a readmission occurrence for the patient.

4.2.3.6 Avoidable admission

In the case of Avoidable Admission, the Osakidetza database contains 76,227 patients. Following the selection and annotation of affirmative cases, 455 patients are left, with the following distribution of missing data in the sequences.

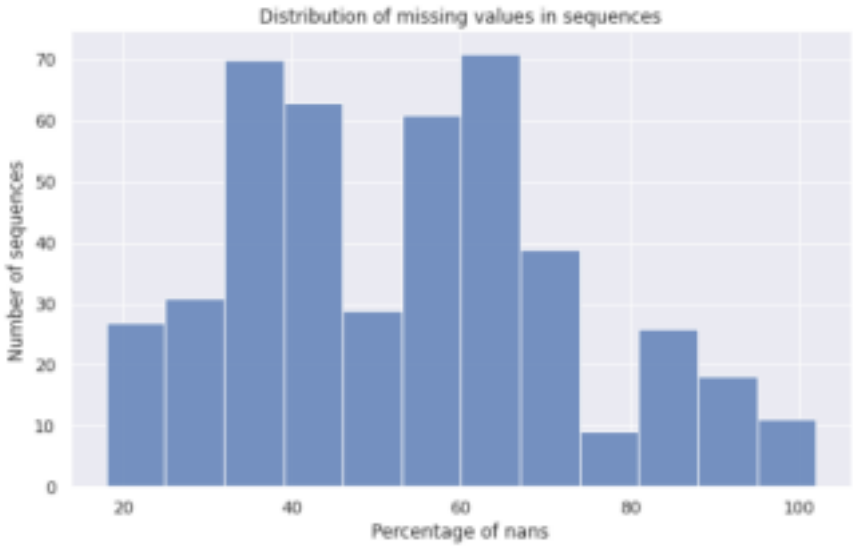


Figure 14 - Distribution of missing values in sequences in avoidable admission outcome.

The majority of sequences are vacant between 20 and 70 percent of the time, as depicted in the preceding diagram. In addition, there are no instances in which the sequences are 100 percent complete, so we will need to establish a loss of information tolerance criterion.

Using a threshold amount of information of 70% per sequence as a reference, the amount of patients lost due to a lack of information in the sequences is 88%, or 401 patients. Below is an analysis of the variables per sequence within the cohort of excluded patients.

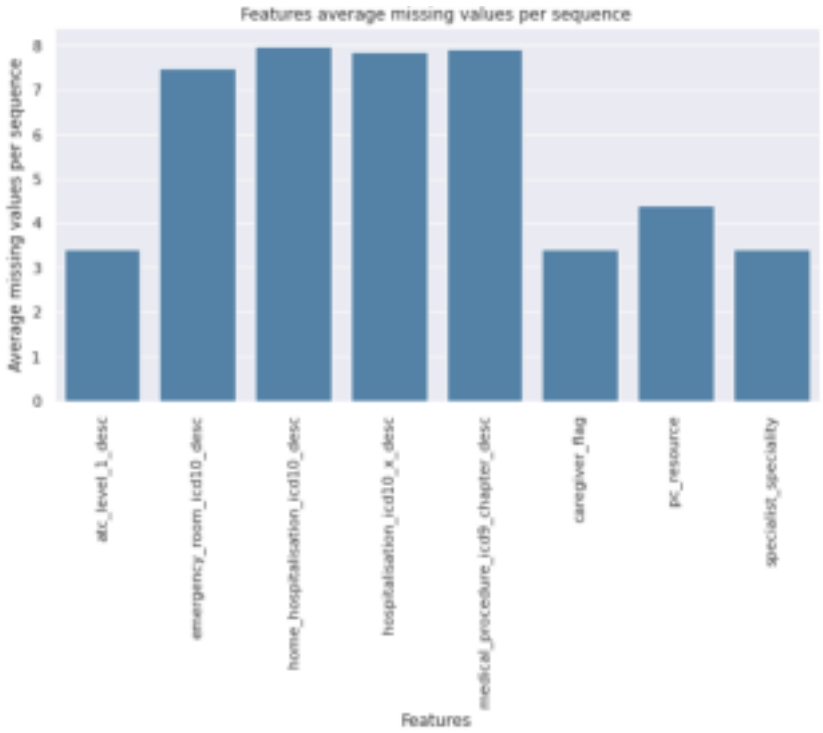


Figure 15 - Features average missing values per sequences in avoidable admission outcome.

With the exception of hospitalisations and ICD9 medical procedures, nearly all variables pertaining to health resources have an average absent value of more than 50 percent for patients who were eliminated.

4.3 Retraining of PPS

The work conducted in this phase of the project focuses on retraining the previously implemented models based on Osakidetza data, allowing the evaluation of the performance variation of these models and the possibility of improving their predictions. The data for this retraining has been provided by AMCA.

Furthermore, an exploration is made on whether the models previously trained are equally applicable to the new data. This provides valuable information on the models' generalization and their ability to adapt to different datasets.

The number of patients with applicable ICD codes for each PPS was very low. Figure 16 shows the comparison between AMCA and Osakidetza of the number of patients with applicable ICD codes for each PPS. As it can be seen (Figure 16), the Avoidable Admission case is the only one in which more data would be available for the retraining than for the training. In the other cases, the difference is very significant, which hinders the retraining.

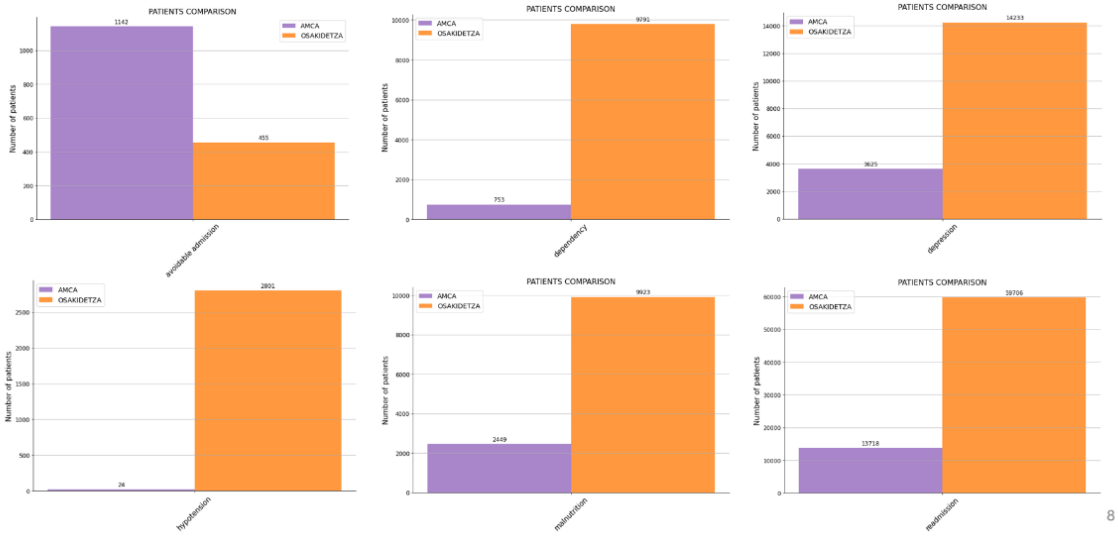


Figure 16 - Comparison between AMCA and Osakidetza database for each PPS (from left to right, and top to bottom: Avoidable admission, dependency, depression, hypotension, malnutrition and readmission).

The number of available instances in the malnutrition and hypotension models is less than 200, a very low number. In addition, the difference with the number of instances with which the model was trained is very large, so these two models were discarded for retraining.

4.3.1 Retraining process

During the retraining process, multiple experiments have been carried out:

- Experiment 1 (EXP1): the models were retrained with the new data without freezing any layer of the neural network. It should be noted that by freezing layers of the neural network, the weight updating of those layers is disabled during the new training, which keeps them fixed.
- Experiment 2 (EXP2): considering that the implemented neural networks had three layers, the models were retrained with the first layer frozen.
- Experiment 3 (EXP3): the same process was repeated with the first and second layers frozen.
- Experiment 4 (EXP4): it was decided to freeze all layers of the neural network, keeping all the weights of the original network fixed during the retraining.
- Experiment 5 (EXP5): the models were retrained using GridSearch, which allowed obtaining the hyperparameters that gave the best results.

4.3.2 Results

In the following tables results obtained from the different experiments for the retraining of the studied PPS are displayed.

4.3.2.1 Dependency

Table 8: Results of dependency model after retraining using AMCA data.

	AUC	Precision		Recall		F1-score		ACC
		Negative	Positive	Negative	Positive	Negative	Positive	
Model	0.68	0.61	0.65	0.7	0.56	0.65	0.6	0.63
Exp 1	0.56	0.53	0.54	0.55	0.51	0.54	0.52	0.53
Exp 2	0.53	0.53	0.53	0.5	0.55	0.51	0.54	0.53
Exp 3	0.53	0.53	0.52	0.47	0.58	0.5	0.55	0.53
Exp 4	0.53	0.57	0.51	0.16	0.88	0.25	0.65	0.52

Overall, the original model showed higher Accuracy and therefore AUC value compared to the other four assessed experiments (Exp1-Epx4).

In the original model, for the prediction of the positive class, it is observed that the PPV is around 0.65. As for sensitivity (recall), it was found to be 0.56. Regarding negative prediction, negative PPV (i.e. NPV) was 0. 61 and the F1 score was around 0.60.

4.3.2.2 Depression

Table 9: Results of depression model after retraining using AMCA data.

	AUC	Precision		Recall		F1-score		ACC
		Negative	Positive	Negative	Positive	Negative	Positive	
Model	0.96	0.94	0.86	0.85	0.95	0.89	0.9	0.9
Exp 1	0.89	0.84	0.86	0.86	0.83	0.84	0.85	0.85
Exp 2	0.89	0.83	0.86	0.85	0.83	0.85	0.85	0.84
Exp 3	0.89	0.81	0.84	0.85	0.81	0.83	0.82	0.83
Exp 4	0.89	0.86	0.86	0.84	0.83	0.86	0.83	0.85
Exp 5	0.89	0.83	0.85	0.84	0.85	0.83	0.84	0.84

In this setting, the original model was able to discriminate better than the other developed five experiments (Exp1-Exp5). Its accuracy and AUC values were about 0.9 and 0.96, respectively. Positive and negative predictive values were between 0.86 and 0.94 whereas sensitivity for the positive class was 0.95. The F1-score was found to be 0.9.

4.3.2.3 Readmission

Table 10: Results of readmission model after retraining using AMCA data.

	AUC	Precision		Recall		F1-score		ACC
		Negative	Positive	Negative	Positive	Negative	Positive	
Model	0.688	0.85	0.33	1	0.01	0.92	0.02	0.85
Exp 1	0.846	0.9	0.54	0.9	0.54	0.9	0.54	0.83
Exp 2	0.871	0.88	0.67	0.95	0.42	0.92	0.51	0.86

Under this setting, the developed two experiments (Exp1 and Exp2) showed higher AUC values compared to the original model, even though accuracy values were quite similar each other. Performance of other screening parameters such as NPV and PPV were also higher in Exp1 and Exp2.

4.3.2.4 Avoidable Admission

Table 11: Results of avoidable admission model after retraining using AMCA data.

	AUC	Precision		Recall		F1-score		ACC
		Negative	Positive	Negative	Positive	Negative	Positive	
Model	0.65	0.6	0.63	0.68	0.54	0.64	0.58	0.61
Exp 1	0.512	0.5	0.51	0.53	0.51	0.5	0.52	0.51
Exp 2	0.51	0.52	0.5	0.51	0.53	0.47	0.55	0.51
Exp 3	0.503	0.51	0.5	0.25	0.76	0.33	0.61	0.5
Exp 4	0.508	0.5	0.51	0.52	0.53	0.51	0.5	0.52
Exp 5	0.501	0.5	0.51	0.54	0.53	0.52	0.53	0.51

Considering the retraining model for avoidable admission, the original model reflected better performance results compared to the distinct experiments (Exp1-Exp5).

4.4 Discussion

During the evaluation period the following tasks were completed: a) evaluation of the properties of each of the proposed PPSs by measuring their ability and capacity to correctly classify; b) analysis of the unobserved values in the created models; c) the interpretability of the PPSs; and d) retraining of the PPSs in the AMCA database.

First, it is crucial to emphasize the discrimination and classification capabilities of the models once they have been developed. The obtained results indicate that, with the exception of depression modelling, none of the PPS have attained the established threshold of the area under the ROC curve (AUC) (0.8). In the case of depression, the AUC value was 0.95, resulting in a strong distinction between events with and without depression. Regarding the missing values, it has been possible to conduct an exhaustive analysis of them, thereby determining the variability of the lack of information in the input variables underlying the corresponding predictions.

Second, it is common knowledge that machine learning-based models are difficult to interpret because no estimates or weights are provided for the associations established between the input and output variables. By utilizing one of the interpretability strategies, such as SHAP, it has been possible to evaluate the developed models in an adequate and straightforward fashion, thereby determining their impact on each of the studied outcome variables. As a consequence of this analysis, it has been determined that certain input variables have the same level of influence across all six evaluated outcome variables.

Retraining the PPSs developed in Osakidetza for the AMCA pilot site database is of equal importance. Four of the initial six models have been retrained. This fact pertains to malnutrition and hypotension PPSs, as the number of available cases in these models is less than 200, which is extremely low. Moreover, the discrepancy between the number of instances used to train the model and the number of instances discarded for retraining is very large. In the remaining PPSs, in the majority of considered scenarios, the classification capacity is either maintained or, in the case of readmission, even increases.

It should be noted as a limitation that the PPS modelling was conducted using data from the Osakidetza EHR. Although they have been retrained using data from the AMCA pilot site, it is evident that they must be run with data from other regions before they can be generalized. The so-called federated learning method is one of the possible means of achieving this while maintaining the confidentiality of data from various locations. In this instance, this novel methodology could only be applied using data from the Osakidetza electronic health record.

Further steps in this evaluation of these prediction models are also planned. Once all the results are gathered and summarized, these findings will be discussed upon the Clinical Reference Group to make an appropriate decision (in terms of clinical utility) for implementing them in the ADLIFE toolbox. After having implemented them and finished the intervention period, WP9 leaders will evaluate their performance.

In conclusion, depression model based on machine learning techniques has robust methodological properties because the impact of each model component on the measured event has been measured. This study demonstrates that ML algorithms can be routinely employed for decision support. The development of such an interpretable ML framework for depression and readmission prediction is an essential and active area of research, as it facilitates the interpretability of the results and the establishment of actionable recommendations for the future in this field.

5 Federated Learning

In ADLIFE Federated Learning was proposed as a methodology for risk prediction models development. Due to the availability of data from the pilot sites at the time of models development, federated learning was not an option. However, a proof of concept (PoC) was conducted to simulate how FL should be implemented. The PoC demonstrates the potential of the FL in enabling the development of privacy-preserving and collaborative machine learning solutions.

Federated learning is a machine learning technique that trains an algorithm across multiple decentralized edge devices or servers containing local data samples, without exchanging them. To summarize, it is the decentralized form of machine learning.

Federated learning allows multiple actors to build a robust and common machine learning model without sharing data, thus addressing critical issues such as privacy, security and data access rights.

Federated learning is based on an iterative process divided into a set of client-server interactions known as a federated learning round. Each round of this process consists of transmitting the state of the current global model to participating nodes, training models of its own on these local nodes by producing a set of possible updates to the model weights, and then aggregating and processing these local updates into a single global update, on the original model. This leads to the model being able to learn from different datasets by generalizing in a noticeable way resulting in improved predictions on previously unknown data.

Federated learning requires continuous communication between nodes during the learning process. Therefore, it requires not only sufficient memory and local computational power, but also high bandwidth connections to exchange machine learning model parameters.

TensorFlow Federated (TFF) have been used, which is an open source framework whose main mission is to generate a viable ecosystem for the implementation of Federated Learning. In addition, TensorFlow Federated provides tools to ensure data privacy when performing federated training. It also offers a collaborative development environment that allows multiple parties to collaborate in building federated learning models.

5.1.1 Requirements to apply Federated Learning

The objective of applying Federated Learning in this project is to provide privacy to the study data while taking advantage of the large volume of data to provide the model with greater generalization and accuracy.

The benefits are clear, an improvement in the predictions of the model and a wide range of applications. The necessary requirements for its correct performance are:

- Quality data.
- Quantity of data.
- Computational capacity.
- Server latency.

5.1.2 Federated Learning in ADLIFE

Federated Learning proof of concept (PoC) has consisted in the recreation of a simulation environment in which a central node sends a previously trained model to 11 different simulated clients for a locally model train on each of those clients and the updating of the model located in the central node using Federated Averaging of the locally trained models.

The TensorFlow Federated Core API has been used to achieve this theorical demonstration of the main functionalities of a Federated environment and a demo has been implemented for the purpose.

1. Data preparation: In order to perform federated learning, the data had to be distributed in both servers in a similar way. They must comply with a structure so that the established preprocessing can take and transform the data from the server.
2. Configuration of the servers: Each server must have the TFF server installed and configured for communication between them.
3. Use of the learning model: After setting up the servers and preparing the data, the learning model is applied and trained in a federated way.
4. Training: The training is performed by communicating between the servers and updating the model with the data in each server. The model training parameters are defined.
5. Evaluation: Once the training is finished, the model results must be evaluated and the accuracy obtained must be verified.
6. Optimization: After the evaluation, adjustments can be made to the model and the training process in order to improve the prediction obtained.

The proof of concept has been documented and shared with the rest of the partners.

6 Conclusions and next steps

The deliverable D9.1 describes the work developed in WP9 regarding both a) the evaluation of ADLIFE intervention; and b) the evaluation of the risk prediction models developed in WP5 for the predictive and continuous risk assessment of potentially preventable situations.

The ADLIFE evaluation main aim is to provide robust scientific evidence on the effectiveness, implementation, technology acceptance and socio-economic assessments of the ADLIFE intervention compared to the SoC. The evaluation framework, data gathering process and analysis plan are available in the project's research protocol, which has been further developed from its version v0.21 (17/03/2021), the basis of deliverable D11. The adaptations have responded to the needs of the ADLIFE intervention, the subsequent design of the evaluation and specific pilot sites' needs and to a better understanding of the research protocol. On the one hand, four data collection guidelines have been designed and developed in order to conduct the data collection of each of the four assessments comprising the ADLIFE evaluation. On the other hand, the ADLIFE project has undergone modifications in the DoA concerning the number of pilot sites deploying the intervention and the intervention starting time; therefore, the evaluation framework has been correspondingly redesigned. Also, the research protocol has been registered in *ClinicalTrials.gov* and adapted to paper-format and published in the International Journal of Environmental Research and Public Health (IF: 4.61; Q1). The general simulation models for the socio-economic impact assessment have been developed and validated. All previous materials are presented through this deliverable D9.1 and are available in the appendixes.

Regarding the evaluation of the risk prediction models, deliverable D9.1 reports results on: a) the evaluation of the properties of each of the proposed PPSs by measuring their ability and capacity to correctly classify; b) the analysis of the unobserved values in the created models; c) the interpretability of the PPSs; and d) the retraining of the PPSs in the AMCA database.

Once the whole evaluation strategy is specified and the intervention performed, WP9 will evaluate the intervention for all pilot sites it in terms of effectiveness, implementation and technology acceptance and adoption and socio-economic impact, as specified in the research protocol. Particularly, since GWMK will not run the ADLIFE pilot as an interventional study in Germany, an observational study will be designed and conducted. Evaluation results will be reported in deliverable D9.2 Final evaluation report in M54. A final evaluation of the prediction models is also planned after the intervention, where the performance of the implemented models will be evaluated.

Appendix A Research Protocol v0.30

GA 875209

Research Protocol v0.30

Horizon 2020
European Union Funding
for Research & Innovation

History

Date	Version	Change
dd/mm/YYYY	X.X	
30/10/2020	0.13	Rephrase of Section 1 (Rationale) and 2 (Scientific question) Update the figure 6, according to the proposed health outcomes framework accepted by the CRG Inputs to section 6.7
25/11/2020	0.14	Contribution and review of MarcinKotwicki, Rachelle Kaye, to sections 1 and 2, Janika Blomeke to sections 3.3 and 5 and Fritz Arndt to Section 5.2
04/12/2020	0.15	Inclusion of Annex 10.7 (pending of being reviewed by CRG) and 10.8
09/12/2020	0.16	Inclusion of implementation research and refinement of qualitative evaluation
11/01/2021	0.17	Inclusion of usability and technology acceptance and review of Section 5.2. Inclusion of Annexes 10.9 and 10.10 describing implementation and usability and technology acceptance assessment.
21/01/2021	0.18	Updated version according to the feedback, comments and questions received from USTRAT, AMCA and OM and OUH on v0.17.Update of Figure 6 (Dimension of disutility of care corrected).
05/02/2021	0.19	Final review from partners. Contribution of OUH, Osakidetza and Kronikgune.
24/02/2021	0.20	Acceptance of the Clinical Reference Group (CRG) of the information to be collected in the project for both evaluation and clinical decision support purposes (Annex 10.7). CONSENSUS FINAL VERSION OF Research Protocol.
17/03/2021	0.21	Minor clarifications to the PR in the quantitative (5.1.1) and qualitative (5.1.2) approach sections, defining the procedures for the submission of patient-level data for quantitative assessment and for the qualitative assessment, respectively.
21/12/2021	0.22	Clarification about the “documentary analysis” mentioned in the section “Implementation assessment”. Initially site visits were planned in which we would also have the chance to check some documents. However, due to the impact of COVID this was/is not possible anymore. We

		needed to clarify that with a “documentary analysis” we did not mean a review of patient data or something similar, it refers more to a review of ADLIFE internal documents on for example IT implementation and preparedness or the secondary use of documents like the technology assessment that was conducted by SRCD.
04/02/2022	0.23	Updated the interview questions for the implementation assessment in Annex 10.09 as these were revised within the preparation of T10.2 and the interviews with stakeholders. Now the final interview questions for the assessment of contextual factors are included.
01/03/2022	0.24	Updated version of the Section 5.1.2 (Health outcomes qualitative approach) and Annex 10.8
08/03/2022	0.25	Updated version of the document
11/03/2022	0.26	Internal review
14/03/2022	0.26_1	Optimedis revisison
23/03/2022	0.26_2	Kronikgune (Socio-economic impact) revision
06/05/2022	0.27	Technology acceptance and update of the data collection guides and other support/reference materials.
10/05/2022	0.28	Correction of one contradiction in section 9.1 Data collection for Effectiveness assessment and reference to the figure 2 describing the Data Flow for further clarification
22/08/2022	0.29	Update of the inclusion criteria according to the decision made by the CRG on 19/07 CRG meeting and update of the updated version of the DCG for quantitative effectiveness v0.4 and inclusion of the data collection Guide for technology acceptance v0.2
02/09/2022	0.30	Minor corrections of typos. Update of the figure 4 (Flowchart of the recruitment, selection process of intervention patients) according to the updated inclusion criteria and link to the updated version of the DCG for quantitative effectiveness v0.5 and the update of the versions of the manual and data collection for technology acceptance in data collection section.

Contents

1 Acronyms

Abbreviation/Acronym	Defintion
ACCF/AHA	American College of Cardiology Foundation/ American Heart Association
AMCA	Samson Assuta Ashdod University Hospital
ATC	Anatomical Therapeutic Chemical code
BIA	Budget Impact Analysis
CAT	COPD Assessment Test
CDSS	Clinical Decision Support Services
CFIR	Consolidated Framework for Implementation Research
HF	Congestive Heart Failure
COPD	Chronic obstructive pulmonary disease
COPDF	COPD Foundation
DOA	Description of the Action
DMP	Data Management Plan
DPO	Data Protection Officer
EHR	Electronic health records
ER	Emergency Room
EQ-5D-5L	5-level EQ-5D version
EQ-VAS	EQ visual analogue scale
FALK	Falkiewicz Specialist Hospital
FEV	Forced expiratory volume
FHIR	Fast Healthcare Interoperability Resources
GAM	Generalized additive model
GAMLSS	Generalized Additive Model for Location, Scale and Shape
GDPR	General Data Protection Regulation
GLM	Generalize linear model
GOLD	Global Initiative for Chronic Obstructive Lung Disease

GP	General Practitioner
HADS	Hospital Anxiety and Depression Scale
HCP	Healthcare Professional
HL7	Health Level Seven
HF	Heart Failure
HIS	Health Information System
ICHOM	International Consortium for Health Outcomes Measurement
IADL	(Lawton) Instrumental Activities of Daily Living Scale
ICD	International Classification of Diseases
ICHOM	International Consortium for Health Outcomes Measurement
ICT	Information and Communications Technology
JITAI	Just-in-time adaptive interventions
KCCQ	Kansas City Cardiomyopathy Questionnaire
mMRC	Modified Medical Research Council Dyspnea Scale
NAASS	Nonadoption, Abandonment, and Challenges to the Scale-Up, Spread, and Sustainability of Health and Care Technologies
MDR	Medical Devices Regulation (MDR).
NPT	Normalisation process theory (NPT
NYHA	New York Heart Association
OM	OptiMedis AG
OUH	Odense University Hospital
PCHA	Personal Connected Health Alliance
PCPMP	Personalized Care Plan Management Platform
PEP	Patient Empowerment Platform
PROM	Patient reported outcome measures
PTC	Project Technical Committee
Q	Quartile
RJH	Region Jämtland Härjedalen
SD	Standard Deviation

SMS	Short Message Service
SoC	Standard of Care
SUS	System Usability Scale
UHCW	UNIVERSITY HOSPITALS COVENTRY AND WARWICKSHIRE -NHS TRUST
USTRATH	University of Strathclyde
UTAUT	Unified Theory of Acceptance and Use of Technology
WEMWBS	Warwick-Edinburgh Mental Wellbeing scale
WP	Work Package
ZBI-22	Zarit Burden Interview: 22-item version

2 Aims of the ADLIFE / Rationale

Due to population ageing and advances in medical science, people with chronic diseases – including advanced severe life-threatening chronic diseases- live longer. They are a special group who may face permanently or temporarily reduced functionality and capabilities. Challenges are how to sustain quality independent living for the patient; support caregivers facing an increasing burden; create sustainable healthcare and social care systems with limited resources. Persons with progressive Advanced Chronic Diseases can greatly benefit from digitally supported interventions to improve or maintain their health, avoid unnecessary deterioration, extend their independence and optimize health resources utilization.

Integrated supportive care can be an effective approach to enhance independence and quality of life and may also positively influence the course of illness from early states. The digitalisation of health services is expected to lead a profound transformation and it is important to evaluate its impact. The coronavirus disease (COVID-19) pandemic has led to a paradigm shift towards a remote telecare highlighting the need for reinforcing the digitalisation of health services worldwide enabling and promoting digital care. ADLIFE aims to provide evidence -based guidance to adopt and use new digital health services supporting integrated care at different levels of the health care system.

The over-arching societal **challenge** addressed by ADLIFE is the provision of appropriate health services to a growing population of aged patients with complex chronic diseases by providing innovative integrated intelligent personalized care. As representative of this increasing group of diseases, we have selected two of the more prevalent ones, Chronic Obstructive Pulmonary Disease (COPD) and Congestive Heart Failure (HF). Chronic obstructive pulmonary disease (COPD) is an important cause of morbidity and mortality with

high social and economic costs[19]. The prevalence of COPD has been reported to vary between 6 and 26.1% worldwide. COPD has also been associated with a high prevalence of one or more comorbid conditions, which have an impact on health status and mortality. Heart failure (HF) is a major and growing medical and economic problem worldwide as 1-2% of the healthcare budget is spent for heart failure[20]. The global economic burden of HF is estimated at $108 billion per annum, with $65 billion attributed to direct and $43 billion to indirect costs. Europe accounts for 6.83% of total global HF costs.

ADLIFE will conduct a large-scale deployment of digitally enabled holistic and integrated supportive care. The ADLIFE ICT solutions (ADLIFE Toolbox) will be integrated and scaled in the actual ICT health systems participating in the intervention. The toolbox comprehends validated and trusted personalised digital solutions, most of them developed in previous FPVII and Horizon 2020 project from the consortium partners following international standards such as HL7 FHIR and PCHA device standards.

The **ambition** of ADLIFE is to:

- Demonstrate that ICT supported ADLIFE intelligent and outcome-based personalized care model of integrated care is flexible and appropriate and can be deployed and replicated at large scale in different environments and be trusted in regard to data access, protection and sharing.
- Achieve gains in patient health outcomes, and quality of life, slowing down clinical and functional deterioration and improving patients' experience.
- Protect functionality and enhance autonomy, empowering patients to participate in decisions making on their own health and adapting to their changing conditions and context.
- Obtain improvements in efficiency by making a better use of resources, increasing the coordination among all the key stakeholders of care and improving working conditions of professionals.

Consequently, the operational **objectives** of ADLIFE are:

- To provide collaborative tools to create personalized care plans for multidisciplinary care team members to efficiently manage the delivery of integrated care services improving working conditions of health care and social care providers, optimizing work time management and multi-disciplinary coordination.
- To implement intelligent tools for clinical decision-making support that seamlessly access and assess the patient's most recent clinical context (EHR and PROMs), by automating evidence-based guidelines and need assessments scales and risk prediction algorithms to early detect health changes or undesired events.

19 https://www.europeanlung.org/assets/files/publications/lung_health_in_europe_facts_and_figures_web.pdf

20 Lesyuk W etal .Cost-of-illness studies in heart failure: a systematic review 2004–2016. BMC Cardiovasc Disord. 2018; 18: 74.

- To securely access, process, share and store patient's data in electronic health records and also other patient generated data (including sensor measurements, interactions with their environments, feedback about their care plans and PROMs) in line with the requirements of GDPR.
- To change the traditional care models for chronic patients with advanced chronic disease by integrating unconnected care tasks performed in different levels and settings addressing the multidimensional nature of their conditions and the secure and quality exchange of data and information.
- To facilitate a more active role of patients and caregivers in managing their own health and symptoms encouraging shared decision making, deliver individualized adaptive interventions.
- To deploy the new tools in hospitals and/or clinics and/or primary care centres in seven different European and associated regions, involving 679 professionals.
- To assess the effectiveness (in terms of gains of health outcomes and use of resources) and efficiency (in terms cost improvements) of the intervention with a large-scale pilot involving 846 patients and 1183 caregivers, evaluating health gain, quality of life, use of resources and economic costs.
- To have a direct impact by contacting/including in healthcare conferences/programmes across the participating regions on more than 102,900 professionals and 2,128 centres in the participating regions where more than 190,000 patients could benefit in a short-term with the project results.
- To produce guidelines and policy recommendations providing financial sustainable, flexible and replicable solutions to disseminate results, transfer and deploy at large-scale to other patient groups in the EU and beyond and create further business and job creation opportunities.

Based on the operational ADLIFE objectives, the **expected impact and consequences** of the ADLIFE intervention will be evaluated, including:

- Systematic assessment and evaluation of the impact of digital health services. The ADLIFE framework for the assessment of the digital transformation of health services and its impact will generate the evidence that is required for decision-making on stimulating, using and/or funding digital health strategies at various levels in the health care system;
- Management of multimorbidity. ADLIFE will demonstrate the benefits of the digital integrated care in producing gains in health status, by means of a number of health outcomes, improving quality of life and use of resources and reducing the socio-economic burden. It will provide evidence to support the sustainability of health systems by optimizing the available resources.
- Real deployment of integrated healthcare services. ADLIFE will demonstrate how Europe can configure more sustainable models for health and care delivery.

3 Scientific question

The overall hypothesis of the ADLIFE software application is that: "The use of the ADLIFE toolbox supporting early detection of care needs and dynamic and personalized care delivers more appropriate targeted and timely care for patients with Advanced Chronic Diseases". Chronic Obstructive Pulmonary Disease (COPD) and Congestive Heart Failure (HF) have been selected as representative of this group of diseases.

The leading research question for the evaluation of the study of ADLIFE application is: When applied in real life settings, is the use of the ADLIFE toolbox able to deliver appropriate targeted and timely care for patients with Advanced Chronic Diseases?

Care will be considered appropriate when it is deployed at the time and in the way is needed in order to generate the best possible gain in health and quality of life. The scientific question reflects the complex innovation intervention and three complementary evaluation approaches will be used.

- An **effectiveness** assessment will be conducted to estimate the ADLIFE intervention impact compared to the Standard of care (SoC), applying mixed-methods combining quantitative and qualitative analysis.
- A **socio-economic impact** assessment will estimate the long-term economic impact of the ADLIFE intervention compared to the SoC, applying a budget impact analysis (BIA) based on a simulation modelling.
- An **implementation** assessment will be performed under three different perspectives: the implementation of the research project itself will be assessed as well as the contextual factors that are relevant for the translation of the innovation action into routine practice and the acceptance of the technology and adoption evaluation.

4 Study description

Three phases can be identified in ADLIFE:

- Phase I – Organizational issues and ICT platforms implementation, formed by 2 blocks: Clinical and organizational and ICT Platforms implementation.
- Phase II – Intervention large scale deployment. ADLIFE intervention will be implemented in 7 Regions across Europe representing six different EU Countries and one Associated Country, involving 75 healthcare facilities, 679 healthcare professionals, 846 patients and 1183 caregivers.
- Phase III. Evaluation: At the end of Phase II ADLIFE intervention the scientific question will be answered by the three complementary evaluation approaches described in section 3.

The evaluation of ADLIFE study has been laid out in three complementary evaluation approaches: Effectiveness, economic impact and implementation process. Effectiveness and economic assessment will be conducted across seven pilot sites where ADLIFE intervention has been deployed (846 patients), compared with the same number of patients under Standard of Care (SoC). Implementation assessment will be only performed in intervention participants under a before/after design.

4.1 Description of intervention

ADLIFE will deploy developed and validated personalised digital solutions for integrated supportive care based on H2020 projects C3- Cloud and Power2DM components, previously tested in two health systems. The ADLIFE solutions include: a Personalised Care Plan Management Platform (PCPMP), Clinical Decision Support Services (CDSS), Interoperability Solutions and a Patient Empowerment Platform (PEP) with a Just-In Time Adaptive Intervention Delivery Engine (JITAIs) (Figure 17).

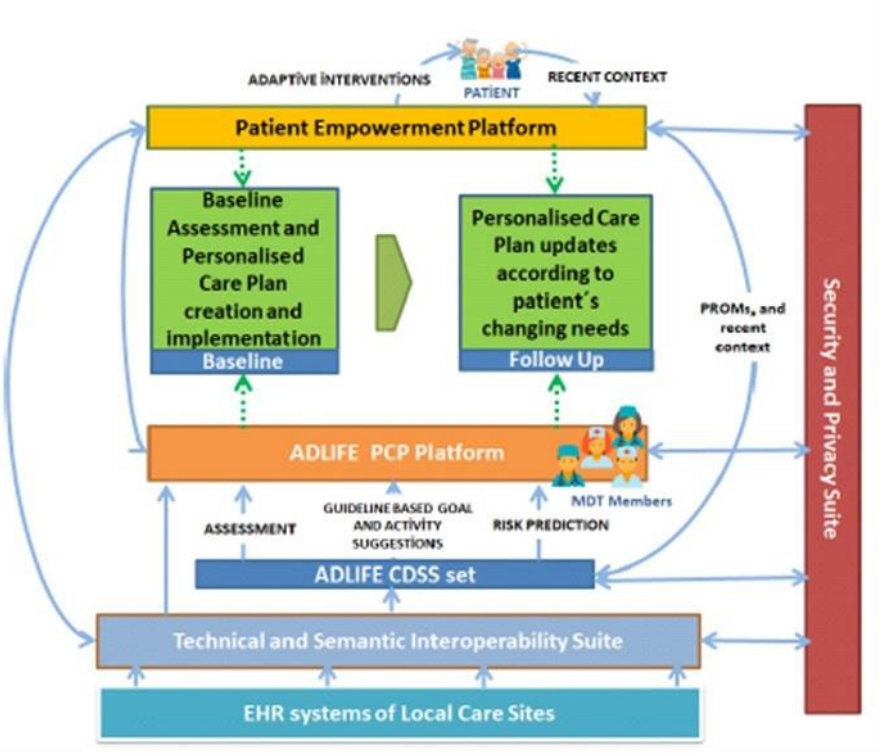


Figure 17. ADLIFE high level system architecture

The ADLIFE intervention consists of the deployment and use of the "ADLIFE toolbox" by patients, informal caregivers and health professionals in the pilot settings mentioned below. The ADLIFE toolbox involves two interconnected platforms: the PEP, used by patients[21] and the PCPMP used by healthcare professionals (C3-Cloud project GA689181). PCPMP includes a Service to assist clinical decision support (CDSS). Patients participating in ADLIFE will have a personalised care plan, created in the ADLIFE toolbox, which will be developed and managed together with their healthcare professionals.

The main task of patients and informal caregivers will be to use the ADLIFE toolbox as part of their healthcare process together with their healthcare professionals. ADLIFE intervention will consider the health-related outcomes relevant for the patient in actual health service planning and evaluation. By identifying the outcome that will be responsive to each measure, professionals and patients will have the chance of reviewing the health-related outcomes and of jointly choosing the activity, objective or goal that boosts the desired one. The health-related outcomes will be reflected as labels that bind every activity, goal and/or indicator included in a care plan. The labelling mechanism has been co-created with health

[21] Erturkmen GBL, Yuksel M, Baskaya M, Sarigul B, Teoman A, Yilmaz G, de Manuel E; ADLIFE Consortium. Interoperability Architecture of the ADLIFE Patient Empowerment Platform. Stud Health Technol Inform. 2021 May 27;281:936-941. doi: 10.3233/SHTI210316. PMID: 34042811.

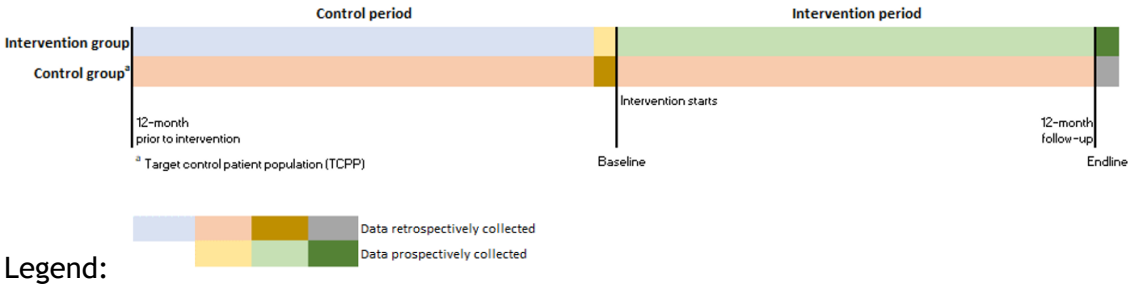
care professionals and automatized to allow health-related outcome tracking over time and over a wide spectrum of patients.

The control group follow the Standard of Care (SoC) according to the health care organizations criteria. The pilot sites have different health care systems. Information of SoC was derived from semi-structured interviews with three stakeholder groups in the sites, 5-7 persons in each group. For further background explanation, the SoCs are described in Task 6.1 in 1st Periodic Report, and they will be detailed in D6.2.

4.2 Study design

This is a quasi-experimental trial following a multicenter, non-randomized, non-concurrent, unblinded and controlled design. The intervention group will be under the ADLIFE intervention, while the control group will follow the standard of care (SoC) (Figure 18. ADLIFE study design

Figure 18).



Legend:

Figure 18. ADLIFE study design

The intervention group (846 patients) will be patients with Advanced Chronic Diseases (HF and/or COPD with/without co-morbidities). Candidates for intervention group will be recruited by healthcare professionals or research assistants according to patient potential benefit of the intervention. Their information will be retrospectively and prospectively collected. Control group will be 846 patients retrospectively selected to guarantee the control group receives usual care (SoC). To correct for potential biases and guarantee comparability between the control and the intervention group caused by this non-random design, the control group selection will be based on the matching with the intervention group, following a propensity score[22] technique on the patient variables of age, sex, number of emergency room (ER) visits and number of hospital admissions observed during the 12 months prior to the ADLIFE intervention. Control group will be retrospectively selected to guarantee the control group receives usual care (SoC).

[22] Diamond A, Sekhon JS. Genetic Matching for Estimating Causal Effects: A General Multivariate Matching Method for Achieving Balance in Observational Studies. Rev Econ Stat. 10 de octubre de 2012;95(3):932-45

As the ADLIFE toolbox will be used by all stakeholders in the intervention group and therefore, they will be aware about the intervention, the study will be unblinded. However, since data will be retrospectively collected for the control and the intervention group, no bias will be expected over the data collection process.

The study plan is shown in Figure 19**¡Error! No se encuentra el origen de la referencia.** . First, healthcare professionals will be invited to participate (M30-M32) and trained (M33-M35). Each pilot site will identify the target population to recruit both intervention and control patient groups by M31. From this list with potential eligible participants, patients for the intervention group will be recruited starting at M33 until M37. Patients will be trained from M35 till the recruitment ends. Then, this group will be followed-up for a year, from M36 until M47. Selection of control patients will take place from M45 to M48. The control group will be selected from the same list of potential eligible participants, excluding those included in the intervention group. The control group will receive usual care and their performance from M36 to M47 will be retrospectively assessed.

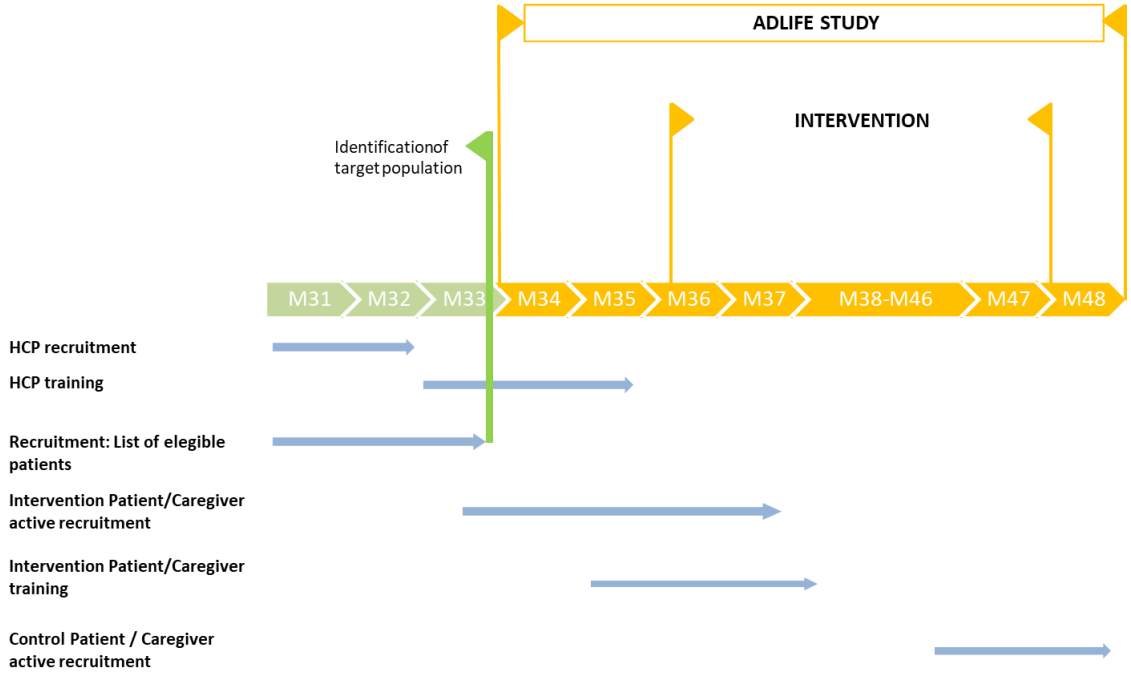


Figure 19. Study plan

The reference of the project months are shown in the Table 1.

Table 1 Reference of the project months

Month	Year	Project Month	Month	Year	Project Month
January	2020	1	January	2022	25
February	2020	2	February	2022	26

March	2020	3	March	2022	27
April	2020	4	April	2022	28
May	2020	5	May	2022	29
June	2020	6	June	2022	30
July	2020	7	July	2022	31
August	2020	8	August	2022	32
September	2020	9	September	2022	33
October	2020	10	October	2022	34
November	2020	11	November	2022	35
December	2020	12	December	2022	36
January	2021	13	January	2023	37
February	2021	14	February	2023	38
March	2021	15	March	2023	39
April	2021	16	April	2023	40
May	2021	17	May	2023	41
June	2021	18	June	2023	42
July	2021	19	July	2023	43
August	2021	20	August	2023	44
September	2021	21	September	2023	45
October	2021	22	October	2023	46
November	2021	23	November	2023	47
December	2021	24	December	2023	48

4.3 Study Setting

The ADLIFE intervention will be set across seven different pilot sites: Basque Country (Osakidetza), United Kingdom (National Health Service Lanarkshire and University Hospital Coventry & Warwickshire - National Health Service Trust), Denmark (Odense University Hospital), Germany (Gesunder Werra-Meißner Kreis), Sweden (Region Jämtland Härjedalen) and Israel (Assuta Ashdod Hospital - Maccabi Healthcare Services Southern Region) involving healthcare professionals, care services and patients and caregivers.

Study settings include all settings that are in any way relevant for the provision of health care, i.e. healthcare centres, General Practitioner GP's offices, hospitals, patients' homes. Participants will be enrolled and the evaluation will be conducted at the seven pilot sites regions.

Table 2 shows the number of participants in ADLIFE project: patients, informal caregivers, professionals and healthcare organizations. Previous to patient recruitment, the healthcare organizations engaged in the intervention will be confirmed.

Table 2. Participants in ADLIFE project

PILOT	PARTICIPANTS IN ADLIFE PROJECT (patients, professionals, caregivers, healthcare organizations			
	PATIENTS	CAREGIVERS	HEALTHCARE PROFESSIONALS	HEALTHCARE ORGANIZATIONS
Basque Country (OSAKIDETZA)	126 intervention + 126 control	160	GP:60 Nurse: 64 Specialist: 16 Total:140	Integrated HealthcareOrganizations (OSI) (9): Araba, Donostialdea; Barrualde-Galdakao;Alto Deba; Debabarrena; Tolosaldea; Ezkerraldea- Enkarterri-Cruces; Bidasoa; Uribe
United Kingdom (NHS Lanarkshire)	126 intervention + 126 control	250	GP: 60 Nurse:100 Specialist: 40 Total: 200	NHS Lanarkshire – 3 Acute Hospitals (Hairmyres, Monklands and University Hospital Wishaw) and over 100 sites in total
Denmark (South Denmark)	126 intervention + 126 control	200	GP: 50 Nurse:40 Specialist: 10 Total: 100	OUH-Svendborg Hospital covers 50% of the Region of Southern Denmark 10 local municipalities and all relevant GPs in these municipalities OUH covers 10% of hospital capacity in Denmark
Germany (Werra-Meißner Kreis)	126 intervention + 126 control	63	GP: 7 Nurse:4 Specialist: 4 Total: 15	2 Hospitals: 2, Hospital Werra-Meißner GmbH: two locations in Witzenhausen and Eschwege 5 centers of primary care and 4 homecare
Sweden-RJH (Region Jämtland Härjedalen)	126 intervention + 126 control	20	GP: 20 Nurse:10	RJH: One hospital: Östersund hospital, 8 primary care health centres, two specialized ambulatory care services;

			Specialist: 15 Total: 45	Mobile team for "nearer" care, Storsjögläntan – specialized unit
Israel (Assuta Ashdod Hospital together with Maccabi Healthcare Services Southern Region)	126 intervention + 126 control	150	GP: 15 Nurse:7 Specialists and healthcare professionals: 38 Total: 67	Assuta Ashdod Hospital Maccabi healthcare Services (includes over 250 GP, over 50 nurses, at least 50 other health professionals) Ashdod Municipality Social Services
United Kingdom (UHCW-NHS Trust)	90 intervention + 90 control	140	GP: 34 Nurse:56 Specialist: 42 Total: 112	NHS will deploy solution in primary and secondary care in the West Midlands.

4.4Sample size calculation

The single variable chosen for the calculation of the sample size has been the number of visits to Emergency Room (ER) Department, as described in Section 7. An effect size of 0.6 ER visits per year was assumed, with a standard deviation of 1.2. With a 5% level of significance, a 90% of statistical power set, assuming a conservative intra-cluster correlation coefficient of 0.06 (each pilot site defines as a cluster) and a drop-out rate of 30%, 1,692 patients will be required (846 per branch) across pilot sites. In this context, 75 healthcare facilities, 679 healthcare professionals and 1,183 caregivers will be involved.

5 Recruitment of Study Participants

5.1Inclusion criteria

The study population consists of patients with advanced chronic diseases (HF and/or COPD with/without co-morbidities), their informal caregivers and their healthcare professionals, fulfilling the following inclusion/exclusion criteria.

Patients are eligible for recruitment if they comply with:

- Senior (over 55)
- Heart failure (NYHA III-IV) in functional stage III/IV according to the NYHA scale and/or stages C and D of the ACCF/AHA classification. Stable-phase (at least two months without decompensation requiring hospital care)
- And/or COPD GOLD scale >2 (FEV1<50) and/or mMRC ≥ 2 and/or CAT ≥ 10 and/or use of oxygen at home
- With or without comorbidities
- They are able to provide informed consent
- They still live and generally plan on living in their home for the intervention duration.
- They or their informal caregivers are able to use digital technology, communication tools, and/or networks and have access to a computer, laptop, tablet or smartphone and wifi/internet connection.
- They or their informal caregivers understand, read and talk the native language.

Each pilot site will identify patients complying with inclusion criteria according to their available databases. Each site will use suitable screening tools for them based on their EHR structure. The EHR search might differ slightly between pilots though the inclusion criteria´s are the same. The diagnosis codes (ICD) and the drugs the patient is taking will be used in the pilot sites to screen for eligible patients (Annex 15.1).

The informal caregiver will be a person who provides occasional or regular support to the patient needs. **Caregivers** are eligible if:

- The patients they care for meet the inclusion criteria
- They give consent to participate

Healthcare professionals are eligible if they care for patients who meet the inclusion criteria and consent to participate. Healthcare professionals taking part into ADLIFE should be:

- involved in the selected patients care.
- open to new ways of working, specifically as part of a coordinative and collaborative teams.
- open to the use of new technology. They should be willing to learn how to use technology to support their work.

5.2 Exclusion criteria

Patients are not eligible for recruitment if:

- Presence of active malignant neoplastic disease.
- Inclusion in the active list of any kind of transplantation.
- No signature of Informed consent by a legally capable patient.

Patients who have participated in ADLIFE and later have withdrawn from their participation in the study the intervention formally are not eligible for the recruitment again.

Caregivers are not eligible if the patients they care for meet the exclusion criteria.

Healthcare professionals are not eligible if they do not care for patients who meet the inclusion criteria or only care for patients who meet the exclusion criteria.

5.3 Recruitment of healthcare professionals

The research team will select the healthcare professionals, using sampling of convenience (not probabilistic), taking into account their individual profiles.

The proposed recruitment process for healthcare professionals is as follows:

- A list of healthcare centers, hospitals, healthcare organizations.... offering clinical assistance to patients who meet the inclusion criteria will be created in each site.
- The health centres or healthcare professionals (whichever is feasible) will be approached by an ADLIFE research team member via email, a letter or face-to-face to provide initial information about the nature of study and the objectives of the evaluation (Annex 15.2).
- A research assistant follows up the first approach with email, a letter or a telephone call to establish whether healthcare professionals in the healthcare centre/hospital/healthcare organization consider participation.
- If healthcare professionals' express interest in participation, the research team member offers a face-to-face meeting for further discussion of the study.
- All healthcare professionals' members who are recruited for participation will be involved in the intervention.

5.4 Recruitment of patients

The recruitment of patients will start once the following activities have already been achieved:

- In each of the seven pilot sites, healthcare professionals responsible for implementing ADLIFE intervention will have been recruited and trained in the use of ADLIFE application.
- Organizational changes required in each site have been put in place to enable ADLIFE care pathways.
- The strategies related to empowerment and shared decision making have been prepared.
- Comprehensive Deployment Plans have been developed in each site.
- Each site has the Ethics Committee Approval and where appropriate, Research and Development Approval.

The following procedure is proposed:

- At M31 each pilot site starts to identify its tentative target patient population which will serve to recruit intervention and select control patient groups. Patients with COPD and/or HF complying with the inclusion and none of the exclusion criteria will be identified from the clinical and administrative data bases in each site, validated and recruited by the healthcare professionals or the project leader. If possible, the degree of severity would be reviewed at this point in order to refine the definition of target population.
- When all patients with the intended characteristics are identified, each pilot site will retain this list with potential eligible participants (M33).

5.4.1 Selection of intervention patients

- The Recruitment of patient for the intervention group will get started (M33)

- The recruitment process will end on M37 or until the defined sample size is reached (whichever occurs first). Recruitment period could be expanded at a maximum of two additional months in the event that the proposed sample size had not been reached in the original period.
- The patients will be selected from the tentative target patient population. These lists (one for each pilot site) will be reviewed by healthcare professionals in the pilot site's health centres to check for inconsistencies with the inclusion and exclusion criteria that are not systematically documented in the health records (e.g. language barriers). This process produces a final target patient population. Patients will be assigned a unique code that data managers at pilot site should keep to be linked to an identification code within the organization.
- Research assistants and/or healthcare professionals approach patients from the final target population to invite them to be intervention patients. This approach will be done according to their subjective assessment looking for the ones who most can beneficiate from the intervention.
- Research assistants or suitable equivalents will contact (email, mail, phone or fact-to-face meetings) the candidates, introducing the study, and enclosing the information sheet, to explain the nature of the study, the objectives of the evaluation and the expected role of the participants.
- The candidates will be informed about the ICT skills required to participate in the intervention. To confirm their ICT literacy, they will be asked about their ability to use digital technology, communication tools, and/or networks and their accessibility to a computer and wifi/internet connection.
    - In case the patient thinks he/she doesn't have the necessary skills but would still like to take part in the study, he/she may nominate an informal caregiver as a 'supporter' who can view and enter information for the patient. If an informal caregiver is supporting the patient for the study, they must be formally consented. The patient must confirm on the consent to participate form that the caregiver agrees to take part and to be contacted by the study team. Patients must also give their consent for the caregiver to access their record.
- Suitable participants will be provided with a summary of evaluation activities that will be expected from the participants. This ensures full transparency and allows potential participants to make an informed decision prior to consenting to join the study. This may be followed by a new contact to clarify possible questions.
- The research assistants/healthcare professionals follow up the first approach with a letter or a telephone call to establish whether patients would consider becoming a study participant. A list of eligible patients that have an interest in participating in the study will be established in all seven pilot sites. Gender parity will be desirable but not compulsory. Prior to the start of collecting evaluation data with the patients, candidates who agree to participate in the study must sign the informed consent for documentation to confirm they have read and understood the information and want to participate in the study. The informed consent forms are presented in the Annex 15.4.
- The participant should retain a copy of the information sheet for his or her own reference.
- The signed informed consent sheet will be scanned so that a copy is digitally available. Where this is not a routine procedure, the informed consent hardcopies will be stored securely to be available for the case being necessary.

- All consented patients will be involved in the study as intervention patients. Each site will mark in the list of the final target population, who of them accepted to participate in the project as intervention group.
- The patients in the intervention branch will receive ADLIFE application training at the pilot sites and online training material in the period of November 2022 (M35) till recruitment ends as described above.
- The intervention group will be followed-up for a year, from M36 until M47.
- All agreed variables, baseline data and use of services will be collected for the whole follow-up period (section 7). The use of resources, will be collected also from the previous year to the intervention (M21-M33), in order to study the evolution, and look at the comparability between intervention and control groups.

All this process is described as a flow-chart (Figure 20

Figure 21).

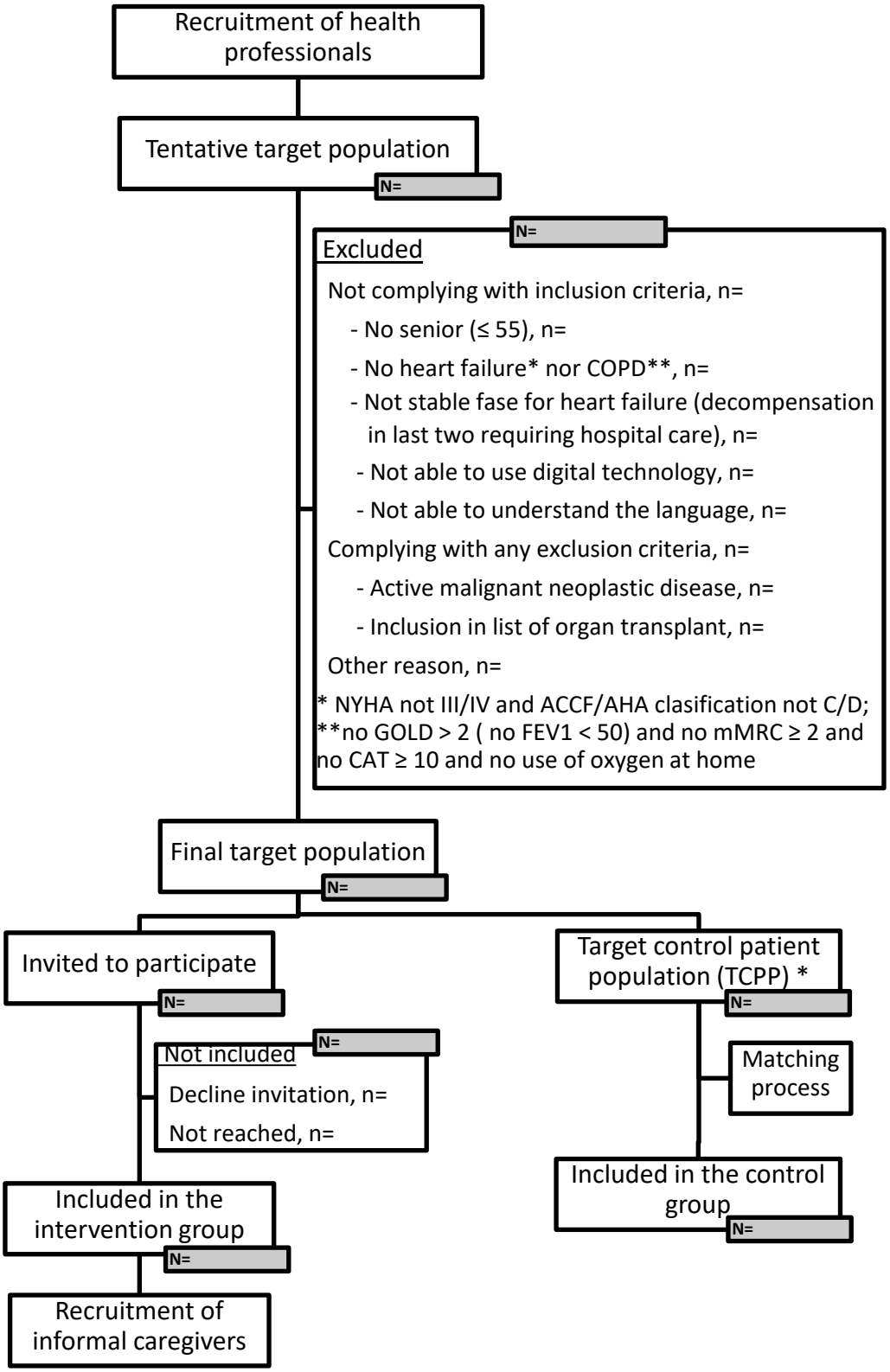


Figure 20.

Flowchart of the recruitment and selection process of intervention patients.

5.4.2 Selection of Control patients

The control group will be patients receiving care according to the health care organizations criteria. Their data will be extracted retrospectively and anonymously from administrative databases considering that patients included in this group should be comparable to the intervention group in demographic and clinical terms. Control patients will have the same clinical inclusion criteria, but the ITC literacy. As we will not contact the control patients, we will not obtain ICT literacy data from them.

After removing those patients who have consented to take part in the intervention from the final target population, a target control population will be identified by M33. Taking part in the intervention means that the patient has signed the informed consent to participate in ADLIFE study as intervention patient. Control patients will be selected from the target control population. Only patients from the initial eligible list who are not in the intervention group can be part of the control group. In case an intervention patient withdraws later the study, he/she won't be able to be selected as control.

To match the intervention and control group per site a propensity score technique will be used (as detailed in D1.1. Data Management Plan). Patients for the control group will be selected considering the following variables: age, sex, number of visits to ER and number of hospitalizations in the year prior to the intervention. A variant of the propensity score developed by Mebane and Sekhon which maximize the balance of observed covariates across matched intervention and control participants[23] will be used. This technique involves selecting individuals from each of the groups with balanced baseline characteristics as a function of the chosen variables with the goal of comparing homogenous groups and thereby reducing selection bias[24]. Different covariables can be balanced at baseline to later carry out the analyses in the weighted samples. Therefore, the number of patients in the intervention and control groups could differ, but they will be balanced by the weights.

5.5 Caregivers supporting patients and participating in the intervention

Each ADLIFE patient who is recruited for participation can appoint a caregiver whose contact details will be stored in the patient care plan. The caregiver is a person who provides occasional or regular support to supplement the patient's potential lack of autonomy. The degree of involvement and input of informal caregivers may vary considerably and is not a matter evaluation. They may or may not have regular face-to-face contact but are available most of the time by other means such as telephone, email or SMS, to respond to calls for

[23] Diamond A, Sekhon JS. Genetic Matching for Estimating Causal Effects: A General Multivariate Matching Method for Achieving Balance in Observational Studies. Rev Econ Stat. 10 de octubre de 2012;95(3):932-45

[24] Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. Multivar Behav Res. 2011;46:399-424. Diamond A, Sekhon JS. Genetic Matching for Estimating Causal Effects: A General Multivariate Matching Method for Achieving Balance in Observational Studies. Rev Econ Stat. 10 de octubre de 2012;95(3):932-45

help. Informal caregivers deliver health care that does not need formal healthcare education and that is in addition to formal care that the patient receives. The patient-informal caregiver pair aims to ensure autonomy, ICT management or the empowerment in their disease self-management, to name a few.

Appointing a caregiver is not mandatory. The appointment of caregivers will be done in writing, preferably when signing the informed consent form, but it could be involved later, if necessary. The appointed caregiver will receive notice (written or oral) about being announced caregiver and must express written informed consent to participate (Annex 15.4). These caregivers will have role-based access to the PEP, which needs to be authorised by the patient, and the patient training materials to assist the patient in adhering to treatment plans, reaching their treatment goals and to use ADLIFE self-empowerment resources.

The procedure to appoint caregivers as patient supporters during the intervention and to include them in the research trial is outlined below:

- Caregivers will also be provided with a patient information sheet.
- Caregivers must sign an informed consent form to confirm they have read and understood the patient information sheet and want to participate in the research trial as an informal caregiver.
- Candidates who agree to participate in the study must sign the informed consent form to confirm that they have read and understood the information and wish to participate in the study. Caregivers should retain a copy of the information sheet for their own reference.
- The signed informed consent forms will be scanned so that a copy is digitally available. Where this is not a routine procedure, the informed consent hardcopies will be stored securely to be available for the case being necessary.
- Caregivers will receive ADLIFE training together with the intervention patients and online training material at the pilot sites.
- Candidates who agree to participate in the study will receive information on when and how the interviews will take place.

Additionally, the same caregivers supporting patient will be invited to participate in the study as subjects of the study as other stakeholder to be evaluated. To do so, the following actions will be undertaken:

- Healthcare professionals will approach caregivers of the participating patients and who meet the inclusion criteria and explain the study, the objectives, the assessment and their expected involvement.
- When they confirm their interest in participating in the study, the healthcare professional will provide them with Participant Information sheet.
- Printed copies of the informed consent will be stored securely to be available in case it is needed.
- Study participants who sign the informed consent form will receive information on when and how the interviews will take place.
- All consented caregivers will be involved in the study as intervention caregivers
- Caregivers taking part in the intervention will receive ADLIFE application training at the pilot sites and online training material in the same period as patients November 2022 (M36) – till recruitment ends.

6 Study frameworks

ADLIFE has developed specific frameworks to support the effectiveness, socio-economic and implementation assessment in the project.

6.1 Health-related outcome framework

A working group of ADLIFE members, including physicians and patient advocates and outcome evaluation researchers, were organized to represent a wide background and define the set of health-related outcomes grouped around relevant domains for ADLIFE target population. Following ICHOM methodology, the group iteratively worked over a period of seven months in the definition of a comprehensive minimum set of health-related outcomes.

Then, the multidisciplinary team of healthcare professionals with representatives from the seven pilot sites agreed that the proposed domains achieved a good balance between feasibility and comprehensiveness. Domains accorded are an adaptation of the ICHOM standard set for ADLIFE target population: the selected domains correspond with the ones on the older person standard set and additional dimensions were proposed within them for including severe chronic patients' matters.

From a project perspective, we developed the health-related outcome framework to have a consensual definition of desired end results, for the outcome-based care planning and for the effectiveness and socio-economic assessment of the project (Figure 21 Health-related AREAS (inner circle) and DIMENSIONS (outer circle) of the data framework.). The framework allows us to group each of the primary and secondary outcomes by the broad health-related outcome to which it is responsive.

This work was conducted using resources from ICHOM, the International Consortium for Health Outcomes Measurement (www.ICHOM.org). The content is solely the responsibility of the authors and does not necessarily represent the official views of ICHOM.

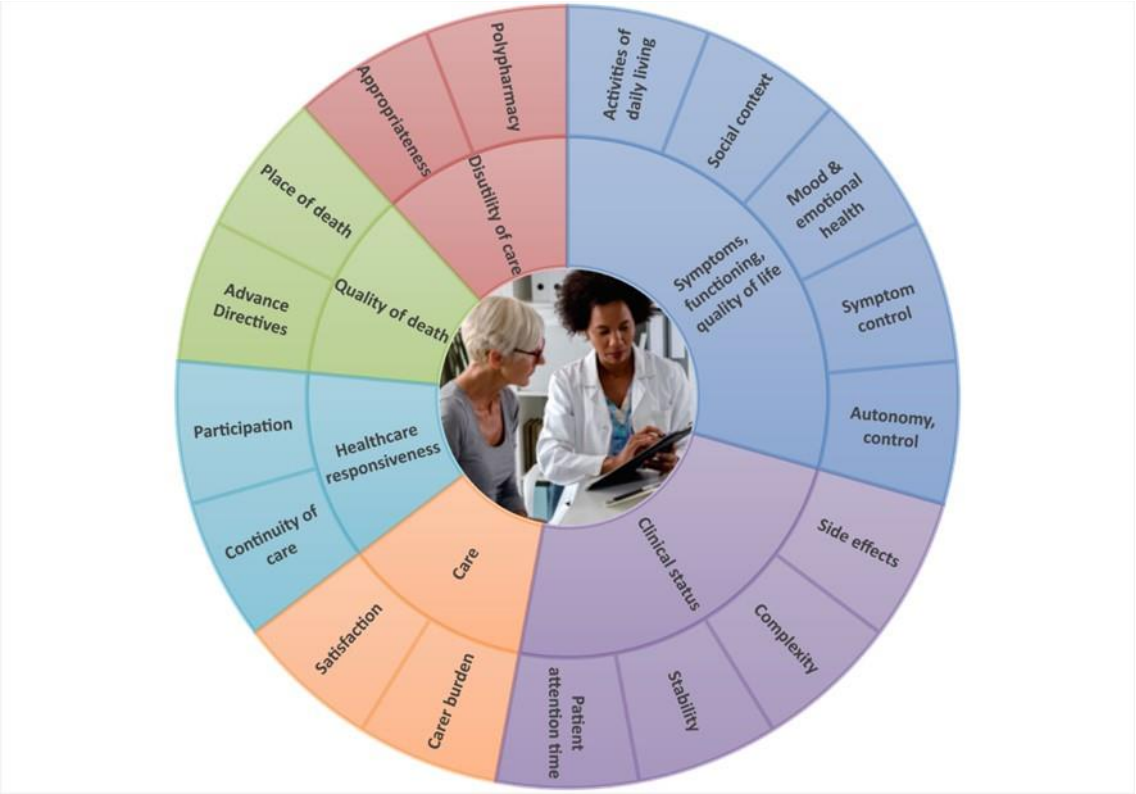


Figure 21 Health-related AREAS (inner circle) and DIMENSIONS (outer circle) of the data framework.

6.2Implementation framework

The implementation evaluation in ADLIFE focuses on three main parts including: (1) the evaluation of the implementation itself including outcomes on communication, coordination, implementation barriers & facilitators, quality of care, satisfaction with accessibility, satisfaction with PCP/usefulness, security and working conditions; (2) the evaluation of the technology acceptance and adoption; and (3) the evaluation of the contextual factors for further exploitation to later scaling-up.

This section focuses on part 3, the evaluation of the contextual factors for further exploitation to later scaling-up. To do that, interviews with relevant stakeholders will be carried out at pilot site level to understand how influencing factors on clinical workflows, financing, governance, and willingness to use of the ADLIFE toolbox can be assessed at the pilot sites.

To structure the process of data collection and the interview guideline, the Health Information System (HIS) evaluation framework HOT Fit by Yusof et al.[25] will be used. The framework consists of the three dimensions human, organization and technology and helps to analyse the "fit" between them (Figure 22). The better these dimensions fit into an HIS, the more likely the implementation will be successful. Besides the HOT Fit framework, the Consolidated Framework for Implementation Research (CFIR) will be used as well and will complement the domains of the HOT Fit framework. Together, these frameworks provide a structured and systematic way to identify constructs influencing the implementation of ADLIFE. Furthermore, these frameworks can be used to better understand and explain how and why the implementation of the innovations succeeds or fails, will guide the assessment of the process, and will identify factors that might influence the implementation effectiveness (Figure 23).

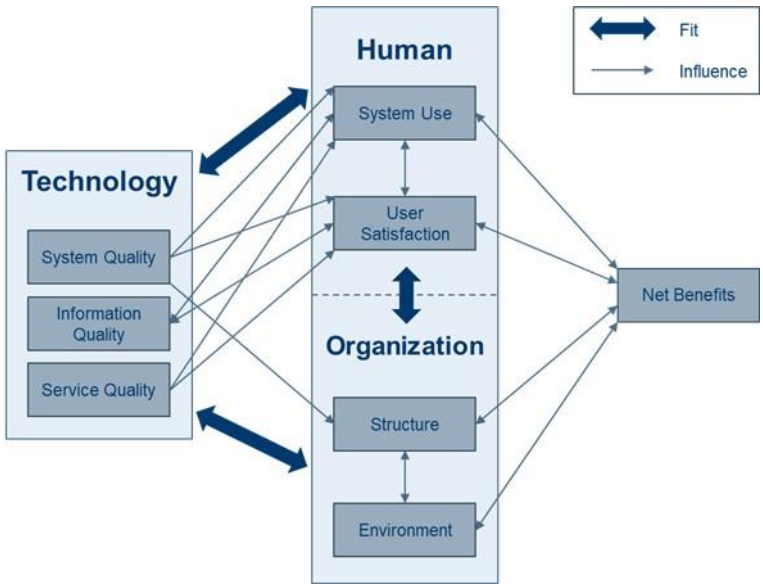


Figure 22. HOT Fit Framework by Yusof et al. (2008)

[25] Yusof, Maryati Mohd; Kuljis, Jasna; Papazafeiropoulou, Anastasia; Stergioulas, Lampros K. (2008): An evaluation framework for Health Information Systems: human, organization and technology-fit factors (HOT-fit). In: *International journal of medical informatics* 77 (6), S. 386–398.

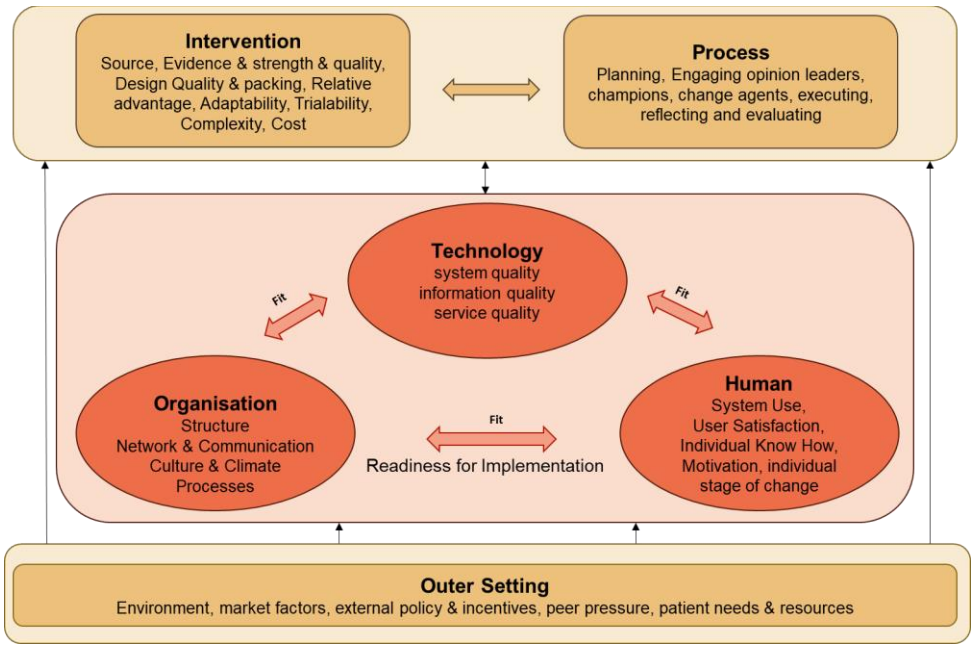


Figure 23. Common framework for Implementation research in ADLIFE

The ADLIFE Framework takes into consideration the aspects that influence implementation and to evaluate the ADLIFE system. It takes into account socio-technical elements of the ADLIFE system, such as the healthcare organisation, the environment and people involved. ADLIFE framework is complemented by the individual focus of the determination of the technology acceptance and adoption of the ADLIFE tools by its users (with the Unified Theory of Acceptance and Use of Technology UTAUT)[26] questionnaire).

7 Study Outcomes

The primary outcome will be the ER visits and will be assessed on patients. ER visits will be collected from EHR. As patient follow-up may range between 9 and 12 months, the average of ER will be measured as the sum of ER by patient divided by his/her length of the follow-up. This primary outcome is a proxy of the appropriateness care in real-life settings for advanced chronic diseases patients and consequently, a gain in health-related outcomes.

The secondary outcomes will be assessed on patients, caregivers and healthcare professionals.

[26] Venkatesh, V., Morris, M. G., & Davis, G. B. (2003). User acceptance of information technology: Toward a unified view. MIS Quarterly , pp. 425-478.

From a quantitative perspective, the Patient-Reported Outcome Measurements (PROMs): health-related quality of life (EQ-5D-5L), mood/emotional health (HADS-Hospital Anxiety and Depression Scale),activities of daily living (Lawton scale, Barthel Index, Kansas City Cardiomyopathy Questionnaire score, and COPD assessment test score) and complexity (Modified Medical Research Council –mMRC- Dyspnea Scale) will be assessed on patients, as well as their resource use and their associated costs. The caregiver burden, which encompasses burden of care (Zarit Burden Interview, ZBI) and the mental well-being (Warwick-Edinburgh Mental Wellbeing Scale, WEMWBS), will be assessed on caregivers. The likelihood of successful adoption and use of the ADLIFE technology by its user will be assessed on the three stakeholders with the Unified Theory of Acceptance and Use of Technology (UTAUT).

From a qualitative perspective, both healthcare responsiveness's dimension will be assessed on all stakeholders: perceived engagement on decision making process for being responsive to participation, and perceived communication among, perceived coordination among settings as well as the quality of care related to integration of care stakeholders for being responsive to continuity of care. Care satisfaction will be assessed on all stake holders with working conditions, accessibility, security and PCPs, and barriers/facilitators related to the implementation process... The clinical status, covering patient attention time and stability dimensions, will be assessed by perceptions on healthcare visits and hospital admissions burden, on healthcare professionals.

Finally, a set of variables will be collected for the descriptive analysis.

In addition, the contextual factors of the local health systems for further exploitation to later scaling-up of ADLIFE will be analysed with the key staff involved in patient care and ADLIFE in terms of human, organizational and technological factors following the main dimensions of the HOT-fit framework, by means of semi-structured interviews.

8 Study Evaluation

The evaluation of ADLIFE study has been laid out in three complementary evaluation approaches: Effectiveness, Economic impact and Implementation process. The analysis methodology has been described for each evaluation approach. ADLIFE evaluation analyses comprises quantitative, qualitative and socioeconomic impact analysis.

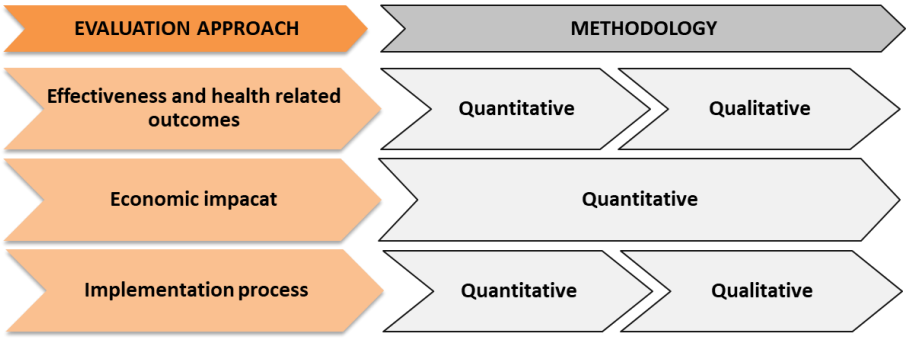


Figure 24. ADLIFE evaluation approaches and methodology

From this section forward, this document details the procedures and requirements of the evaluation phase of the project.

9 Data collection

Figure 8 timeline represents the sequential order of the data collection tasks required by the three evaluation approaches.

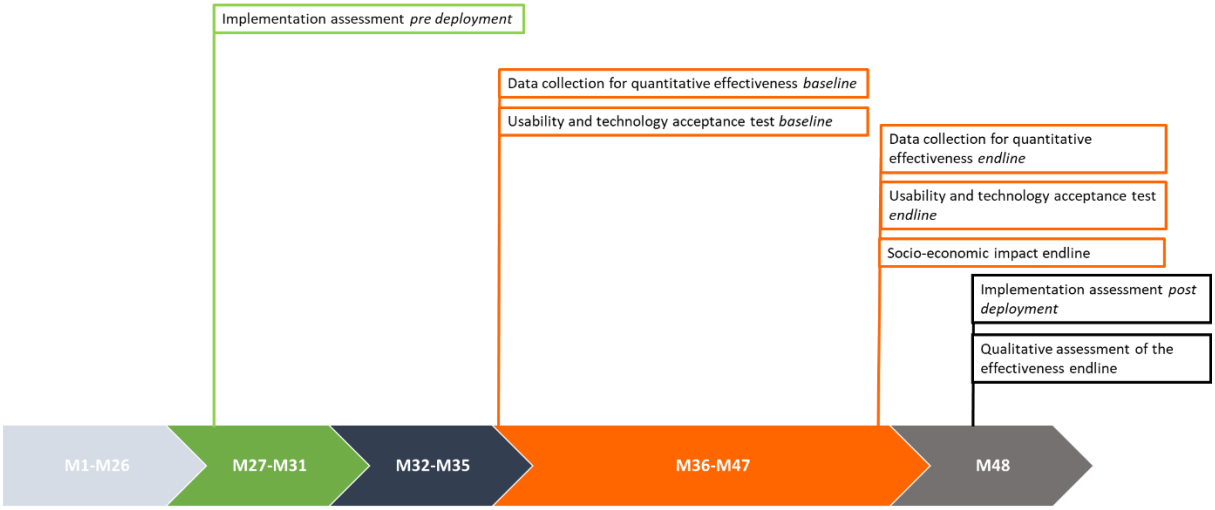


Figure 25. Timeline of data collection

Data collection follows the instructions and guide contained in the following documents, as described in Table 3.

Table 3. Supporting documents for data collection

Supporting documents for data collection	**Aim**	**Status by 05/05/2022**
Data collection guide for quantitative effectiveness v0.5	Effectiveness (Quantitative analysis)	Provided
Detailed protocol for qualitative assessment of ADLIFE intervention	Effectiveness (Qualitative analysis)	To be provided at a later stage
Data collection for the Economic assessment	Socio-economic impact	Provided
Interview Manual for Implementation Assessment	Contextual factors that are relevant for the translation of the innovation action into routine practice as part of the implementation assessment	Provided
Manual for technology acceptance and adoption evaluation v0.7	Explanation of the user intention towards the application of a new technology and the resulting	Provided

	user behavior as part of the implementation assessment	
Data collection guide for technology acceptance v0.3	Technology acceptance	Provided

9.1 Effectiveness assessment

A data collection guide, a codebook and three templates will be circulated across pilot sites to conduct the quantitative data collection on socio-demographic, clinical and resource use variables. Variables will be observed at baseline and at end of follow-up, except for the resource use which will be measured during the 12-months before and after the baseline. Data from control group and intervention period of the intervention group, will be retrospectively collected at 12-months follow-up. Data from control period of the intervention group will be retrospectively collected at 1-month follow-up. Intervention period of the intervention group will be prospectively collected. Data collection flow are shown in Figure 18.

Data will be collected from three data sources: the EHR, questionnaires and the FHIR repository. Each pilot site will provide its corresponding dataset to the evaluator site to be merged into a single data space. Further details can be found in the Data Collection Guide for the quantitative effectiveness evaluation (already provided, dcg_adlife_quant_effectiveness).

For the qualitative approach, semi-structured interviews conducted on patients, informal caregivers and healthcare professionals at end of follow-up, will be used to collect in detail the scheme of meanings of respondents. A purposeful sampling will be used to select the participants, recruiting those participants who might provide in-depth and detailed information about the ADLIFE intervention. These post-intervention interviews will involve: one medical director, six healthcare professionals (two physicians, two general practitioners and two nurses), two IT staff, three to six patients and, three to six informal caregivers. Interviews will preferably take place face-to-face, or virtually if necessary (telephone or videoconference). The interviews will be recorded and transcribed to a structured template. Further details can be found in the Detailed protocol for qualitative assessment of ADLIFE intervention (to be provided at a later stage).

9.2 Socio-economic impact assessment

9.2.1 Simulation modelling

About data collection for the simulation modelling, accessible healthcare databases will be used to obtain necessary data to calculate the mathematical functions and the simulation parameters that will guide the general simulation model, being in this case Basque Health Service databases (Osakidetza). From this source demographic, epidemiological and resource consumption patient-level data will be obtained in an anonymised way, that will be related to the population under study and the healthcare resources identified in the

conceptual model. That way, the population that will be used to develop the general simulation model will be in line with the specifications used to define the target population of ADLIFE project.

Regarding the unit cost data of different healthcare resources identified in the conceptual model, the idea is to obtain the unit costs that are applied in each pilot site to later adapt the model to each one. Because of that, if possible, the information about the unit costs will be obtained from official health service sources of each pilot site. The necessary unit cost information will be on the Data Collection Guide for Economic assessment.

Regarding population projections needed to foresee the impact of ADLIFE in time, they will be obtained from national statistics institutes databases of each pilot site.

9.2.2 ADLIFE intervention effect calculation

The evaluation of ADLIFE intervention effect will be developed measuring the change in the resource use profile of the patients participating in the project. The information relating to intervention and historic control groups will be obtained from pilot site experiences. All the resource use information necessary to develop this task can be found on the Data Collection Guide for the quantitative effectiveness evaluation (already provided). Nevertheless, to address the change in the drug consumption profile, the patient-level information about their total drug prescription cost will be on the Data Collection Guide for Economic assessment.

9.3 Implementation assessment

For contextual factors evaluation, further details on data collection can be found in the Interview Manual for Implementation Assessment, provided by WP10.

For Technology Acceptance and Adoption Evaluation, a structured questionnaire will be used for data collection. It will be adapted from the original UTUAT study, with additional questionnaire items for the constructs from related studies[27][28]. All the information necessary to develop this task can be found on the ADLIFE_Manual for Technology Acceptance and Adoption Evaluation_v0.6 and the Data Collection guide for Technology acceptance v0.2.

[27] Algharibi, A.J. and Arvanitis, T. N. Adapting the Unified Theory of Acceptance and Use of Technology (UTAUT) as a Tool for Validating User Needs on the Implementation of e-Trial Software Systems. DOI: 10.14236/ewic/HCI2011.1

[28] Algharibi, A. J. H. 2016. Technology validation for e-trial systems. Ph.D. thesis, University of Birmingham, UK.

10 Analysis

10.1 Effectiveness assessment

A mixed evaluation strategy will be performed combining quantitative and qualitative analysis as described in this section.

Additionally, an outcome-based evaluation of the care plan design will be conducted as part of the quantitative analysis. The set of outcomes will be reflected seamlessly in the ADLIFE workflow as labels that bind every activity, goal and/or indicator included in a care plan to a health outcome. The labelling mechanism allows us to get the needed data to track outcomes over time and over a wide spectrum of patients.

10.1.1 Quantitative analysis

Statistical analysis

For the quantitative approach, first a descriptive analysis followed by univariate statistical tests will be conducted. Categorical variables will be presented using the frequencies and percentages, n (%). Differences between groups will be analysed employing the x2 test. Continuous variables with a normal distribution will be presented as means and standard deviations (SD), while non-normal distributed continuous variables as median and first and third quartile, (Q1, Q3). Differences between groups will be examined using the Student's t-test and nonparametric Wilcoxon rank-sum test, respectively. Pre-post differences for categorical variables will be evaluated using McNemar's test for paired data. For continuous variables, Student's t-test and Wilcoxon signed-rank test for paired data will be used for normal and non-normal distributed variables, respectively.

The effect of the intervention will then be assessed by generalized mixed models for longitudinal data, taking into account the clustered structure of the data. Linear models will be used for continuous variables and logistic models for dichotomous variables. All models will be adjusted for potentially confounding factors and variables of interest. The pilot site of the patient will be included as random effect, in order to control the variability introduces by the differences between sites, and in order to obtain generalizable results. In order to consider the different time of follow-up of each participant, all models will be adjusted by this factor, i.e., the time of follow up will be included in the models as an extra covariable.

Health services data are usually characterized by being discrete, zero-inflated counts, and right-skewed. Therefore, special attention will be payed to the selection of the distribution which best fits the data. For this purpose, generalized additive model for location, scale and shape (GAMLSS) models will be considered in this study. These models are a generalization of the generalize linear model (GLM) and generalized additive model (GAM), and they allow the parametrization not only of the location parameter, but also the scale

and shape parameters in order to find the best distribution that fits the data[291]. GAMLSS models will be considered to evaluate the differences in use of health resources between the intervention and control groups, including the weights derived from the genetic matching algorithm.

In all quantitative analyses, we will use an intention-to-treat approach and set the level of significance at $p<0.05$.

10.1.2 Qualitative analyses

The qualitative assessment will take place at the end of the intervention, with the stakeholders' group that will participate in it. Qualitative techniques will generate a deeper understanding of the evaluation process, using patients, families and professionals' experiences and perceptions to provide a multi-perspective approach to the phenomenon. Through qualitative methodology, we try to better understand the situations, interpret phenomena and develop concepts in their natural context, emphasizing the meaning, experience and views of the participants. The health related outcomes for qualitative evaluation are described in section 7.

The main objectives of this qualitative evaluation are the following:

- To get patients, caregivers, professionals and managers' experiences and perceptions with the intervention.
- To evaluate the main outcomes from the point of view of the stakeholders.
- To explore healthcare professional´s satisfaction and working conditions.
- To complement the information obtained by the quantitative data.

Participants' selection

All the patients, caregivers, professionals and managers who fulfil with the following inclusion criteria will be eligible for this qualitative evaluation:

- Accept taking part in the intervention. Sign the informed consent.
- Participate in the intervention

[29] Stasinopoulos, D. M., & Rigby, R. A. (2007). Generalized additive models for location scale and shape (GAMLSS) in R. Journal of Statistical Software. https://doi.org/10.18637/jss.v023.i07

- Preferably: equal number of males and females

Sampling: Identifying and selecting individuals or groups of individuals that are especially aware or informed about or experienced with a phenomenon of interest is essential for reaching significant feedback and information. We will employ a purposeful sampling to select the participants, recruiting those patients, caregivers, professionals and managers who can provide in-depth and detailed information about the intervention.

Procedure

The semi-structured interview is the selected qualitative technique. It is useful technique to learn behaviors, experiences, opinions, beliefs, feelings, knowledge, sensations or other aspects. Its aim is to discover in detail the scheme of meanings of the respondent[30]. It is suitable when the interest is to know personal views rather than reach consensus, for which there are other techniques. Specifically, we have chosen the semi-structured interview because, although we must employ a standardized set of questions, which ensures collecting information in a systematic way, it allows introducing changes in the order of the questions and also in the content of the questions as well (adding questions if necessary). The aim is always to delve deeply into the topic that is studied and to understand the answers provided.

In particular, this is the proposal to be performed in each pilot site:

- patients (n=3-6);
- caregivers (n=3-6);
- clinicians (n=6-10);
- and managers (n=6-10)

The interviews will be carried out together with the post-intervention interviews for the assessment of contextual factors for further exploitation (Section 10.3.1). The interviews will take place in a suitable location, may be conducted face-to-face, via telephone or video call and will comply with all local COVID-19 related restrictions in place at that time. All interviews will be recorded on encrypted recording devices to allow the local research team to download the audio files, transcribe them and listen to/read interviews as many times as necessary after the interaction itself in order extract all the information required to complete the analysis. Interview data (audio or text) will be stored in a secure database in the local clinical site that can be accessed only by members of the local ADLIFE research team via password protected computers.

The coordinators of the evaluation (WP9) will send the evaluation detailed protocol to the pilot sites, where guidelines for the implementation of the interviews, the set of questions to be formulated to the stakeholders and the templates for the reporting of the results will be included. The templates will not contain any sensitive data from the patient. They will collect the age, gender, role and pilot site origin of the interviewee and regarding the content of the interviews, will include a summary of the answers given by the participants to each question asked in the interviews, and literal quotes from participants that support the summary.

[30] Harrell MC, Bradley MA. Data Collection Methods. Semi-Structured Interviews and Focus Groups. RAND Corporation, 2009.).

The templates containing the qualitative data will be hosted in sharepoint, in a folder created ad hoc for this purpose where the administrator, who is the Project Coordinator, will manage access and editing permissions to ensure the protection of the data uploaded.

These are the steps to be followed for the performance of the qualitative evaluation:

- Qualitative Evaluator partner (KG, WP9) informs the designated staff in each pilot that the templates for the qualitative evaluation are available in the ad hoc folder in sharepoint (M46)
- Designated staff in each site performs the qualitative work (interviews, transcription, analyses....) (M47-M50)
- Designated staff in each site completes the qualitative templates, upload the results (the filled in templates) in the ad-hoc folder in the sharepoint and informs Evaluator partner (M50)
- Qualitative Evaluator partner carries out the qualitative analyses of ADLIFE intervention (M50-M53)
- Preparation of the documentation for D9.2 (M54)
- WP9 submits the results in D9.2 (led by WP9) (end of M54).

The tasks to be done in this qualitative evaluation and their responsible are presented in the following graphic (Figure 26):

Figure 26 Qualitative evaluation tasks

Qualitative Analysis

Once the interviews have been transcribed, the analyses will follow two phases: (1) a within country content analysis in the national language, to be performed by each pilot site and (2) an aggregated analysis in English, merging the data collected in all the pilot sites in a uniform manner, to be done by the WP9 coordinators.

Phase 1: The content analysis is a systematic coding approach to explore large amount of information to determine trends (codes) and patterns within the text[31]. The qualitative outcomes (section 7) will guide the analyses, using them to deductively organize the main codes identified and the relationships between them. During the analysis additional codes

[31] Vaismoradi M, Turunen H, Bondas T. Content analysis and thematic analysis: Implications for conducting a qualitative descriptive study. Nurs Health Sci. 2013 Sep;15(3):398-405. doi: 10.1111/nhs.12048

can be inductively added. For each main code, a comprehensive set of quotes will be transcribed to ensure comparability between the different regions.

Phase 2: these results will be further validated through the process of data triangulation between the sites and data sources. It is expected that comparing the results between sites and different stakeholders will add breadth and perspective to these qualitative insights.

10.2 Socio-economic impact assessment

A socio-economic impact assessment will be carried out to develop scenarios for the long-term sustainability of ADLIFE intervention, feeding business planning for the exploitation and sustainability of technology. For that purpose, simulation models will be used. Simulation models can be usefully employed to estimate the economic impact and long term prediction of interventions like ADLIFE. They can provide behavior information of the system under study without actually testing it in real life[32], as far as they mathematically simulates a real-life situation using simulation software. As different predictions can be made by changing the variables used in the simulation, simulation modelling is a tool to virtually study and assess different scenarios.

The principal idea is to develop a general simulation model that will be common for all pilot sites and then adapt it to try to capture each pilot site situation. In an initial phase the natural history and the conceptual model of patients with advanced chronic diseases like heart failure (HF) and/or chronic obstructive pulmonary disease (COPD) will be defined. In a second phase, the general simulation model will be developed and validated using available databases. In a third step, the ADLIFE intervention effect will be calculated and added to the model from pilot site experience. Finally, the economic impact and long term prediction of the ADLIFE project will assessed running the simulation models. All the information will be obtained from accessible databases or from the codebooks defined for the quantitative effectiveness and socio-economic impact assessment.

10.2.1 Simulation modelling

Simulation modelling methodology will be used to (i) represent in a dynamic way the natural history of patients with advanced chronic conditions and to (ii) calculate the economic and long term impact of the project. To carry out the task discrete event simulation (DES) technique will be used[33]. DES is a flexible modelling method that can represent complex behaviours and interactions between different individuals, levels and environments.

First the conceptual model that will rule all the interactions of the simulation model will be defined, taking into account that the natural history of patients with advanced chronic diseases is characterized by frequent transitions between compensated and decompensated

[32] Stahl JE. Modelling methods for pharmacoeconomics and health technology assessment. An overview and guide. Pharmacoeconomics. 2008;26:131-48.

[33] Karnon J, Stahl J, Brennan A, Caro JJ, Mar J, Moller J. Modeling using discrete event simulation: a report of the ISPOR-SMDM modeling good research practices task force-4. Value Health. 2012;15:821-7.

states over time. After that, the mathematical functions will be calculated and the general simulation model will be built up to represent the evolution and care pathways of patients in the current scenario. Once the model is properly calibrated and validated, the intervention effect will be added to represent the ADLIFE scenario. Finally, for a current epidemiological scenario and a scenario altered by ADLIFE, the burden of the disease will be obtained multiplying resource consumption rate by unit costs and projected in time using population projections. In order to run the model and obtain results for all the pilot sites, the population projections and unit cost used can be adapted per site. That way, the impacts will be determined for each pilot site under both scenarios.

Among the analyses needed, the mathematical functions that will rule the simulation model will be obtained developing a parametric survival analysis of the data. In the analysis different distributions will be tested as survival functions and all the functions will be adjusted by independent variables (age group, sex and diseases). The type of function that best fit with the observed data will be selected using the statistical Akaike Information Criteria (AIC).

10.2.2 ADLIFE intervention effect calculation

The evaluation of ADLIFE intervention effect will be obtained from pilot sites experience during the trial measuring the change in the resource use profile. First a descriptive statistical analysis will be carried out, in the same way as described in the quantitative evaluation part, to see if there are differences in sociodemographic, clinical and resource use data by group. Second, adjusted regression models will be used to perform the analysis and assess the effect of the intervention. All models will be adjusted by age group, sex and diseases. From this analysis hazard ratios (HRs) will be obtained, the ones that will later be incorporated to the general simulation model in order to differentiate the ADLIFE scenario from the current scenario.

10.2.3 Economic impact and long term prediction

Economic, epidemiological and quality of life impacts in the long term will be obtained running the simulation models. As resource consumption and cost of both scenarios will be projected in time using the population projections, the burden of the disease will be determined under both scenarios and a budget impact analysis (BIA) will be carried out[34]. The BIA estimates the financial consequences of adoption and diffusion of a new healthcare intervention[35]. That way, the changes that can occur in in the expenditure of the healthcare system after the adoption of the ADLIFE intervention will be addressed.

[34] Soto-Gordoa M, Arrospide A, Merino Hernandez M, Mora Amengual J, Fullaondo Zabala A, Larrañaga I, et al. Incorporating budget impact analysis in the implementation of complex interventions: A case of an integrated intervention for multimorbid patients within the CareWell study. Value Health. 2017;20:100-6.

[35] Luo Z, Ruan Z, Yao D, Ung COL, Lai Y, Hu H. Budget impact analysis of diabetes drugs: a systematic literature review. Frontiers in Public Health. 2021;9.

10.3 Implementation assessment

10.3.1 Assessment of contextual factors for further exploitation to later scaling-up

With the aim of evaluating the contextual factors that are relevant for the translation of the innovation action into routine practice, the initial step will be the conduction of semi-structured interviews (or if possible, focus groups) with relevant stakeholders (e.g., IT staff, physicians) at the German pilot site. The aim of the initial interviews/focus groups will be to find out more about the existing technical infrastructure, the environment and structure of the organizations as well as the motivation of participating persons and to test the qualitative assessment approach in analyzing contextual factors. Based on the results and experiences we will determine how the contextual factors can be assessed at the other pilot sites. Thus, this initial step will be a pilot for the overall assessment of the contextual factors that will be assessed in more depth in all pilot sites.

To interview relevant stakeholders at the German pilot site, semi-structured interview guidelines will be developed which are based on the dimensions of the ADLIFE framework for implementation assessment and include questions on the status quo of technological, organizational, and human aspects, as well as questions about the ADLIFE project itself. Stakeholders that will be included are: Physicians (planned N=10), nurses (planned N=4), health guides (planned N=4), IT staff (planned N=1) and the clinic CEO (planned N=1).. Since this assessment will take place before the actual implementation, not all sub dimensions of the actual HOT-fit framework can be considered. Prior to the implementation, information quality and user satisfaction cannot be assessed. Thus, a modified HOT-Fit framework will be used.

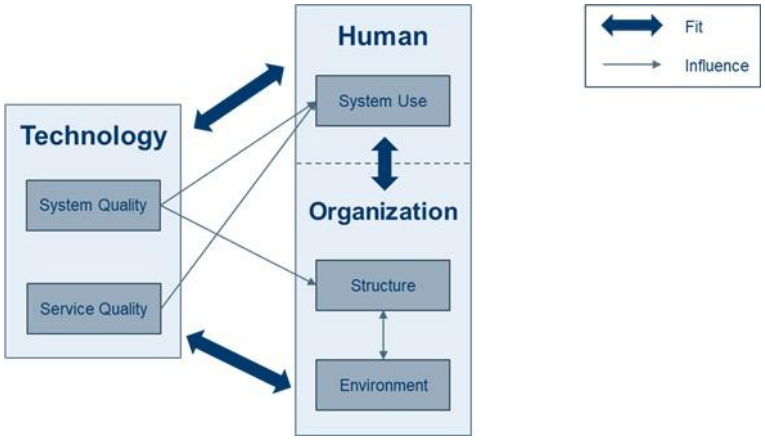


Figure 27. Modified HOT Fit Framework

For the analysis, all interviews will be verbally transcribed and pseudonymized. The data will be analysed using the qualitative analysis[36] (Kuckartz, 2014) and the qualitative analysis program MAXQDA. In the analysis key aspects of the questions will be summarized and structured according to human-, organizational-, technological factors. Subsequently, the results will be embedded in the current literature Based on the results, a guideline for the implementation assessment will be developed which includes key elements that are worth assessing in the other pilot sites and need to be considered for an effective IT implementation . The result is the guideline to assess the current status on human-, organizational-, technological factors in the other pilot sites (Interview Manual - Implementation Assessment), which facilitates a homogenous data collection at all pilot sites. The manual provides the methodology and analysis guidelines to identify, analyse and synthesise the contextual and implementation factors that influence the adoption, scaling and effectiveness of ADLIFE tools in different pilot clinical sites, based on interviews with key stakeholders.

After the implementation of the ADLIFE toolbox a follow-up assessment is planned to learn from the implementation process in the different pilot sites (M47). Both assessments will be done using qualitative interviews (or focus groups if possible) with key staff. The post assessment will be done together with the qualitative analyses of the effectiveness assessment (Section 10.1.2). To enrich the qualitative data assessed with the interviews, ADLIFE internal documents that were developed within other project task (e.g., documents on IT implementation and preparedness of the pilot sites) will be reviewed and will feed in the analysis. If it is not possible to conduct interviews, the interview guidelines will be sent out to to provide written feedback alternatively.

10.3.2 Technology acceptance and adoption

Survey data will be exported from Qualtrics to a statistical software package, such as STATA. Descriptive statistics will be used to summarise the participants' demographics and core set of constructs. To measure the reliability of the model's constructs and form correlations between then, data analysis will be done using technique such as structural equation modelling, a multivariate statistical analysis technique that is used to analyse structural relationships and tests the underlying factors and hypotheses.

A structured questionnaire will be used for data collection and will adapted from the original UTUAT study, with additional questionnaire items for the constructs from related studies[37][38]. The questionnaire has an open-ended question at the end for participants to express their opinions, concerns or give suggestions. Depending on the quality of responses, some qualitative data analysis will be done to identify themes and related comments.

[36] Kuckartz U. (2014). Qualitative Inhaltsanalyse: Methoden, Praxis, Computerunterstützung. Weinheim und Basel: Beltz Juventa.

[37] Algharibi, A.J. and Arvanitis, T. N. Adapting the Unified Theory of Acceptance and Use of Technology (UTAUT) as a Tool for Validating User Needs on the Implementation of e-Trial Software Systems. DOI: 10.14236/ewic/HCI2011.1

[38] Algharibi, A. J. H. 2016. Technology validation for e-trial systems. Ph.D. thesis, University of Birmingham, UK.

11 Data management

A member of Kronikgune (project coordinator) will be the Data Protection Officer (DPO). This Officer will guarantee that the data collection and analysis are performed according to current EU and national legislation. The DPO will analyze whether pilot sites have to conduct an impact assessment. The detailed information related to the GDPR COMPLIANCE CHECK and the impact assessments required are included in D11.2. ADLIFE Impact Assessment.

Data Protection Officer (DPO) and will work closely with Data and Safety Management Group (see below). The Data and Safety Management Group will be formed by representatives of 6 pilot sites. These local Data and Safety managers will assure that data collection is done according to the current legislation meaning that privacy, confidentiality and ethical approvals are covered. This Data and Safety Management Group will report in a regular basis to the Data Protection Officer and the documentation will be included in dedicated sections of the Periodic Report to the EC. The Data Management Plan will describe how this Data Protection Officer proceeds as well as the data sharing agreement and the corresponding permissions in relation to data import and export

ADLIFE Data Management Plan (DMP) D1.1. determines which datasets can/cannot be considered open access, along with the following data sources that have been identified:

- Technical reports by the Project Technical Committee (PTC): project partners and WP leaders will jointly produce technical reports. The Quality Assurance Plan will detail the management procedures required to guarantee that project documents are correctly and efficiently produced, updated, distributed and stored.
- Generated data on main results: this data will reflect the quantified impacts that ADLIFE displays under real piloting conditions in the seven regional healthcare models (WP9). Key results will be disseminated among all involved stakeholders. Dissemination/sharing and/or exploitation/protection of results generated will be subjected to the decision of the consortium, with the supervision of the coordinator.
- Scientific publications, conferences, EU Events, trade fairs and workshops: results and achievements in the project will be disseminated among the healthcare professionals, managers and regulators; scientific community; industry, and further key stakeholders. The publications shall include acknowledgements to the project and be communicated to the technical coordination.
- Open Access (OA): prior to publishing any scientific publication, the partner involved will contact the SC for revision and validation. Partners will provide OA to all peer-reviewed scientific publications relating to its results. The authors of all peer-reviewed scientific publications will choose the most appropriate way of publishing their results, and these publications will be stored in an OA repository, during and after the project's life. The consortium will also select access research data (free of charge or restricted access and/or use).
- ADLIFE Data collected/generated: ADLIFE is going to collect very sensitive data from the participants in the pilots and health systems. ADLIFE will provide anonymization, authentication, and authorization and audit services based on widely accepted international standards. Evaluation data will be stored in centralized repository so no direct access to participating health systems information will be feasible. The accession and re-use of this will stored information (data sharing) will be analysed during the project but it is expected that partners will require that any use of these data by a third party must address a scientific question in ADLIFE research area that will be evaluated and approved/rejected by ADLIFE´s committee.

- Data collected from newsletters and website subscribers: The project and all partners are committed to respect the personal data processing principles under the GDPR, and will be led by i-HD, expert in the area.

11.1 Data protection, security and privacy

The project will act in accordance with the European Human Rights Convention, especially with regard to privacy and autonomy. Each test and intervention conducted within ADLIFE will follow the guidelines set out by the World Health Organization on its "Handbook for good clinical research practice (GCP)", the Helsinki Declaration of 1964 (Recommendation for conduct of clinical research), the Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine, the UNESCO Universal Declaration on Bioethics and Human Rights, and the recommendations from the UNESCO World Commission on the Ethics of Scientific Knowledge and Technology (COMEST), among others.

Regarding data access, protection and sharing, ADLIFE will follow the procedures indicated in the new general data protection regulation No 2016/679 that has been recently applied in Europe and will seek local Ethics Committees approval ensuring data access, process and storage. Agreement of the consortium partners will be necessary to access and to share data.

ADLIFE is a research project where we will collect and process data related to patients, care givers and healthcare professionals taking part in the intervention to evaluate ADLIFE application. Therefore, internally within ADLIFE, two principles must operate - pseudonymisation of data (coding protection) to reduce the risks of identification; and confidentiality (the duty of care to protect the privacy of the individual, especially where the individual remains identifiable). ADLIFE must equally operate in a way that outside the project, data is always unidentifiable/anonymised.

11.2 Compliance with legislation

ADLIFE will provide anonymization or pseudonimization, as applicable, authentication, authorization and audit services based on widely accepted international standards. The implementation of this revised methodology will comply with the data protection legislation of the European Union GDPR and additional legislation in each country on health care data and medical research.

ADLIFE proposes to conceive the digital solutions as "medical devices" so they can fulfil not only the General Data protection regulation but also the Medical Devices Regulation (MDR). Therefore, all the necessary security and privacy mechanisms will be implemented to safeguard the secure access, sharing and storing´s of patients 'personalized information. Audit trails for electronic health records will be analysed and suitable profiles for integrated care will be selected. ADLIFE will provide an Audit Record Repository that maintains audit trail records implemented as an FHIR AuditEvent resource.

ADLIFE will generate a robust and large amount of data to support the recommendations in the digital health sector.

According to GA Article 18 the beneficiaries have the obligation to keep records and other supporting documentations for a period of five years after the payment of the balance.

11.3 Pseudonymization of data from intervention branch

Data from intervention participants will be pseudonymized for the evaluation process to reduce risks from the perspective of the data subject. Pseudonymization (coding protection) enables to uncouple specific data aspects from a data subject whereby the most identifying and/or sensitive data fields in the record are replaced by pseudonyms. In ADLIFE, secondarily processed data will be obtained as a result of quantitative and qualitative analysis. Depending on the evaluation purpose, raw data (surveys, questionnaires, records of focus groups and interviews) will be manipulated accordingly in order to assure the privacy and security of data. This data processing will be carried out following the data protection regulation No 2016/679. The project will only collect essential data (clinical, health-related, use of resources, perception of participants) that will enable assessing the impact of the ADLIFE intervention in terms of patient health status, functionality and autonomy and system efficiency. The collected data will be used for the purposes of evaluation, impact assessment and growing the evidence base.

During the evaluation phase, the outcomes from intervention patients will be exchanged and discussed with the evaluation team at the project level. This process will not include any identified patient data. The evaluation team will work only on pseudonymized data collected from intervention patients from the seven sites. Each site will create its own data bases from patients taking part in ADLIFE. A local Data Manager will be responsible for the pseudonymization of intervention data in its site. Only the data manager, who has the authorization, will be able to reverse the pseudonymized data, if required. In each site, the pseudonymized data base will be transmitted from the site to the evaluator partners.

For the pseudonymization, the intervention patients will be assigned with a unique code, study ID, associated with the patient, when are registered in ADLIFE. The study ID will be generated automatically at the registration time or at a later time of a patient in the PCPMP, by the Data Manager of each site. The mapping between study ID and real ID will be managed by each Data Manager in each site.

The following numeric coding has been proposed to identify the pilot sites:

Pilot site	**Numeric coding for intervention patients**
Basque Country (OSAKIDETZA)	1001-1999
United Kingdom (University of Strathclyde - NHS Lanarkshire)	2001-2999
United Kingdom (UHCW NHS Trust)	3001-3999
Denmark (Odense University Hospital - OUH)	4001-4999
Germany (Gesunder Werra-Meißner Kreis -GWMK)	5001-5999

Sweden (Region Jämtland Härjedalen - RJH)	6001-6999
Israel (Assuta Ashdod Hospital together with Maccabi Healthcare Services Southern Region)	7001-7999

11.4 Anonymization of data from control branch

The control patient data for the period M36–M47 will be extracted from the respective care centres in M48. This one-time extraction will be undertaken, at the end of the pilot study, so that the extracted data covers the same period as the intervention group. Control data on the agreed clinical and empowerment variables, use of services and healthcare consumption, will be retrieved retrospectively at individual level.

For the analysis off site, robustly anonymised data will be extracted from control group in each site. For the anonymization of the control data, an automated solution will be provided to the sites. To have this process automatized reduces the risk and training issues for the sites and also provides a reliable standardized solution. The approach for the automatic anonymization of the control patient data will be based on the NTTData's script used for anonymizing machine learning training healthcare data.

The anonymization techniques selected as the rules to be applied to ADLIFE databases before any processing from control group data have been defined by the consortium and described in 20211006_UPDATE_ADLIFE_setoftechniques_anonymization. The variables to be extracted include: Demographic information and diagnoses, Scales and questionnaires, Tests and measurements, Lab tests results, Use of healthcare resources. For this purpose, variables have been classified as Direct and Indirect identifiers. The description of the identifiers and the transformation type agreed in the project are described in the Table 4.

Table 4. Description of the identifiers and the transformation type

Classification	Description	Transformation type
Direct identifiers	Patient ids	Substitute by a number that is not linked to the real ID. No key required. If a scenario where re-identification may be required, a pseudonymization procedure will be considered.
	Geographic ids and socio-economic stratification	To be defined: Geographical sectors/areas related with the socio-economic stratification. The proposed index is the Deprivation Index.
Indirect identifiers	Precise dates	A random date previous to all dates of birth in the data base will be selected as the date of reference (date 0) for every patient in the data base. All precise dates in the extracted patient data will be referred to the time lapsed in days from that date of reference. Owing very precise connection between items may reveal relevant patterns and results (such as the date of a test result and a change in treatment based on the result), no additional protections are advised.
	Measurement or lab results	We consider them as sensitive attributes to be protected as-is for the sake of the research question with the transformation of the precise date *(see precise dates row)* associated to each measure/result.
	Number of contacts with a service	We consider them as sensitive attributes to be protected as-is for the sake of the research question with the transformation of the precise date *(see precise dates row)* associated to each contact.
	Diagnostic/ Treatment code	We consider them as sensitive attributes to be protected as-is for the sake of the research question with the transformation of the precise date *(see precise dates row)* associated to the clinical finding or prescription

The quality assurance of the set of anonymization rules in ADLIFE has been carried out over the Osakidezta's database for the tasks of machine learning training (more detail can be found in 20211006_ADLIFE_anonymization_methodology). The results of the quality assessment show that the equivalence class with the highest re-identification risk is the demographic information file including: id_patient, birth_date, exitus_date, sex, deprivation_index, nursing_home and exitus_place. The results conclude that the re-identification risk amounts to 0.00131%.

The anonymization techniques will be run on site. Each site will create its own data bases with control patient data. This data base will have neither identifier nor demographic descriptors. This data base will be modified according to the ADLIFE anonymization set of techniques following the script provided by NTTData and the resulting data base will be transmitted from each site to evaluation partners. Therefore, control data won't be able to be traced back.

11.5 Organizational processes to support privacy

Privacy and other rights of the data subjects participating in the intervention will be assured by organization process described in D11.2 ADLIFE Impact Assessment. The mechanisms for authentication and authorization of users who access to sensitive data are explained in depth. ADLIFE procedures are based on widely accepted international standards that ensure the confidentiality and integrity of the data communication among ADLIFE components, eg. application of industry standard cryptographic algorithms and protocols, user accountability through audit trail mechanism, etc.

11.6 Data transfer for evaluation

Evaluation analyses will be carried out with control healthcare data and intervention healthcare and patient/healthcare professional reported data collected in each pilot site. The data for project evaluation purposes will only be available to the site from which the data is originated, it will be kept within the healthcare provider infrastructure. For the evaluation process, these data will be coded protected as described above in order to reduce risks. The relevant individual-level data for study evaluation will be processed as described above (sections 11.3 and 11.4) and will be sent to the evaluation partner in a manner to be agreed upon. Evaluation partners will carry out the clinical evaluations of the ADLIFE solution as described in section 8. D1.1 Data Management Plan describes in more detail the envisaged data flows and processing for evaluation purposes within the ADLIFE pilot sites. The evaluation data will be stored by evaluator partners in physical servers within the secure environment of the evaluator partner, under the terms of the ethical approval.

12 Future work

The future research work will focus on several areas.

- The implementation of more decision support systems based on clinical guidelines for other conditions than the diseases tested in the project
- The adoption of ADLIFE care model for addressing any chronic diseases, achieved by the customization of the toolbox.
- Long-term priorities in the field of senior care management providing solid grounds for more effective and efficient personalized care plans.
- Development of innovative solutions aiming at sustainability and cost effectiveness of public health

A Data Access Committee will be created within the consortium to determine the policies for data access. These policies will aim to identify the data sets for open data access and

to ensure the required approvals are in place. More information about the access to data and ownership of data to support future studies and activities by members of the consortium and external partners are detailed in the D1.1 Data Management Plan v0.4.

13 Significance

ADLIFE responds to the societal and health system challenge in Europe of an increasing number of persons with Advanced Chronic Diseases, often with accompanying co-morbidity, polypharmacy, frailty and sometimes isolation. ADLIFE will provide a solution for the integration of therapies and approaches targeting the early detection and assessment of deterioration, advanced and well-coordinated care planning and integrated supportive care to enhance quality of life, reduce suffering and accelerate recovery from illness deterioration.

ADLIFE is going to demonstrate that it is feasible to provide a personalized integrated care to improve the health situation, deliver more appropriate targeted and timely care for patients with Advanced Chronic Diseases by the means of the use of an innovative ADLIFE toolbox that will support early detection. ADLIFE will produce guidelines and policy recommendations providing financial sustainable, flexible and replicable solutions to disseminate results, transfer and deploy at large-scale to other patient groups in the EU and beyond and create further business and job creation opportunities.

The strong inclusion and commitment by the public health care organisations in the seven regions implies that there is a strong probability of the results to be taken further after the study period transformed into routine improved health care services for this important group of patients.

ADLIFE is based on secure and robust digital solutions for management of chronic diseases, developed and implemented in previous projects such as C3-Cloud, Power2DM, ASSEHS and CAREWELL.

The ADLIFE technical development will be completed and demonstrated as prototypes to the European Commission by M34. Results of the evaluation study are anticipated to become available by Mid-2024.

14 Ethical considerations

Several ethical challenges have been identified in addition to the issues regarding recruitment and consent of study participants.

14.1 Protection of confidentiality including anonymity of patient identifiers

ADLIFE security measures protect patient privacy to an extent that meets information security requirements of health systems internationally, and complies with the latest data protection legislation (including the GDPR). Only the already assigned healthcare professionals working with the patients in the participating health care organizations have access to identifiable data in a protected environment.

The project has no direct control over the environment in the patient's home where the patients will have access to their care plan information. However, it is considered that the risk of an unintended confidentiality breach here is minimal and controllable by the data subjects. In many cases it is expected that other persons of the household would act as an informal caregiver e.g. a spouse and will actively participate as a receiver of information to aid the patient. This is of course subject to patient consent at the project start.

14.1.1 Unexpected findings and new discoveries

The healthcare and medical treatments provided to the patient therefore do not differ from control patients or regular patients. The patient thus has a right to know about any unexpected findings or discoveries unearthed as part of research carried out in ADLIFE just as if the patient were not participating in the ADLIFE study.

14.1.2 Limitations of the study

This study has specific limitations which reduce the comparability of intervention and control patient cohorts. These include:

- Participants are not randomly selected, so a number of limitations will be derived from that. Thought, the technique for the selection of controls and the analysis methods proposed, will allow to the control of the main potential bias and assure the generalization of the results.
- ITC literacy shall not be checked in control patients. This may introduce some bias for the type of patient who does know how to use technologies.
- Selection of intervention by HCPs/Research assistants will be done according to their subjective assessment, looking for the ones who most can beneficiate from the intervention.
- Gender parity in both intervention and control groups will be sought but it won't be compulsory. The recruitment is a tough task and it would make it more difficult.

14.2 Drop-out

In the event participants drop-out of the project, their previously collected data will be retained, unless otherwise stated, and analysed under the intention-to-treat principle. Drop-out reasons will be defined as: i) death, iii) not interested in the intervention anymore, iv) too much time-consuming, v) technology issues, vii) other and, vii) no response. Patients may also declare institutionalization or lack of help from the informal caregiver as drop-out reason. The patient's decision to drop-out will be registered. Informal caregivers will be automatically drop-out of the project if their patients do so. In the case of healthcare professionals, any position change will be also considered as drop-out reason. ADLIFE partners have developed Withdrawal of consent forms (Annex 15.5).

14.3 Publication of study results

The study results will be made public as reports in international scientific papers, as press releases and verbally at local, national and international scientific meetings. An ADLIFE Publications Policy Board is convened and will be chaired by Dr. Lisa McCann, co-Lead of WP2. The role of this Board is to advise on the suitability of publication plans and have final editorial responsibility to implement Steering Committee (SC) and Project Technical

Committee (PTC) decisions regarding the approval of submission to a journal, a conference or other. Additional information on the publication of study results is detailed in deliverable D2.1 “Communication and Dissemination Plan and Communication material”.

The project may also produce a summary of the findings to be communicated to the study participants

15 Annexes

15.1 Screening of eligible patients

- The ICD diagnosis codes used in the pilot sites to screen for eligible patients are listed in next table.

Diagnosis codes used for patient screening **(*=all sub-groups).** Condition	ICD-9	ICD-10
Heart Failure	428*, 401, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93	I50*, I11.0, I13.0, I13.2 and I13.9.
COPD	492*	J44*

- Drugs for Selecting Patients Who meet Inclusion Criteria

COPD Drugs	**Generic Names**	**ATC Codes**	**Yarpeh Codes**
Daliresp (roflumilast)	Roflumilast	R03DX07	
injections of Diprospan (betamethasone)	Betamethasone Dipropionate	D07XCO1	
long acting bronchodilators			
arformoterol (Brovana)	Arormoterol	R03AL07	
Foradil	Eformoterol Formoterol Fumarate	X X X	
glycopyrrolate:	Glycopyrronium bromide	R03AL05	
Lonala Magnair	Glycopyrrolate	X	
olodaterol :	olodaterol	R03AL07	
Respimat	Tiotropium bromide	R03AL06	
salmeterol (Serevent)	salmeterol	R03CC02	

Anoro	Umeclidinium Vilanterol	R03AL08 R03AK10	
Ultibro	Glycopyrronium bromide	R03AL05	
Foster		R03AK08	
Seretide	Fluticasone propionate/ Salmeterol xinafoate	R01AD08 R03AK10	
Trelegy	Fluticasone, Umecilidinium, Vilanterol	R01AD08 R03AL08 R03AK10	
Duoresp	Budesonide, Formoterol	R03BA02 R03AK07	
Prednisone tablets	Prednisone	X	
aclidinium (Tudorza)	aclidinium	X	
formoterol:	formoterol	R03AK09	
Perforomist)	Formoterol fumarate	R03AK07	
Seebri Neohaler,	Glycopyrrolate	R03BB06	
indacaterol (Arcapta)	indacaterol	R03AK14	
Striverdi	Olodaterol	R03AL01	
revefenacin (Yupelri)	revefenacin	R03BB08	
Spiolto	Tiotropium + Olodaterol	R03AL07	
Duaklir	Aclidinium + Formoterol	R03AL05	

Onbrez	indacaterol	R03AK14	
Oxis			
Flutiform			
Relvar	Fluticasone+ Vilanterol	R03AK10	
Symbicort	Budesonide + Formoterol	R03BA02	

HF Drugs	**Generic Name**	**ATC Codes**	**Yarpeh Codes**
Entresto:	Sacubitril + Valsartan	X	
sacubitril	sacubitril	C09DX	
valsartan	valsartan	C09DX01	
Fusid (Furosemide)	Furosemide	C03CA01	
Aldactone (Spironolactone)	Spironolactone	C03DA01	

15.2 Participants (patients and informal caregivers) Information Sheet

Find pilot sites Patient and Informal caregiver Information Sheet in Master file for Ethics applications folder in ADLIFE sharepoint.

15.3 Healthcare professional Information Sheet

Find pilot sites Healthcare professional Information Sheet in Master file for Ethics applications folder in ADLIFE sharepoint.

15.4 Informed Consent Forms

Find pilot sites Informed consent forms in Master file for Ethics applications folder in ADLIFE sharepoint.

15.5 Withdrawal of consent form

Find pilot sites Withdrawal of consent forms in Master file for Ethics applications folder in ADLIFE sharepoint.

Appendix B DCG for quantitative effectiveness assessment

The DCG for quantitative effectiveness assessment is available in the project's SharePoint in excel format. The content of each of the excel sheets is provided bellow:

B.1 Instructions

GENERAL

This **data collection guide (DCG)** contains eight further sheets: *version history, contact details, gantt chart&study design* and *flow-chart*, and four sheets compiling the **codebook**: *cb_baseline, cb_endline, cb_patient healthcare visits* and *cb_patient hospital admissions*. This **DCG** also refers to **three data collection templates**.

• In sheet *version history* you will find the changelog.
• In sheet *contact details* you will find the contact details of the pilot sites' data managers and the evaluation coordinator.
• In sheet *gantt chart&study design*, you will find the gantt chart of the required tasks on the data collection process and, the **study design** for better comprehension.
• In sheet *flow-chart* you will find the **flow-chart of the recruitment and selection process** to be completed. Each pilot site will complete and send the recruitment flow-chart.
• In sheets *cb_baseline, cb_endline, cb_patient healthcare visits and cb_patient hospital admissions the* codebook has been allocated.

You have also been provided with **three data collection templates (template 1, 2 and 3)** to enter the data**.** The **study design** and the **gantt chart** show comprehensive information of the data collection templates content.

Fullfilled **data collection templates** and **flow-chart of the recruitment and selection process** will be shared on deadlines showed in the **gantt chart** on the corresponding sharepoint folder with restricted access to each pilot site (data manager & project manager) and the evaluation coordinator. Please, find the link below to the sharepoint folder where each pilot site will find their private folder to share the above-mentioned documents.
https://kronikgune.sharepoint.com/:f:/r/sites/ADLIFE/WP9/T9.2%20-%20EVALUATE%20OUTCOMES%20AT%20DIFFERENT%20TIME-POINTS%20LEAD/Data%20collection?csf=1&web=1&e=BlkhHW

Please, before reading the specific instructions below, have a look at the *gantt chart&study design* sheet for a better comphrension.

SPECIFIC

• Throughout the DCG, reference is made to the following patient populations, which are defined bellow:

- **Tentative target population**: patients from electronic health records (EHR) meeting the elegibility criteria
- **Final target patient population**: patients in final target population after the checking process conducted by health professionals
- **Intervention patients**: the subset of final target population included in ADLIFE intervention
- **Target control patient population (TCPP)**: the subset of final target population removing the intervention patients
- **Control patients:** the subset of the TCPP after matching

• **Dates definitions:**

• **Intervention group**

• The baseline date is defined as the 14-days after the date on which the patient care plan is created.

• The endline date is 31/12/2023

• The control period ranges from 01/09/2022 to the baseline date

• The intervention period ranges from the baseline date to 31/12/2023

• **Control group**

• The baseline date is 01/09/2023

• The endline date is 31/12/2023

• The control period ranges from 01/09/2022 to 31/08/2023

• The intervention period ranges from 01/09/2023 to 31/12/2023

• Please, find below the **elegibility criteria** to conduct **Task 1 and 2**:

The study population consists of patients with advanced chronic diseases (HF and/or COPD with/without co-morbidities), their informal caregivers and their healthcare professionals, fulfilling the following inclusion/exclusion criteria.

Eligible patients will have to meet the below inclusion criteria:

1) Senior (over 55)

2) Heart failure (NYHA III-IV) in functional stage III/IV according to the NYHA scale and stages C and D of the ACCF/AHA classification. Stable-phase (at least two months without decompensation requiring hospital care)

3) And/or COPD GOLD >2 (FEV1<50) and/or mMRC ≥ 2 and/or CAT ≥ 10 and/or use of oxygen at home

4) With or without comorbidities

5) They are able to provide informed consent

6) They still live and generally plan on living in their home for the intervention duration

7) They or their informal caregivers are able to use digital technology, communication tools, and/or networks and have access to a computer, laptop, tablet or smartphone and wifi/internet connection.

8) They or their informal caregivers understand, read and talk the native language.

The informal caregiver will be a person who provides occasional or regular support to the patient needs. Caregivers will be eligible if the patient they care for meet the inclusion criteria and it is included in the study. Health professionals will be eligible if they are involved in the included patients care, open to new ways of working, specifically as part of a coordinative and collaborative teams and, open to the use of new technology.

Patients presenting any active malignant neoplastic disease, being in any active list of transplantation or, refusing to sign the informed consent, will not be included. Patients having participated in ADLIFE but having withdrawn from their participation, will not be eligible for the recruitment anymore. Caregivers will not be eligible if the patients they care for meet the exclusion criteria. Healthcare professionals not caring for patients who meet the inclusion criteria or only caring for patients who fulfil the exclusion criteria, will not be included.

• Please, find below details to conduct the **data cleaning process** on **Task 7 and 12**:

Before sending the dataset to the evaluation coordinator, the following issues have to be checked and accordingly rectified to ensure the accuracy and completeness of the data: i) missing values; ii) on quantitative variables, the values falling outside the min-max predefined range of possible values; iii) on categorical variables, the values not related to the predefined categories and, iv) on date variables, the impossible or not adequate dates.

• Please, find below details to conduct the **anonymization** on **Task 13**:
In order to make healthcare data accessible for research within the consortium, it needs to be protected. Intervention patients have given consent and have a GDPR legal basis to be used as personal data. Anonymization is necessary for control patients since these will not have a GDPR legal basis.The anonymisation method will utilise the ADLIFE ad-hoc script or the corporate anonymization tools, according to each site's preference, provided the corporate tools are configured to apply the following two anonymisation techniques: patients ID will be substituted by a random UUID (according to RFC 4122); precise dates will be referred to the time lapsed in days from a random date previous to all dates of birth in the data base (selected as the date of reference (date 0) for every patient in the data base). Owing very precise connection between items may reveal relevant patterns and results (such as the date of a test result and a change in treatment based on the result), no additional protections are advised. NTTDATA has created and shared with the pilot sites an executable and instructions, which are available in the project's Sharepoint:

- Link for anonymization material: https://kronikgune.sharepoint.com/:f:/r/sites/ADLIFE/WP5/T5.4%20RISK%20PREDICTION%20MODEL%20DESIGN%20AND%20IMPLEMENTATION/Data%20anonymisation?csf=1&web=1&e=DCdajI

• Please, find below details to conduct the collection on **Task 14**: To be informed

B.2 Version history

Table 12 - Version history of DCG for quantitative effectiveness evaluation

Date	Version	Change
10/08/2022	v0.4	Extension of deadlines for tasks 1 and 2 in gantt chart&study design
02/09/2022	v0.5	Contact details completed for every site
	v0.5	Update of the inclusion criteria in "instrucions sheet" according to version v0.30 of the research protocol
	v0.5	Update of the flow-chart according to version v0.30 of the research protocol
21/11/2022	v0.6	Intervention starts on month 39 instead of month 36. Deadlines on gantt chart&study design are changed accordingly: Task 2-9
22/02/2023	v0.7	Intervention starts on month 41 instead of month 39. Deadlines on gantt chart&study design are changed accordingly
	v0.7	Intervention ends on month 48 instead of month 47. Deadlines on gantt chart&study design are changed accordingly
	v0.7	Flowchart updated with indications to help its compliance
	v0.7	Task descriptions on "gantt chart&study design" expanded for better understanding
	v0.7	Instrucions reformulated for better understanding
07/06/2023	v0.8	Links to data anonymization executable and instructions are provided
07/06/2023	v0.8	Intervention starts on month 45 instead of month 41. Deadlines on gantt chart&study design are changed accordingly

B.3 Contact details

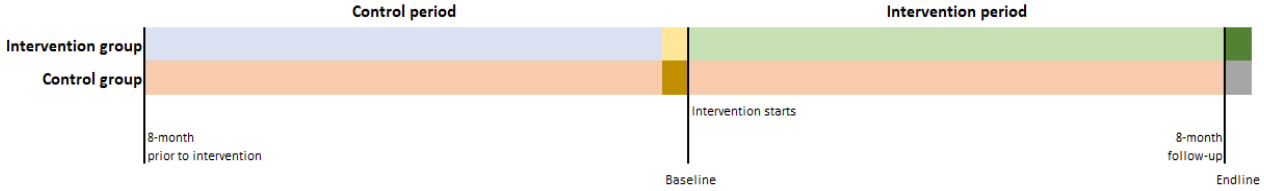
Table 13 - Data managers contact details

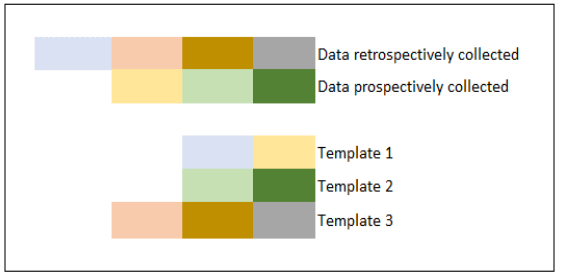
Pilot site	Person in charge	Email
OSAKIDETZA	Remedios Vega Iñigo	MARIAREMEDIOS.VEGAINIGO@osakidetza.eus
University of Strahclyde - NHS Lanarkshire	Barry McAlister	Barry.Mcalister@nhs.scot
UHCW - NHS Trust	Rajan Mattu	Rajan.mattu@uhcw.nhs.uk
Odense University Hospital - OUH	Anne Dichmann Sorknæs	anne.dichmann.sorknaes@rsyd.dk
Gesunder Werra-Meißner Kreis - GWMK	Fritz Arndt	f.arndt@gesunder-wmk.de
RJH	Robin Henriksson	robin.henriksson@regionjh.se
Assuta Ashdod Hospital - Maccabi Healthcare Services Southern Region	Yamit Baruch- Vald	yamitba@assuta.co.il

Table 14 - Evaluation coordinators contact details

Partner	Person in charge	Email
Kronikgune	Borja Garcia-Lorenzo	bgarcia@kronikgune.org
Kronikgune	Ania Gorostiza	agorostiza@gmail.com

B.4 Gannt chart & study design





Task nº	Task	Task description	May-23	Jun-23	Jul-23	Aug-23	Sep-23	Oct-23	Nov-23	Dec-23	Jan-24
			M41	M42	M43	M44	M45	M46	M47	M48	M49
1	Identification of tentative target patient population	Identify and save the EHR ID list of patients meeting the elegibility criteria from electronic health records (EHR). Elegibility criteria are available in *instructions* sheet									
2	Identification of final target patient population	Identify and save the EHR ID list of patients of the final target population according to the checking process conducted by health professionals									
3	Intervention patients sign up on ADLIFE platform	Sign up the intervention patients, previously recruited by health professionals, on the ADLIFE platform. The ADLIFE platform will automatically assign an ADLIFE ID									
4	Saving intervention participants	Save the list of intervention participants with their corresponding ADLIFE ID and EHR ID.									
5	Indentification of target control patient population (TCPP)	Identify and save the EHR ID list of target control population defined as the subset of final target population removing the intervention patients									
6	Baseline and control period of intervention participants data collection	Collect baseline and control period data on intervention patients and their caregivers (Template 1). - Template 1 should be populated following the structure provided in the codebook (cb_baseline, cb_patient healthcare visits and cb_patient hospital admissions). - Data on *cb_baseline* must be observed at baseline date (14-days after the date on which the patient care plan is created) - Data on *cb_patient healthcare visits* and *cb_patient hospital admissions* must be observed over the control period (from 01/09/2022 to the baseline date)									
7	Preliminar data cleaning process	Conduct data cleaning process according to guideline described in sheet *instructions*									
8	Share data collected on task 6 with evaluation coordinator	Share Template 1 on the corresponding sharepoint folder (to be provided). This template will contain baseline and control period data of intervention patients and their caregivers									
9	Fulfil and share recruitment flowchart with evaluation coordinator	Fulfil and share on the corresponding sharepoint folder (to be provided) the recruitment flow-chart, which can be found in sheet *flow-chart*									
10	Endline and intervention period of intervention participants data collection	Collect endline and intervention period data on intervention patients and their caregivers (Template 2) - Template 2 should be populated following the structure providedin the codebook (cb_endline, cb_patient healthcare visits and cb_patient hospital admissions). - Data on *cb_endline* must be observed at endline date (31/12/2023) - Data on *cb_patient healthcare visits* and *cb_patient hospital admissions* must be observed over the intervention period (from the baseline date until 31/12/2023)									
11	Control period and baseline + intervention period and endline of TCPP data collection	Collect control period and baseline +intervention period and endline data on TCPP (Template 3) - Template 3 should be populated following the structure provided in the codebook (*cb_baseline, cb_endline, cb_patient healthcare visits* and *cb_patient hospital admissions*). - Data on *cb_baseline* must be observed at baseline date (01/05/2023) - Data on *cb_patient healthcare visits* and *cb_patient hospital admissions* must be observed over the control period (from 01/09/2022 to 30/04/2023) - Data on *cb_endline* must be observed at endline date (31/12/2023) - Data on *cb_patient healthcare visits* and *cb_patient hospital admissions* must be observed over the intervention period (from 01/05/2023 to 31/12/2023)									
12	Data cleaning process	Conduct data cleaning process on Template 2 and Template 3 according to guideline described in sheet *instructions*									
13	Anonymization of TCPP data (Template 3)	Anonymize data in Template 3 following the anonymization methods described in *instructions* sheet. Anonymization is necessary for control patients since these will not have a GDPR legal basis.									
14	Health-related outcome log and Potentially Preventable Situations (PPSs) log data collection	Conduct data collection of health-related outcome log and Potentially Preventable Situations (PPSs) log according to the provided instructions in *instruction* sheet									
15	Share data collected on tasks 10, 11 and 14 with evaluation coordinator	Share a) Template 2 , b) Template 3, c) the Health-related outcome log and d)Potentially Preventable Situations (PPSs) log on the corresponding sharepoint folder (to be provided)									

Legend

- Task deadline
- Intervention starts
- Intervention ends

B.5 Flow-chart

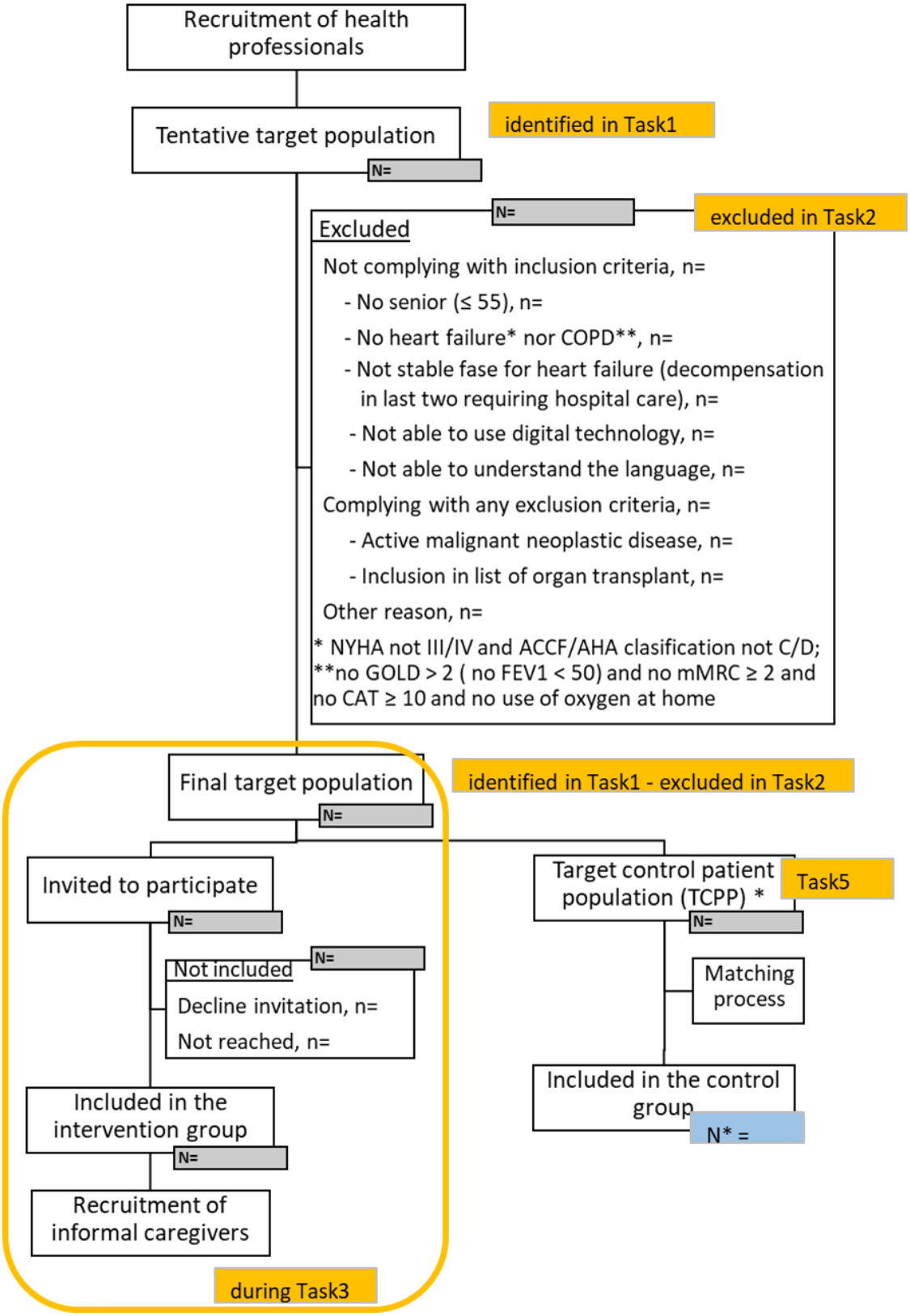


Figure 28 - Flow-chart of the recruitment and selection process

B.6 Baseline codebook

variable	label	type	value	value label	intervention	control	source	observations / comments
patient								
id_patient	patient id	string	n.a.	n.a.	X	X	intervention group: FHIR control group: local EHR	- intervention group: four-number format automatically assigned by ADLIFE platform
site	site of reference	categorical	1	osakidetza	X	X	intervention group: FHIR control group: local EHR	
			2	ustrath				
			3	uhcw				
			4	ouh				
			5	gwmk				
			6	rjh				
			7	amca				
baseline_date	date of baseline	date (dd/mm/yyyy)	intervention group: see *observations* contorl group: 01/09/2023	n.a.	X	X	intervention group: FHIR control group: local EHR	intervention group: defined as 14-days after the date on which the patient care plan is created
birth_year_pat	year of birth	date	≤1977	n.a.	X	X	intervention group: FHIR control group: local EHR	
			999	unknown				
sex_pat	sex	categorical	0	male	X	X	intervention group: FHIR control group: local EHR	
			1	female				
			999	unknown				
hf_diag	diagnoses of heart failure	categorical	0	no	X	X	intervention group: FHIR control group: local EHR	ICD-9: 428*, 401, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93 ICD-10: I50*, I11.0, I13.0, I13.2, I13.9
			1	yes				
			999	unknown				
copd_diag	diagnoses of copd	categorical	0	no	X	X	intervention group: FHIR control group: local EHR	ICD-9: 492* ICD-10: J44*
			1	yes				
			999	unknown				
nyha	funcional stage acording to the NYHA	categorical	1	I	X	X	intervention group: FHIR control group: local EHR	
			2	II				
			3	III				
			4	IV				
			999	unknown				
accf_aha	ACCF/AHA classification	categorical	1	A	X	X	intervention group: FHIR control group: local EHR	
			2	B				
			3	C				
			4	D				
			999	unknown				
kccq_score	total score of the kansas city cardiomyopathy questionnaire	discrete	0-100	n.a.	X		intervention group: FHIR	
			999	unknown				

variable	label	type	value	value label	intervention	control	source	observations / comments
patient								
gold_score	total score of gold scale of copd	categorical	1	A	X	X	intervention group: FHIR control group: local EHR	
			2	B				
			3	C				
			4	D				
			999	unknown				
cat_score	total score of the copd assessment test (cat)	discrete	0-40	n.a.	X	X	intervention group: FHIR control group: local EHR	
			999	unknown				
mmrc_score	total score of the modified medical research council of dypsnea (mmrc)	categorical	0	dyspnea only with	X	X	intervention group: FHIR control group: local EHR	
			1	dyspnea when hurrying				
			2	walks slower than people of the same age				
			3	stops for breath after				
			4	too dyspneic to leave				
			999	unknown				
fev1/fvc_score	forced expiratory volume divided by forced vital capacity in %	continuous	0-100	n.a.	X	X	intervention group: FHIR control group: local EHR	
			999	unknown				
polypharmacy	whether patient has been prescribed with five or more drugs	categorical	0	no	X	X	intervention group: FHIR control group: local EHR	
			1	yes				
			999	unknown				
oxygen	whether patient needs oxygen at home	categorical	0	no	X	X	intervention group: FHIR control group: local EHR	ICD-9: V46.2 ICD-10 Z99.8
			1	yes				
			999	unknown				
niv	whether patient needs non-invasive ventilation	categorical	0	no	X	X	intervention group: FHIR control group: local EHR	ICD-9: 96.0, 96.7, V46.1 ICD-10: Z99.1X, J95.850, J95.851, J95.859
			1	yes				
			999	unknown				

variable	label	type	value	value label	intervention	control	source	observations / comments
patient								
euroqol_mo	patient response to the mobility dimension of the eq5d5l questionnaire	categorical	1	I have no problems in	X		intervention group: FHIR	
			2	I have slight problems in				
			3	I have moderate				
			4	I have severe problems				
			5	I am unable to walk				
			999	unknown				
euroqol_sc	patient response to the self-care dimension of the eq5d5l questionnaire	categorical	1	I have no problems	X			
			2	I have slight problems				
			3	I have moderate				
			4	I have severe problems				
			5	I am unable to wash or				
			999	unknown				
euroqol_ua	patient response to the usual activities dimension of the eq5d5l questionnaire	categorical	1	I have no problems doing	X			
			2	I have slight problems				
			3	I have moderate				
			4	I have severe problems				
			5	I am unable to do my				
			999	unknown				
euroqol_pd	patient response to the pain/discomfort dimension of the eq5d5l questionnaire	categorical	1	I have no pain or	X			
			2	I have slight pain or				
			3	I have moderate pain or				
			4	I have severe pain or				
			5	I have extreme pain or				
			999	unknown				
euroqol_ad	patient response to the anxiety/depression dimension of the eq5d5l questionnaire	categorical	1	I am not anxious or	X			
			2	I am slightly anxious or				
			3	I am moderately anxious				
			4	I am severely anxious or				
			5	I am extremely anxious				
			999	unknown				
lawton_score	total score of lawton scale	discrete	women: 0-8 men: 0-5	n.a.	X		intervention group: FHIR	
			999	unknown				
barthel_score	total score of barthel index	discrete	0-100	n.a.	X		intervention group: FHIR	
			999	unknown				
had_score	total score of had scale	discrete	0-42	n.a.	X		intervention group: FHIR	
			999	unknown				
had_a_score	anxiety score of had scale	discrete	0-21	n.a.	X			
			999	unknown				
had_d_score	depression score of had scale	discrete	0-21	n.a.	X			
			999	unknown				

variable	label	type	value	value label	intervention	control	source	observations / comments
patient								
co_mi	myocardial infarct	categorical	0	no	X	X	intervention group: FHIR control group: local EHR	CIE9: 410.x, 412.x CIE10: I21.x, I22.x, I25.2
			1	yes				
			999	unknown				
co_chf	congestive heart failure	categorical	0	no	X	X		CIE9: 428.x CIE10: I09.9,I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43.x, I50.x, P29.0
			1	yes				
			999	unknown				
co_pvd	peripheral vascular disease	categorical	0	no	X	X		CIE9: 443.9, 441.x, 785.4, V43.4 Procedure 38.48 CIE10: I70.x, I71.x, I73.1, I73.8, I73.9, I77.1,
			1	yes				
			999	unknown				
co_cervd	cerebrovascular disease	categorical	0	no	X	X		CIE9: 430.x-438.x CIE10: G45.x, G46.x, H34.0, I60.x-I69.x
			1	yes				
			999	unknown				
co_dem	dementia	categorical	0	no	X	X		CIE9: 290.x CIE10: F00.x-F03.x, F05.1, G30.x, G31.1
			1	yes				
			999	unknown				
co_pulmonary	chronic pulmonary disease	categorical	0	no	X	X		CIE9: 490.x-505.x, 506.4 CIE10: I27.8, I27.9, J40.x-J47.x, J60.x-J67.x, J68.4, J70.1, J70.3
			1	yes				
			999	unknown				
co_rheumatic	rheumatic disease	categorical	0	no	X	X		CIE9: 710.0, 710.1, 710.4, 714.0-714.2, 714.81, 725.x CIE10: M05.x, M06.x, M31.5, M32.x-M34.x,
			1	yes				
			999	unknown				
co_ulcer	peptic ulcer disease	categorical	0	no	X	X		CIE9: 531.x-534.x CIE10: K25.x-K28.x
			1	yes				
			999	unknown				
co_mild_liver	mild liver disease	categorical	0	no	X	X		CIE9: 571.2, 571.4-571.6 CIE10: B18.x, K70.0-K70.3, K70.9, K71.3-K71.5, K71.7, K73.x, K74.x, K76.0, K76.2-
			1	yes				
			999	unknown				
co_dm_uncompl	diabetes without chronic complication	categorical	0	no	X	X		CIE9: 250.0-250.3, 250.7 CIE10: E10.0, E10.l, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0,
			1	yes				
			999	unknown				
co_dm_compl	diabetes with chronic complication	categorical	0	no	X	X		CIE9: 250.4-250.6 CIE10: E10.2-E10.5, E10.7, E11.2-E11.5, E11.7, E12.2-E12.5, E12.7, E13.2-E13.5, E13.7, E14.2-
			1	yes				
			999	unknown				
co_plegia	hemiplegia or paraplegia	categorical	0	no	X	X		CIE9: 344.1, 342.x CIE10: G04.1, G11.4, G80.1, G80.2, G81.x, G82.x, G83.0-G83.4, G83.9
			1	yes				
			999	unknown				
co_renal	renal disease	categorical	0	no	X	X		CIE9: 582.x, 583-583.7, 585.x, 586.x, 588.x CIE10: I12.0, I13.1, N03.2-N03.7, N05.2-N05.7, N18.x, N19.x, N25.0, Z49.0-Z49.2,
			1	yes				
			999	unknown				
co_malignancy	any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin	categorical	0	no	X	X		CIE9: 140.x-172.x, 174.x-195.8, 200.x-208.x CIE10: C00.x-C26.x, C30.x-C34.x, C37.x-C41.x, C43.x, C45.x-C58.x, C60.x-C76.x,
			1	yes				
			999	unknown				
co_mod_sev_liver	moderate or severe liver disease	categorical	0	no	X	X		CIE9: 456.0-456.21, 572.2-572.8 CIE10: I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
			1	yes				
			999	unknown				
co_metastasis	metastatic solid tumor	categorical	0	no	X	X		CIE9: 196.x-199.1 CIE10: C77.x-C80.x
			1	yes				
			999	unknown				
co_aids	AIDS/HIV	categorical	0	no	X	X		CIE9: 042.x-044.x CIE10: B20.x-B22.x, B24.x
			1	yes				
			999	unknown				

variable	label	type	value	value label	intervention	control	source	observations / comments
caregiver								
caregiver	whether patient have an informal caregiver and his/her link with the caregiver	categorical	0	No caregiver	X		intervention group: FHIR	
			1	Familiar				
			2	External				
			3	Other				
			999	unknown				
birth_year_care	year of birth	date	yyyy	n.a.	X			applies if caregiver ≠ 0
			999	unknown				
sex_care	sex	categorical	0	male	X			applies if caregiver ≠ 0
			1	female				
			999	unknown				
wemwbs_score	total score of the warwick-edinburgh mental wellbeing	discrete	14-70	n.a.	X			applies if caregiver ≠ 0
			999	unknown				
zbi22_score	total score of the zarit caregiver burden interview	numeric	0-88	n.a.	X			applies if caregiver ≠ 0
			999	unknown				

B.7 Endline codebook

variable	label	type	value	value label	intervention	control	source	observations /
patient								
id_patient	patient id	string	n.a.	n.a.	X	X	intervention group: FHIR control group: local	- intervention group: four-number format automatically assigned by
collection_date	date of data collection/extraction	date (dd/mm/y	01/01/2024 - 31/01/2024	n.a.	X	X	intervention group: FHIR	- control group: anonymized format
dropout_pat	whether the patient have dropped-out of the study	categorical	0	no	X		intervention group: FHIR	
			1	yes				
dropout_date_pat	date of patient drop-out	date (dd/mm/y	intervention group:	n.a.	X			applies if dropout_pat = 1
dropout_reason_pat	reason of drop-out	categorical	1	death	X			applies if dropout_pat = 1
			2	not interested anymore				
			3	too much time consuming				
			4	technology issues				
			5	lack of help caregiver				
			6	institutionalization				
			7	other				
			999	no reponse				
exitus	whether the patient has died during the study	categorical	0	no	X	X	intervention group: FHIR control group: local	
			1	yes				
			999	unknown				
exitus_date	date of patient exitus	date	intervention group:	n.a.	X	X	intervention group: FHIR control group: local	applies if exitus = 1 control group: anonymized format
			999	unknown				
exitus_place	place of exitus	categorical	0	hospital	X	X	intervention group: FHIR control group: local EHR	applies if exitus = 1
			1	home				
			2	other				
			999	unknown				

variable	label	type	value	value label	intervention	control	source	observations /
patient								
hf_diag	diagnoses of heart failure	categorical	0	no	X	X	intervention group: FHIR control group: local	ICD-9: 428*, 401, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93
			1	yes				
			999	unknown				
copd_diag	diagnoses of copd	categorical	0	no	X	X	intervention group: FHIR control group: local	ICD-9: 492* ICD-10: J44*
			1	yes				
			999	unknown				
nyha	funcional stage acording to the NYHA	categorical	1	I	X	X	intervention group: FHIR control group: local EHR	
			2	II				
			3	III				
			4	IV				
			999	unknown				
accf_aha	ACCF/AHA classification	categorical	1	A	X	X	intervention group: FHIR control group: local EHR	
			2	B				
			3	C				
			4	D				
			999	unknown				
kccq_score	total score of the kansas city cardiomyopathy	discrete	0-100	n.a.	X		ıtervention group: FHI	
			999	unknown				
gold_score	total score of gold scale of copd	categorical	1	A	X	X	intervention group: FHIR control group: local EHR	
			2	B				
			3	C				
			4	D				
			999	unknown				
cat_score	total score of the copd assessment test (cat)	discrete	0-40	n.a.	X	X	intervention group: FHIR	
			999	unknown				
mmrc_score	total score of the modified medical research council of dypsnea (mmrc)	categorical	0	dyspnea only with	X	X	intervention group: FHIR control group: local EHR	
			1	dyspnea when hurrying or				
			2	walks slower than people of the same age because of dyspnea or has to stop				
			3	stops for breath after walking 100 yards (91 m)				
			4	too dyspneic to leave house or breathless when				
			999	unknown				
fev1/fvc_score	forced expiratory volume divided by forced vital	continuous	0-100	n.a.	X	X	intervention group: FHIR	
			999	unknown				

variable	label	type	value	value label	intervention	control	source	observations /
patient								
polypharmacy	whether patient has been prescribed with five or more drugs	categorical	0	no	X	X	intervention group: FHIR control group: local	
			1	yes				
			999	unknown				
oxygen	whether patient needs oxygen at home	categorical	0	no	X	X	intervention group: FHIR control group: local	ICD-9: V46.2 ICD-10 Z99.8
			1	yes				
			999	unknown				
niv	whether patient needs non-invasive ventilation	categorical	0	no	X	X	intervention group: FHIR control group: local	ICD-9: 96.0, 96.7, V46.1 ICD-10: Z99.1X, J95.850, J95.851, J95.859
			1	yes				
			999	unknown				
euroqol_mo	patient response to the mobility dimension of the eq5d5l questionnaire	categorical	1	e no problems in walking a	X		intervention group: FHI	
			2	slight problems in walking				
			3	oderate problems in walkir				
			4	severe problems in walking				
			5	I am unable to walk about				
			999	unknown				
euroqol_sc	patient response to the self-care dimension of the eq5d5l questionnaire	categorical	1	problems washing or dressi	X			
			2	t problems washing or dres				
			3	ate problems washing or dr				
			4	e problems washing or dres				
			5	unable to wash or dress my				
			999	unknown				
euroqol_ua	patient response to the usual activities dimension of the eq5d5l questionnaire	categorical	1	problems doing my usual a	X			
			2	ht problems doing my usual				
			3	rate problems doing my usu				
			4	re problems doing my usua				
			5	unable to do my usual activ				
			999	unknown				
euroqol_pd	patient response to the pain/discomfort dimension of the eq5d5l questionnaire	categorical	1	have no pain or discomfort	X			
			2	ave slight pain or discomfo				
			3	ve moderate pain or discom				
			4	ave severe pain or discomf				
			5	ve extreme pain or discomf				
			999	unknown				
euroqol_ad	patient response to the anxiety/depression dimension of the eq5d5l questionnaire	categorical	1	am not anxious or depresse	X			
			2	n slightly anxious or depres				
			3	noderately anxious or depr				
			4	severely anxious or depres				
			5	extremely anxious or depre				
			999	unknown				

variable	label	type	value	value label	intervention	control	source	observations /
patient								
lawton_score	total score of lawton scale	discrete	women: 0-8 men: 0-5	n.a.	X		ntervention group: FHI	
			999	unknown				
barthel_score	total score of barthel index	discrete	0-100	n.a.	X		ntervention group: FHI	
			999	unknown				
had_score	total score of had scale	discrete	0-42	n.a.	X			
			999	unknown				
had_a_score	anxiety score of had scale	discrete	0-21	n.a.	X		ntervention group: FHI	
			999	unknown				
had_d_score	depression score of had scale	discrete	0-21	n.a.	X			
			999	unknown				

variable	label	type	value	value label	intervention	control	source	observations /
caregiver								
caregiver	whether patient have an informal caregiver and his/her link with the caregiver	categorical	0	No caregiver	X			
			1	Familiar				
			2	External				
			3	Other				
dropout_care	whether the patient have dropped-out of the study	categorical	0	no	X			applies if caregiver ≠ 0
			1	yes				
dropout_date_care	date of caregiver drop-out	date (dd/mm/y	intervention	n.a.	X			applies if caregiver ≠ 0
			999	unknown				
dropout_reason_care	reason of drop-out	categorical	1	death	X		ntervention group: FHI	applies if caregiver ≠ 0
			2	not interested anymore				
			3	too much time consuming				
			4	technology issues				
			5	patient's drop out				
			6	other				
			999	no reponse				
wemwbs_score	total score of the warwick-edinburgh mental	discrete	14-70	n.a.	X			applies if caregiver ≠ 0
			999	unknown				
zbi22_score	total score of the zarit caregiver burden	discrete	0-88	n.a.	X			applies if caregiver ≠ 0
			999	unknown				

B.8 Patient healthcare visits codebook

variable	label	type	value	value label	intervention	control	source	observations / comments
patient								
id_patient	patient id	string	n.a.	n.a.	X	X	intervention group: FHIR control group: local EHR	- intervention group: four-number format automatically assigned by ADLIFE platform e.g. 1006 - control group: anonymized format
visit_type	type of healthcare visit	categorical	0	general practice at healthcare centre	X	X	intervention group: local EHR control group: local EHR	- In case no breakdown across type of general practice/nurse visits is available (*at the healthcare centre by telephone or at home*), visits will be entered in *at the healthcare centre* category. - More than one visit per patient is possible, one row per visit is expected
			1	general practice by telephone				
			2	general practice at home				
			3	primary care nurse at healthcare centre				
			4	primary care nurse by telephone				
			5	primary care nurse at home				
			6	cardiology				
			7	respiratory				
			8	endocrinology				
			9	nephrology				
			10	neurology				
			11	psychiatry				
			12	internal medicine				
			13	other				
			14	emergency department				
visit_date	date of visit	date (dd/mm/yyyy)	intervention group: template 1: 01/09/2022 - *baseline_date* template 2: *baseline_date* - 31/12/2023 control group: template 3: 01/09/2022 - 31/12/2023	n.a.	X	X	intervention group: local EHR control group: local EHR	- *baseline_date*: defined on patient&caregiver_baseline sheet - control group: anonymized format - more than one visit per patient is possible, one row per visit is expected
			999999999	unknown				

B.9 Patient hospital admissions codebook

variable	label	type	value	value label	intervention	control	source	observations / comments
patient								
id_patient	patient id	string	n.a.	n.a.	X	X	intervention group: FHIR control group: local EHR	- intervention group: four-number format automatically assigned by ADLIFE platform e.g. 1006 - control group: anonymized format
admission_type	type of hospital admission at healthcare center	categorical	0	conventional hospital	X	X	intervention group: local EHR control group: local	More than one hospital admission per patient is possible, one row per hospital admission is expected
			1	intensive care unit (icu)				
			2	hospital at home				
admission_date	date of hospital admission at healthcare center	date (dd/mm/yyyy)	intervention group: template 1: 01/09/2022 - *baseline_date* template 2: *baseline_date* - 31/12/2023 control group: template 3: 01/09/2022 - 31/12/2023	n.a.	X	X	intervention group: local EHR control group: local EHR	- *baseline_date* : defined on patient&caregiver_baseline sheet - control group: anonymized format - more than one admission per patient is possible, one row per admission is expected
			999999999	unknown				
admission_los	length of stay of hospital admissions in days	discrete	1-730	n.a.	X	X	intervention group: local EHR	more than one admission per patient is possible, one row per admission is
			999	unknown				

Appendix C Data collection templates for quantitative effectiveness assessment

The Data Collection Templates for quantitative effectiveness assessment is available in the project's SharePoint in excel format. A screenshot of the excel sheets is provided bellow:

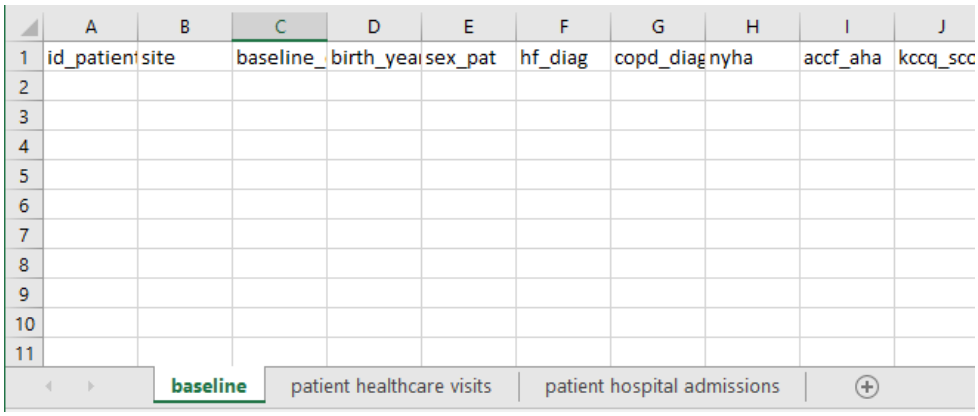


Figure 31 - Screenshot of Template 1 for quantitative effectiveness assessment

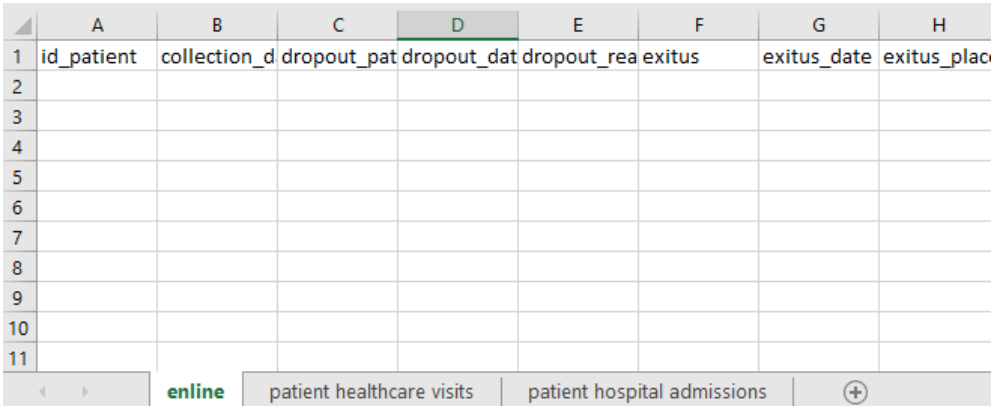


Figure 30 - Screenshot of Template 2 for quantitative effectiveness assessment

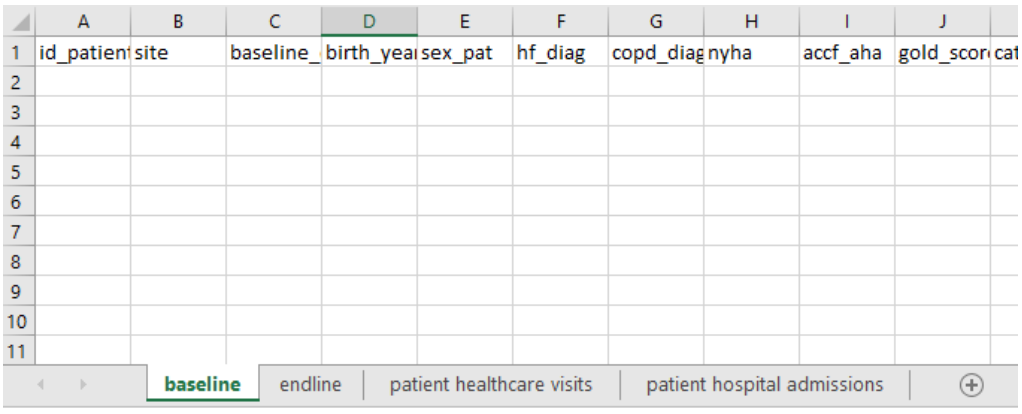


Figure 29 - Screenshot of Template 3 for quantitative effectiveness assessment

Appendix D DCG for implementation assessment

The DCG for implementation assessment is available in the project's SharePoint in excel format. Its content is provided bellow:

Dimension	Construct/Subcategories	Stakeholders involved	Pre-questions before implementation (targeting WP10/Exploitation)	Post questions after implementation (targeting WP9 and WP10)
Intervention (CFIR)	Evidence Strengh & Quality	#1 Physician, GP, Nurse, Medical director	#1: What are your thoughts and opinion on the ADLIFE project and the participation of your organization in the ADLIFE project? What is your attitude towards the project (e.g., in favuor for change, against change)? #1: What do you think of the integrated, personalized and digitally supported care of patients with COPD or chronic heart failure as envisaged within the ADLIFE project? #1: Only for IT staff: What do you think about the clinic board´s decision to participate in the ADLIFE project?	
	Relative advantage	#1 Physician, GP, Nurse, Medical director #3 MDTs, patients, caregivers	*#1: Question is listed in the Net Benefits dimension*	#3: PATIENTS: Please, describe how ADLIFE/the PCP has generated a change in your attitude in relation to your illness. For instance: Has it helped you understand better your illness? How? / Does it help you cope better with your illness? How? / Does it make you more confident about your health? #3: CAREGIVERS: Please, describe how ADLIFE has generated a change in your attitude in relation to your familiar's illness. For instance: Has it helped you understand better the illness? How? Does it make you more confident about how you can help him/her? #3/#1: Please, describe how ADLIFE has generated a change in your patient's attitude in relation to his/her illness. For instance: Has it helped him/her understand better the illness and to take control of their health? How? / Does it help him/her cope better with the illness?
	Adaptability	#1 Physician, GP, Nurse, Medical director, IT Staff #3 MDTs, managers	#1 : What are important requirements for a new system like the ADLIFE platform? a) What support do you need from the project team in order to be able to fully implement the ADLIFE toolbox in your organization? What could facilitate it? #1: Only for IT staff: From an IT point of view: What is important for you when a new digital system is implemented? #1: Only for IT staff: What are important requirements that a new system like the ADLIFE platforms should meet from an IT point of view? What support do you need from the project team in order to be able to introduce the ADLIFE platforms to your organization and to fully implement it?	
	Complexity	#1 Physician, GP, Nurse, Medical director, #3 MDTs, managers	#1: What are your main concerns in relation to the project? Where do you expect problems? a) a. How do you think these problems/concerns can be best addressed?	

Dimension	Construct/Subcategories	Stakeholders involved	Pre-questions before implementation (targeting WP10/Exploitation)	Post questions after implementation (targeting WP9 and WP10)
Process (CFIR)	Reflecting & Evaluating	#3 Patients, caregivers, MDTs, managers		#3: MDTs: Which do you perceive that have been the main resistances/barriers to ADLIFE? What do you think have been the main aspects that have facilitated the implementation of ADLIFE? #3: MANAGERS: Which do you perceive that have been the main resistances/barriers to ADLIFE? What do you think have been the main aspects that have facilitated the implementation of ADLIFE?
Organization (HOT-FIT / CFIR)	Enviornment	#1: Physicians, GP, nurse, meidcal director	#1: What do you think is needed in order to convince other health care providers to participate in this innovative project? From your perspective, what are the main selling points to take part in the project? What could possible incentives be?	#1: From your perspective, what are the main selling points for further health care providers or policy makers to use the ADLIFE digital platform in the future? #1: What is needed to increase the usability and acceptance of digital tools in patient care?
Organization (HOT-FIT / CFIR)	Networks & Communication	#3 Patients, caregivers, MDTs, managers #1 Physician, GP, Nurse, Medical director, IT Staff	#1: How would you describe the current cooperation/coordination between different care providers (e.g., between general practitioner and nurse practitioner; between primary and specialist care or between care providers in the hospital)? (Prompts: Do they transfer information? Are they working together well? Is their care well connected?) #1: Which channels/online methods do you use to communicate with patients (inside/outside your organization? (Note: refers to all kind of online methods such as phone, video, other remote options such as e-mail, text message, massaging through patient platforms) #1: Which channels/online methods do you use to communicate with other health care providers insight your organization? Which channels/online methods do you use to communicate with other health care providers outside your organization? (Note: refers to all kind of online methods such as phone, video, other remote options such as e-mail, text message, massaging through patient platforms) #1: How would you like to cooperate and communicate with other healthcare providers in the future? What is needed to further improve the cooperation and communication between healthcare providers? #1: Only IT Staff: How do departments and units communicate internally with each other? Are there digital communication channels in place?	#1/#3: MDTs: How has the implementation of ADLIFE changed the way you communicate with other MDTs in your same care level? Has it improved your ability to exchange information with them? Have you found new communication channels? How do you use the functions of the ADLIFE digital platforms to communicate with other healthcare providers (e.g., between general practitioner and nurse practitioner)? #1: How has the implementation of ADLIFE changed the way you communicate with patients? How do you use the functions of the ADLIFE digital platforms to communicate with patients?
Organization (HOT-FIT / CFIR)	Culture	#1 Physician, GP, Nurse, Medical director	#1: How are clinical guidelines implemented and used in your organization? a. To what extent do you take official clinical guidelines into account when caring for patients? b. If clinical guidelines are not used: Are there other standardized care processes that apply in your organization? Please describe the processes. #1: What are the roles and functions of the nurses working in your organization (with regard to chronic care management)? #1: Are patients within your organization provided with an individualized patient care plan? *What does the patient care plan include? (e.g., self-management goals, clinical goals, follow-up plan) #1: To what extend is the patient/caregiver involved in the development of the care plan? (e.g., is the care plan collaboratively developed between patients, nurses, physicians, and caregivers) #1: Which is the profile/s of the professionals involved in care plan formulation, evaluation, follow-up and adaptation? (e.g., primary care provider, nurse, social worker, specialist etc.)	#1/#3: MDTs: What changes has ADLIFE brought about in the distribution of tasks among MDTs and especially nurses?

Dimension	Construct/Subcategories	Stakeholders involved	Pre-questions before implementation (targeting WP10/Exploitation)	Post questions after implementation (targeting WP9 and WP10)
Organization (HOT-FIT / CFIR)	Implementation Climate	#1 Physician, GP, Nurse, Medical director, IT Staff	#1: How would you rate your (and your colleagues) willingness to change when implementing new IT solutions? What/Who would support the implementation of new IT systems? #1 Only IT Staff: How do you rate the willingness to change of healthcare professionals when new IT solutions will be implemented?	
Organization (HOT-FIT / CFIR)	Leadership Engagement	#1 Physician, GP, Nurse, Medical director, IT staff	#1: Do you perceive high level support (e.g., by the clinic board, chief physician) when implementing new digital strategies and do you receive commitment for implementation? #1: Only for IT staff: Do you follow a strategy to expand the level of digitalization in your organization? If yes, please describe the strategy.	#1: MDTs: How did you perceive the high level support (e.g., by the clinic board, chief physician) when the ADLIFE digital platforms was implemented?
Organization (HOT-FIT /	Available Resources	#1: IT Staff	#1: Only for IT staff: Are there enough qualified employees to implement IT projects/the IT strategy?	
Technology (HOT-FIT)	System quality	#1 Physician, GP, Nurse, Medical director, IT staff #3 Patients, caregivers, MDTs	#1: Which digital systems/platform do you currently use to manage patient care in your organization? (e.g., systems to establish and store digital medical records, systems for communication and data exchange, systems for patient care, computerized decision support systems) #1: How is your IT infrastructure organized and technically implemented in your organization? (e.g., IT information, technical conditions, functions and standards; digital user interface, data protection) #1 Only for IT staff: Which digital platforms are used by the healthcare professionals in their everyday work? How is patient data recorded? Which technical standards are the basis for your digital platforms? #1 Only for IT staff: How can individual systems/digital platforms interact with each other? (e.g., with regard to interfaces, which interfaces are used to link the systems with each other or to link them with new systems? #1: Only for IT staff: Do you have digital platforms to check drug prescription for interactions? Are these being used?	#1: MDTs: How are the ADLIFE digital platforms organized and technically implemented in your organization? (Prompts: database contents, availability, features and functions) #1/#3: MDTs: How did you experience the use of the technical devices employed in ADLIFE? (Prompts: ease of use, usefulness of systems features and functions). Please tell me about your experience with these technology resources and how it fit into your work patterns. (Prompts: resource utilization, ease of learning, flexibility) #3: PATIENTS: Have you encountered any difficulties with the technical devices employed in ADLIFE? Could you tell me about your experience with these technology resources? #3: CAREGIVERS: Have you or your familiar encountered any difficulties with the technical devices employed in ADLIFE? Could you tell me about your experience with these technology resources? #3: MANAGERS: How has the experience been with accessing and using the platforms and applications used in ADLIFE?

Dimension	Construct/Subcategories	Stakeholders involved	Pre-questions before implementation (targeting WP10/Exploitation)	Post questions after implementation (targeting WP9 and WP10)
Technology (HOT-FIT)	Information quality	#1 Physician, GP, Nurse, Medical director, IT staff	#1: Is there information lacking when treating a patient and if yes, what information is lacking when treating a patient? (e.g., patient history, visits, diagnostic test results in medical records)? #1: Is the care plan frequently updated and planned interventions revised according to patient changing needs? Which elements are incorporated? When are those activated? #1: Only for IT Staff: How is your IT infrastructure organized and what are its key features? a) Do you cooperate with external organi-zations regarding your IT-infrastructure (e.g., consulting, security, installation, …)? Please describe the cooperation.	#1: How do you perceive the information quality when using the ADLIFE digital platforms? Prompts: Completeness: When using the ADLIFE digital platforms, is there information lacking when treating a patient and if yes, what information is lacking? (e.g., patient history, visits, diagnostic test results in medical records)? Reliability/Availability: How do you perceive the availability of all relevant information in the care plan when treating a patient? is the system reliable? Timeliness: Are patient care plans frequently updated and planned interven-tions revised according to patient changing needs? Further prompts: Usefulness, relevance.
Technology (HOT-FIT)	Service quality	#1 Physician, GP, Nurse, Medical director, IT staff	#1: How often do system failures or malfunctions of the used technical systems occur? a.Are you able to solve system failures or malfunctions independently or is external support needed? b.When technical problems occur: How satisfied are you with technical support by the IT-team?	#1: How often do system failures or malfunctions of the ADLIFE digital platforms occur? a. Are you able to solve system failures or malfunctions independently or is external support needed? b.When technical problems occur: How satisfied are you with technical support by the IT-team? How quick do you receive the support? How satisfied were you with the solution?
Human (CFIR / HOT-FIT)	System use	#1 Physician, GP, Nurse, Medical director #3 MDTs, patients	#1: How do you use digital systems/platforms in your current work situation? #1: How confident do you feel in handling the digital systems/platforms you use? #1: How willing are you to use digital systems/platforms that support care of the patients? #1: How secure do you think patient data is in your organization (also with respect to digitalization in health care)?	#3: PATIENTS: Do you feel safe/cared using this technology? Have you experienced any inconvenience (annoyance/adverse events/unsafety) using the application? If yes, could you explain these inconveniences? #3: CAREGIVERS: Does he/she feel safe/cared using this technology? Has he/she experienced any inconvenience (annoyance/adverse events/unsafety) using the application? If yes, could you explain these inconveniences? #1: How do you use the ADLIFE digital platforms in your current work situation? #1: MDTs: How frequent do you use the ADLIFE digital platforms in your current work situation? #1: MDTs: How confident do you feel in handling the ADLIFE digital platforms? #1: MDTs: How would you describe the willingness to use the ADLIFE digital platforms by you and your colleagues?
	User satisfaction	#1 Physician, GP, Nurse, Medical director, IT staff #3 Patients, caregivers, MDTs, managers	#1: How satisfied are you with the existing digital systems/platforms and how do you feel supported by them? #1: Only for IT staff: How satisfied are you with the existing digital platforms from an IT point of view?	#1: How satisfied are you with the ADLIFE digital platforms? How do you feel supported by the ADLIFE digital platforms in your work?

Dimension	Construct/Subcategories	Stakeholders involved	Pre-questions before implementation (targeting WP10/Exploitation)	Post questions after implementation (targeting WP9 and WP10)
Outer setting (CFIR / HOT-FIT)	Overall Environment	#1 Policy makers #1 Physician, GP, Nurse, Medical director		#1: From your perspective, what are the main selling points for further health care providers or policy makers to use the ADLIFE digital platform in the future? What is needed to increase the usability and acceptance of digital tools in patient care?
	Cosmopolitanism	#1: IT staff	#1: Only IT Staff: How can the organization communicate/cooperate with external organizations? Which digital exchange options with external organizations exist?	
NET BENEFITS	Net benefits by cooperation between professionals	#3 Patients, caregivers, MDTs, managers		#3: PATIENTS: Thinking about all the health services you have used in the last months, how do you experience or think your care has been coordinated (For example, the way different doctors, nurses, social workers and organizations work together)? / Which changes have you noticed in the overall care you have been receiving lately? (since….months, when you entered in the ADLIFE program). #3: CAREGIVERS: Thinking about all the health services he/she has used in the last months, how do you experience or think the care has been coordinated (For example, the way different doctors, nurses, social workers and organizations work together)? / Which changes have you noticed in the overall care he/she has been receiving lately? (since….months, when he/she entered in ADLIFE). #1/#3: MDTs: How has the implementation of ADLIFE changed the way you coordinate with other MDTs in your same care level? How do you perceive the impact of cooperation with other MDTs in your same level of care? #1/#3: MDTs: How do you use the functions of the ADLIFE digital platforms to coordinate with other healthcare providers?
NET BENEFITS	Individual and organizational Net benefits by-ADLIFE	#1: Physicians, GP, nurse, meidcal director #3 MDTs, managers	#1: Which advantages/benefits or disadvantages do you expect for yourself and your work and for your patients through the implementation and use of digital platforms such as the ADLIFE toolbox in patient care (especially in the care of patients with COPD and or CHF)? (Prompts: Job effects, clinical outcomes in patient care, error reduction, productivity) *Which benefits do you see through a closer cooperation and communication of different providers in patient care?	1/#3 MDTs: After having used the ADLIFE digital platform, what do you think of the integrated, personalized and digitally supported care of patients with COPD or chronic heart failure? #1: MDTs: How do you perceive the quality of care when using the ADLIFE digital platform in patient care? #1: MDTs: Which advantages/benefits or disadvantages do you see for yourself and your work through the implementation and use of the ADLIFE digital platform in patient care (especially in the care of patients with COPD and or CHF)? (Prompts: Job effects, clinical outcomes in patient care, error reduction, productivity) #1: MDTs: How does the use of the ADLIFE digital platform effects your work and/or your workload? #3: MANAGERS: Which has been the impact of ADLIFE on the daily work with the PATIENTS, on the routine of the MDTs, on their workflow and attitudes? How has it influenced coordination with other MDTs and between levels of care?

Dimension	Construct/Subcategories	Stakeholders involved	Pre-questions before implementation (targeting WP10/Exploitation)	Post questions after implementation (targeting WP9 and WP10)
NET BENEFITS	Self-empowerment of patients through ADLIFE	#3 MDTs, managers		#1/#3: MDTs and managers: To what extent has ADLIFE enhanced patient empowerment and involvement in decision-making? Is there now more awareness of the importance of facilitating this culture?
NET BENEFITS	Expected benefits from ADLIFE	#3 MDTs, managers		#1/#3: MDTs and managers: What changes have personalised care plans brought about in the way care for these patients is managed? What are the main benefits?
NET BENEFITS	Expected benefits from ADLIFE	#3 MDTs, managers		#3: MDTs: How has the implementation of ADLIFE changed the services use pattern (less emergency visits, home care nurse visits ...)? #3: MANAGERS: How has the implementation of ADLIFE changed the services use pattern (less emergency visits, home care nurse visits ...)?

Description:

- #1: Relevant for WP 10 (Exploitation - Implementation assessment)
- #3: Relevant for WP 9 (Evaluation - Qualitative effectiveness assessment)
- Dimension: Dimensions of the Framework for implementation assessment
- Construct/Subcategories: Construct of the Framework for implementation assessment + subcategories of the coding system
- Stakeholders involved: Stakeholders involved /Stakeholder to be interviewed

Appendix E DCG for technology acceptance and adoption assessment

E.1 Instructions

The DCG for technology acceptance and adoption assessment is available in the project's SharePoint in excel format. Its content is provided bellow:

GENERAL

This **data collection guide for technology acceptance and adoption evaluation** contains three further sheets: *contact details, gantt chart&study design* and *flow-chart*, and refers to one additional documents: the protocol for the evalution study and the questionnaires to be completed by the participants (patients&carers group and health professionals group). Note that participants will complete the questionnaires themselves online. The pilot site is responsible for contacting the participants at the specified time for them to complete the questionnaires.

On sheet *contact details* you will find the contact details of the pilot sites' data managers and the evaluation coordinator.
On sheet *gantt chart&study design*, you will find the gantt chart of the required tasks on the data collection process and, the **study design** for better comprehension.
On sheet *flow-chart* you will find the **flow-chart of the recruitment and selection process** to be completed. Each pilot site will complete and send the recruitment flow-chart. The flowchart is the same as for the **quantitative effectiveness evaluation,** with an additional step to allocate participants to a main group or detailed evaluation group. The detailed evaluation group will be asked to complete 2 questionnaires at baseline and at endline, while the main group will be asked to complete 1 questionnaire at endline.
The **study design** and the **gantt chart** shows comprehensive information on the data collection periods and the activities around these.
Completed **flow-chart of the recruitment and selection process** will be sent to the evaluation coordinator on deadlines showed on the **gantt chart**.
Please**,** before reading the specific instructions below, have a look at the *gantt chart&study design* sheet for a better comphrension.

SPECIFIC

• For the Technology Acceptance & Adaoption evaluation, **health professionals**, as well as intervention **patients & informal caregivers** are involved - the whole intervention group.
• Please, find below the **elegibility criteria** to conduct **Task 1 and 2**:
The study population consists of patients with advanced chronic diseases (HF and/or COPD with/without co-morbidities), their informal caregivers and their healthcare professionals, fulfilling the following inclusion/exclusion criteria.

Eligible patients will have to meet the below inclusion criteria:

1) Aged over 55

2) Heart failure (NYHA III-IV) in functional stage III/IV according to the NYHA scale and stages C and D of the ACCF/AHA classification.

3) Stable-phase (at least two months without decompensation requiring hospital care)

4) And/or COPD (FEV1<50), >2 GOLD or MRC>2 or CAT> 10 or use of oxygen at home

5) With or without comorbidities

6) They are able to provide informed consent

7) They still live and generally plan on living in their home for the intervention duration

8) They or their informal caregivers are able to use digital technology, communication tools, and/or networks and have access to a computer, laptop, tablet or smartphone and wifi/internet connection.

9)They or their informal caregivers understand, read and talk the native language.

The informal caregiver will be a person who provides occasional or regular support to the patient needs. Caregivers will be eligible if the patient they care for meet the inclusion criteria and it is included in the study. Health professionals will be eligible if they are involved in the included patients care, open to new ways of working, specifically as part of a coordinative and collaborative teams and, open to the use of new technology.

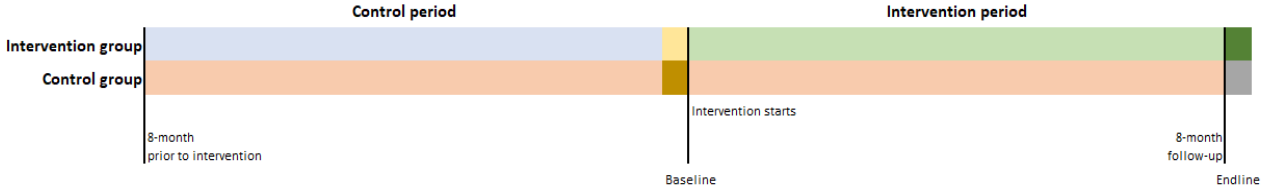
Patients presenting any active malignant neoplastic disease, being in any active list of transplantation or, refusing to sign the informed consent, will not be included. Patients having participated in ADLIFE but having withdrawn from their participation, will not be eligible for the recruitment anymore. Caregivers will not be eligible if the patients they care for meet the exclusion criteria. Healthcare professionals not caring for patients who meet the inclusion criteria or only caring for patients who fulfil the exclusion criteria, will not be included.

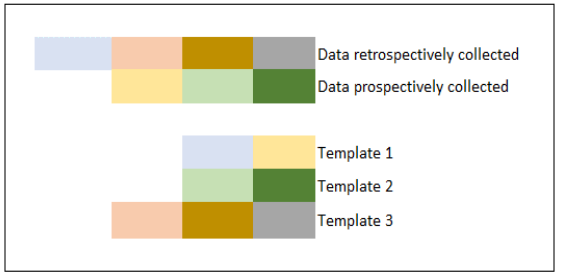
- For pilot sites deploying the ADLIFE Toolkit:
  - For **Timepoint 1 technology acceptance evaluation communication** in **Task 6.1a and 6.1b**: BIRMINGHAM will provide you with the survey link(s) and instructions to be communicated to the participants using the ADLIFE Tools (any translations will have been completed) to send to the participant groups. In the baseline evaluation period, after the participants have been trained and set up on the ADLIFE platform, contact the participants to complete the baseline questionnaires (after a quarter of the time in the study).
  - For **Timepoint 2 technology acceptance evaluation communication in Task 10.1a and 10.1b:** BIRMINGHAM will provide you with the survey link(s) and instructions to be communicated to the participants using the ADLIFE Tools (any translations will have been completed) to send to the participant groups. In the endline evaluation period, contact the participants to complete the endline questionnaires (after three-quarters of the time in the study).
- For pilot sites deploying their own systems:
  - For **Timepoint 1 technology acceptance evaluation communication** in **Task 6.2a and 6.2b**: BIRMINGHAM will provide you with the survey link(s) and instructions to be communicated to the participants using the ADLIFE Tools (any translations will have been completed) to send to the participant groups. Contact the participants to complete the questionnaires (halfway into the study).

E.2 Version history

Date	Version	Change
01/09/2022	v4	Update of inclusion criteria according to Research Protocol v0.29 and addition of a new page for version history tracking.
19/01/2023	v5	Update to the timeline for data collection, with the main pilot study starting March 2023. Update of Birmingham team contacts. Instructions updated to clarify that data collection timepoint 1 and 2 correspond to a quarter and three-quarters into the study period respectively.
31/05/2023	v6	Update of the data collection instructions to cater for the 2 types of pilot sites: (i) sites deploying the ADLIFE Toolbox (GWMK, NHSL, OSAKIDETZA, UHCW); and (ii) sites using their own systems (AMCA, OUH).

E.3 Gantt chart & study design





Task nº	Task	Task description
1	Identification of tentative target patient population	Identify patients meeting the elegibility criteria from electronic health records (EHR)
2	Identification of final target patient population	Identify final target population according to the checking process conducted by health professionals
3	Intervention patients sign up on ADLIFE platform	Sign up the intervention patients, previously recruited by health professionals, on the ADLIFE platform. The ADLIFE platform will automatically assign an ADLIFE ID
4	Saving intervention participants	Save the intervention participants with their corresponding ADLIFE ID and EHR ID.
5	Indentification of target control patient population (TCPP)	Identify target control population defined as the subset of final target population removing the intervention patients
6	Baseline and control period of intervention participants data collection	Collect baseline and control period data on intervention patients and their caregivers (Template 1)
6.1a	***Technology acceptance for sites deploying ADLIFE Toolkit - Timepoint 1 data collection (1/4 through study period, e.g. for 9 months study, T1 will be after 2 months in the study)***	**3 months into the study, send technology acceptance evaluation questionnaire link to the HCP and Patients & Caregiver intervention groups.**
6.1b	***Technology acceptance or sites deploying ADLIFE Toolkit - Send reminders for completion of Timepoint 1 data collection***	**One week after initial communication, send a reminder for completion of questionnaires.**
6.2a	***Technology acceptance for sites using their own systems - Timepoint 1 data collection (halfway through study period)***	**3 months into the study, send technology acceptance evaluation questionnaire link to the HCP and Patients & Caregiver intervention groups.**
6.2b	***Technology acceptance for sites using own systems - Send reminders for completion of Timepoint 1 data collection***	**One week after initial communication, send a reminder for completion of questionnaires.**
7	Preliminar data cleaning process	Conduct data cleaning process according to guideline described on sheet *instructions*
8	Send data collected on task 6 to evaluation coordinator	Send data collection template fullfilled with baseline and control period data of intervention patients and their caregivers (Template 1)
9	Fulfil and send recruitment flowchart to evaluation coordinator	Fulfil and send the recruitment flow-chart, which can be fond in Annex 1 of the study protocol
10	Endline and intervention period of intervention participants data collection	Collect endline and intervennton period data on intervention patients and their caregivers (Template 2)
10.1a	***Technology acceptance for sites deploying ADLIFE Toolkit - Timepoint 2 data collection (3/4 through study period, e.g. for 9 months study, T2 will be after 7 months in the study)***	**9 months into the study, send evaluation questionnaire links to the intervention groups.**
10.1b	***Technology acceptance for sites deploying ADLIFE Toolkit - Send reminders for completion of Timepont 2 data collection***	**One week after initial communication, send a reminder for completion of questionnaires.**
11	Control period and intervention period of TCPP data collection	Collect control and intervention period data on TCPP (Template 3)
12	Data cleaning process	Conduct data cleaning process according to guideline described on sheet *instructions*
13	Anonymization of data collected on task 11	Anonymize data collected on task 11 following the anonymization methods described on *instructions* sheet
14	Health-related outcome log and Potentially Preventable Situations (PPSs) log data collection	Conduct data collection of health-related outcome log and Potentially Preventable Situations (PPSs) log according to the provided instructions in *instruction* sheet
15	Share data collected on tasks 10, 11 and 14 with evaluation coordinator	Share a) Template 2 , b) Template 3, c) the Health-related outcome log and d)Potentially Preventable Situations (PPSs) log

Task nº	Jul-22	Aug-22	Sep-22	Oct-22	Nov-22	Dec-22	Jan-23	Feb-23	Mar-23	Apr-23	May-23	Jun-23	Jul-23	Aug-23	Sep-23	Oct-23	Nov-23	Dec-23
	M31	M32	M33	M34	M35	M36	M37	M38	M39	M40	M41	M42	M43	M44	M45	M46	M47	M48
1																		
2																		
3																		
4																		
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6																		
6.1a																		
6.1b																		
6.2a																		
6.2b																		
7																		
8																		
9																		
10																		
10.1a																		
10.1b																		
11																		
12																		
13																		
14																		
15																		

Legend

Appendix F DCG for socio-economic impact assessment

The DCG for the socio-economic impact assessment is available in the project's SharePoint in excel format. Its content is provided bellow:

F.1 Instructions

GENERAL INFORMATION

This **data collection guide (DCG)** is focus on the **economic assesment** and contains two further sheets compiling the **codebook**. The sheets are **"cb_unit costs"** and **"cb_drug prescription cost"** and their content is explained in more detail below. This DCG also refers to the three data collection **templates** that you will be provided to enter the data.

cb_unit costs

In this sheet you will find the requested information about the unit costs that works in each pilot site. The information described will be collected in the template "**adlife_economic assessment_template 1**". The information is necessary to adapt the general simulation model to each pilot site. We kindly ask pilot sites to confirm the data availability to see if any change need to be implemented.

cb_drug prescription

In this sheet you will find the requested information about the total drug prescription cost that patients have during the intervention period. The information will be collected in the template "**adlife_economic assessment_template 2**" for the intervention patients and in the template "**adlife_economic assessment_template 3**" for the target control patient population (TCPP). We kindly ask pilot sites to confirm the data availability to see if any change need to be implemented.

TASKS AND DEADLINES

This section shows comprehensive information of the tasks, data collection templates content and deadlines. Fullfilled data collection templates will be sent to the evaluation coordinator on deadlines showed below.

Task nº	Task	Task description	Nov-23	Jan-24
			M47	M49
1	Collect and send unit cost data to evaluation coordinator	Collect and send the "adlife_economic assessment_template 1" fulfilled with each pilot site unit cost data.		
2	Collect and send intervention patients drug prescription cost data to evaluation coordinator	Collect send the "adlife_economic assessment_template 2" fulfilled with the drug prescription cost data of intervention patients.		
3	Collect and send control patients drug prescription cost data to evaluation coordinator	Collect send the "adlife_economic assessment_template 3" fulfilled with the drug prescription cost data of target control patient population (TCPP).		

CONTACT DETAILS

EVALUATION COORDINATOR (ECONOMIC ASSESSMENT)		
Partner	**Person in charge**	**Email**
Kronikgune	Igor Larrañaga Uribeetxebarria Javier Mar Medina	ilarranaga@kronikgune.org franciscojavier.marmedina@osakidetza.eus

F.2 Unit costs codebook

resource		variable	label	type	Notes
pilot site information		unit_cost_monetary_unit	monetary unit of the unit costs	text	
		unit_cost_year	reference year of the unit costs	discrete	
primary care	gp	unit_cost_gp_centre	general practitioner (consultation at healthcare centre)	numeric	(1), (2)
		unit_cost_gp_telephone	general practitioner (consultation by telephone)	numeric	(1), (2)
		unit_cost_gp_home	general practitioner (consultation at home)	numeric	(1), (2)
	pc nurse	unit_cost_pcnurse_centre	primary care nurse (consultation at healthcare centre)	numeric	(1), (2)
		unit_cost_pcnurse_telephone	primary care nurse (consultation by telephone)	numeric	(1), (2)
		unit_cost_pcnurse_home	primary care nurse (consultation at home)	numeric	(1), (2)
hospital care	outpatient services	unit_cost_cardiology_first	cardiology (first consultation)	numeric	(1), (3), (4)
		unit_cost_cardiology_successive	cardiology (successive consultation)	numeric	(1), (3), (4)
		unit_cost_respiratory_first	respiratory (first consultation)	numeric	(1), (3), (4)
		unit_cost_respiratory_successive	respiratory (successive consultation)	numeric	(1), (3), (4)
		unit_cost_endocrinology_first	endocrinology (first consultation)	numeric	(1), (3), (4)
		unit_cost_endocrinology_successive	endocrinology (successive consultation)	numeric	(1), (3), (4)
		unit_cost_nephrology_first	nephrology (first consultation)	numeric	(1), (3), (4)
		unit_cost_nephrology_successive	nephrology (successive consultation)	numeric	(1), (3), (4)
		unit_cost_neurology_first	neurology (first consultation)	numeric	(1), (3), (4)
		unit_cost_neurology_successive	neurology (successive consultation)	numeric	(1), (3), (4)
		unit_cost_psychiatry_first	psychiatry (first consultation)	numeric	(1), (3), (4)
		unit_cost_psychiatry_successive	psychiatry (successive consultation)	numeric	(1), (3), (4)
		unit_cost_internal_medicine_first	internal medicine (first consultation)	numeric	(1), (3), (4)
		unit_cost_internal_medicine_successive	internal medicine (successive consultation)	numeric	(1), (3), (4)
		unit_cost_other_first	other (first consultation)	numeric	(1), (3), (4)
		unit_cost_other_successive	other (successive consultation)	numeric	(1), (3), (4)
	emergency room	unit_cost_er	emergency room (per contact)	numeric	(1)
	hospitalisation	unit_cost_hospitalisation	hospitalisation (per day)	numeric	(1), (5)
		unit_cost_home_hospitalisation	home hospitalisation (per day)	numeric	(1), (5)
		unit_cost_icu	icu (per day)	numeric	(1), (5), (6)

** Add rows in the table if necessary*

Notes:

- (1) If any resource is not included in the pilot site, related information is not necessary. If some resource that works in the pilot site is misssing, related information can be added to table by adding rows.
- (2) In case no breakdown available across type of contacts with gp/nurse, total unit costs will be entered in "at the healthcare centre" category.
- (3) In case no breakdown available across type of speciality, total unit costs will be entered in "other" category.
- (4) In case no breakdown available across first/succesive consultations, total unit costs will be entered in "first consultation" category.
- (5) If unit cost per day is not available, unit cost per stay will be entered.
- (6) If ICU cost is considered into hospitalisation cost, this information is not necessary.

F.3 Drug prescription cost codebook

variable	label	type	value label	intervention	control	Notes
id_patient	patient id	string	n.a.	X	X	- intervention group: four-number format automatically assigned by ADLIFE platform e.g. 1006 - control group: anonymized format
drug_prescription_cost	total drug prescription cost that patient had	numeric	n.a.	X	X	

Appendix G Data collection templates for socio-economic impact assessment

The Data Collection Templates for socio-economic impact assessment is available in the project's SharePoint in excel format. A screenshot of the excel sheets is provided bellow:

	A	B	C	D
1	pilot site			
2				
3	*Pilot site information*			
4	information	variable	value	
5	monetary unit	unit_cost_monetary_unit		
6	reference year of the unit costs	unit_cost_year		
7				
8	*Healthcare unit costs*			
9	resource	variable	value	
10	general practitioner (consultation at healthcare centre)	unit_cost_gp_centre		
11	general practitioner (consultation by telephone)	unit_cost_gp_telephone		
12	general practitioner (consultation at home)	unit_cost_gp_home		
13	primary care nurse (consultation at healthcare centre)	unit_cost_pcnurse_centre		
14	primary care nurse (consultation by telephone)	unit_cost_pcnurse_telephone		

Figure 32 - Screenshot of Template 1 for socio-economic impact assessment

	A	B	C	D	E
1	id_patient	drug_prescription_cost	*Target control patient population (TCPP)*		
2					
3					
4					
5					
6					
7					

Figure 33 - Screenshot of Template 2 for socio-economic impact assessment

	A	B	C	D
1	id_patient	drug_prescription_cost	*Intervention patients*	
2				
3				
4				
5				
6				
7				

Figure 34 - Screenshot of Template 3 for socio-economic impact assessment

Appendix H Materials for socio-economic impact assessment

H.1 Unit costs

Table 153: Unit costs of different resources obtained from Basque Health Service databases for the year 2019.

Resource	Basque Country EUR (€)
PC nurse (at centre)	12,00
PC nurse (at home)	21,80
PC nurse (by telephone)	6,00
General practitioner (at centre)	27,20
General practitioner (at home)	38,10
General practitioner (by telephone)	13,60
Cardiology (first consultation)	133,09
Cardiology (successive consultation)	78,27
Endocrinology (first consultation)	157,09
Endocrinology (successive consultation)	85,97
Internal medicine (first consultation)	134,55
Internal medicine (successive consultation)	78,96
Nephrology (first consultation)	142,23
Nephrology (successive consultation)	81,21
Neurology (first consultation)	133,09
Neurology (successive consultation)	78,27
Psychiatry (first consultation)	120,65
Psychiatry (successive consultation)	69,84
Respiratory (first consultation)	133,09
Respiratory (successive consultation)	78,27
A&E services (per contact)	168,3
Hospitalisation (per stay)	2,310.08

H.2 Prevalence and incidence

Table 164: Prevalent and incident cohorts from 2012 to 2019 obtained from Basque Health Service databases.

		Prevalence	Incidence						
		2012	2012	2013	2014	2015	2016	2017	2018	2019
Women	55-59	1145	156	190	215	215	344	397	424	501
	60-64	917	112	117	131	139	301	339	374	428
	65-69	1325	130	151	163	182	323	396	398	423
	70-74	2092	233	220	242	233	458	461	473	486
	75-79	3092	466	420	383	453	555	530	507	614
	80-84	3331	804	719	746	818	933	991	871	820
	85-89	2399	863	792	863	909	1048	1154	1103	1160
	90-94	861	480	485	482	589	705	786	803	800
	≥95	96	106	118	129	119	150	192	211	220
Men	55-59	2938	361	330	432	425	711	689	728	838
	60-64	1889	226	276	259	285	572	656	631	574
	65-69	2109	309	299	333	370	883	824	718	704
	70-74	2478	347	311	358	442	1039	1026	950	886
	75-79	2816	554	485	470	519	974	908	880	923
	80-84	2169	654	634	688	722	1256	1118	938	890
	85-89	1110	501	454	596	587	976	981	881	861
	90-94	275	192	210	235	269	386	407	371	421
	≥95	25	41	42	39	38	66	76	71	75

Table 175: Incident cohort forecast from 2019 to 2030 obtained from Basque Health Service databases and Basque Statistics Institute (EUSTAT).

		Incidence										
		2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
Women	55-59	506	509	513	514	511	507	505	506	509	513	520
	60-64	442	452	458	463	467	473	476	480	480	479	475
	65-69	424	431	441	453	465	481	492	500	505	510	515
	70-74	493	491	492	498	497	498	506	520	534	548	566
	75-79	661	688	719	748	768	779	778	779	789	789	792
	80-84	771	768	741	741	794	850	891	930	970	996	1013
	85-89	1189	1189	1208	1173	1115	1047	1054	1025	1034	1105	1192
	90-94	831	884	923	971	1002	1029	1042	1064	1042	989	936
	≥95	244	260	288	312	340	364	396	420	448	476	500
Men	55-59	849	858	868	878	885	881	884	892	901	908	919
	60-64	594	607	614	619	627	636	644	651	660	665	664
	65-69	704	713	733	752	771	796	816	828	835	846	860
	70-74	901	904	904	916	914	914	927	955	982	1006	1043
	75-79	1001	1036	1093	1136	1173	1198	1206	1208	1223	1226	1231
	80-84	838	844	835	853	912	992	1032	1087	1136	1183	1210
	85-89	892	905	910	896	865	817	835	835	861	927	1011
	90-94	463	499	541	583	619	644	662	674	668	644	613
	≥95	86	96	113	123	139	155	171	198	209	236	246

H.3 Input characteristics

Table 186: Logistic regression parameters used to set patients input characteristics.

		Heart failure	COPD	Charlson group	
				1-2	3-4
Sex	Women	0,000	0,000	0,000	0,000
	Men	-0,808	1,104	-0,721	-0,343
Age group	55-59	0,000	0,000	0,000	0,000
	60-64	0,172	-0,293	-0,230	-0,001
	65-69	0,494	-0,173	-0,444	-0,032
	70-74	0,933	-0,336	-0,596	-0,056
	75-79	1,426	-0,501	-0,729	-0,063
	80-84	2,019	-0,528	-0,768	-0,030
	85-89	2,516	-0,555	-0,761	0,058
	90-94	2,928	-0,736	-0,663	0,212
	≥95	3,254	-0,751	-0,608	0,245
Heart failure	No	0,000	0,000	0,000	0,000
	Yes	0,000	-25,910	-1,769	-0,569
COPD	No	0,000	0,000	0,000	0,000
	Yes	0,000	0,000	-1,104	-0,236
Constant		1,794	18,800	4,717	1,760

H.4 Time until event functions

Table 197: Distributions and parameters of the time until event functions for primary care.

		PC doctor						PC nurse					
		Centre		Home		Telephone		Centre		Home		Telephone	
		First	Between	First	Between	First	Between	First	Between	First	Between	First	Between
Type of function		Weibull	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull
Sex	Women	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
	Men	0,064	-0,006	-0,181	0,040	-0,167	-0,111	0,120	0,070	-0,172	-0,008	-0,050	-0,012
Age group	55-59	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
	60-64	0,236	0,047	0,349	-0,006	0,054	0,007	0,240	0,062	0,290	0,102	0,200	0,062
	65-69	0,188	0,101	0,617	0,095	0,024	0,102	0,318	0,094	0,548	0,160	0,244	0,105
	70-74	0,232	0,146	0,998	0,150	0,095	0,174	0,403	0,133	0,827	0,215	0,319	0,173
	75-79	0,219	0,155	1,254	0,190	0,173	0,252	0,409	0,126	1,073	0,234	0,396	0,212
	80-84	0,130	0,143	1,579	0,262	0,269	0,345	0,342	0,115	1,374	0,286	0,474	0,268
	85-89	0,000	0,083	1,912	0,338	0,379	0,425	0,218	0,037	1,700	0,288	0,586	0,302
	90-94	-0,217	0,049	2,231	0,438	0,415	0,486	0,029	0,056	1,949	0,333	0,632	0,338
	≥95	-0,405	0,137	2,536	0,581	0,528	0,638	-0,133	0,027	2,172	0,440	0,680	0,483
Heart failure	No	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
	Yes	0,156	0,107	0,284	0,079	0,131	0,029	0,335	0,305	0,381	0,121	0,397	0,107
COPD	No	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
	Yes	0,044	0,014	0,060	0,023	0,008	0,008	0,093	-0,002	-0,024	-0,035	0,175	0,056
Charlson group	1-2	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
	3-4	0,023	0,044	0,169	0,021	0,131	0,081	0,099	0,023	0,173	0,065	0,153	0,076
	≥5	-0,020	0,070	0,362	0,032	0,238	0,154	0,148	0,067	0,392	0,148	0,314	0,190
Constant		-2,985	-3,324	-6,304	-2,770	-4,544	-2,669	-3,488	-3,170	-5,462	-2,162	-4,745	-2,786
Beta		0,554	0,799	0,642	0,607	0,647	0,575	0,526	0,744	0,548	0,583	0,565	0,588

Table 208: Distributions and parameters of the time until event functions for outpatient services.

		Outpatient services													
		Cardiology		Endocrinology		Internal medicine		Nephrology		Neurology		Psychiatry		Respiratory	
		First	Between	First	Between	First	Between	First	Between	First	Between	First	Between	First	Between
Type of function		Weibull	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull	Weibull
Sex	Women	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
	Men	0,301	0,069	-0,445	0,091	0,104	0,008	0,214	0,051	-0,055	0,023	-0,510	0,082	0,203	-0,006
Age group	55-59	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
	60-64	0,184	-0,046	-0,056	-0,013	0,180	0,020	0,003	0,030	0,158	-0,014	-0,308	-0,188	0,205	-0,042
	65-69	0,200	-0,097	-0,167	0,030	0,322	0,047	0,027	-0,125	0,304	-0,021	-0,636	-0,173	0,184	-0,046
	70-74	0,180	-0,134	-0,359	0,005	0,364	0,046	-0,037	-0,132	0,466	0,001	-0,783	-0,251	0,140	-0,052
	75-79	0,087	-0,156	-0,613	-0,005	0,442	0,044	-0,196	-0,223	0,585	-0,029	-0,933	-0,281	0,031	-0,055
	80-84	-0,097	-0,172	-1,006	0,036	0,430	0,077	-0,460	-0,334	0,568	-0,058	-1,201	-0,310	-0,230	-0,080
	85-89	-0,505	-0,201	-1,593	0,066	0,277	0,089	-0,913	-0,389	0,327	-0,057	-1,519	-0,299	-0,677	-0,074
	90-94	-1,153	-0,179	-2,384	-0,005	-0,034	0,092	-1,498	-0,443	-0,255	-0,068	-1,827	-0,213	-1,277	-0,046
	≥95	-1,776	-0,057	-3,198	0,552	-0,610	0,172	-2,591	-0,486	-0,709	-0,003	-1,881	-0,077	-1,755	-0,035
Heart failure	No	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
	Yes	1,047	0,167	0,189	0,036	0,671	0,112	0,490	0,130	-0,110	-0,035	-0,008	0,072	0,294	0,069
COPD	No	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
	Yes	-0,386	-0,046	-0,182	-0,090	0,261	-0,007	-0,385	-0,046	-0,177	-0,027	0,104	0,140	1,235	0,070
Charlson group	1-2	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000	0,000
	3-4	0,042	0,052	0,584	-0,003	0,218	0,002	1,144	0,284	0,232	-0,021	0,163	0,049	-0,016	-0,006
	≥5	-0,016	0,052	1,196	0,097	0,381	0,057	1,916	0,392	0,352	-0,046	0,263	-0,029	-0,129	0,020
Constant		-5,256	-5,437	-5,472	-5,962	-6,681	-4,117	-6,745	-4,307	-6,539	-5,898	-5,279	-3,466	-5,494	-5,446
Beta		0,523	1,006	0,513	1,135	0,524	0,916	0,481	0,876	0,654	1,097	0,485	0,841	0,517	1,054

Table 19: Distributions and parameters of the time until event functions for hospital care and death.

		A&E services		Hospitalisation		Death
		First	Between	First	Between	
Type of function		Weibull	Weibull	Weibull	Weibull	Gompertz
Sex	**Women**	0.000	0.000	0.000	0.000	0.000
	Men	-0.004	0.039	0.119	0.048	0.222
Age group	**55-59**	0.000	0.000	0.000	0.000	0.000
	60-64	0.100	0.008	0.160	-0.010	0.317
	65-69	0.171	0.030	0.303	-0.021	0.553
	70-74	0.257	0.052	0.425	-0.008	0.850
	75-79	0.360	0.068	0.548	-0.007	1.115
	80-84	0.396	0.077	0.650	-0.002	1.496
	85-89	0.473	0.085	0.789	0.014	1.953
	90-94	0.513	0.122	0.892	0.061	2.496
	≥95	0.616	0.274	1.047	0.215	3.375
Heart failure	**no**	0.000	0.000	0.000	0.000	0.000
	yes	0.305	-0.027	0.692	-0.020	0.623
COPD	**no**	0.000	0.000	0.000	0.000	0.000
	yes	0.150	-0.007	0.262	0.020	0.201
Charlson group	**1-2**	0.000	0.000	0.000	0.000	0.000
	3-4	0.190	0.086	0.188	0.083	0.220
	≥5	0.375	0.160	0.380	0.142	0.482
Constant		-5.774	-3.636	-6.324	-4.123	-9.738
Beta		0.710	0.705	0.663	0.755	0.000

H.5 Goodness of fit test

Table 210: Goodness of fit test for different resources from 2012 to 2014.

2012															
Total	PC Doctor Centre	PC Doctor Home	PC Doctor Telephone	PC Nurse Centre	PC Nurse Home	PC Nurse Telephone	Card.	Endo.	Int. Med.	Nep.	Neu.	Psych.	Resp.	ED	Hosp.
R: > 0.8	0.882	0.886	0.884	0.877	0.881	0.886	0.879	0.863	0.868	0.853	0.858	0.866	0.876	0.884	0.882
NMSE: < 0.5	0.191	0.100	0.108	0.032	0.012	0.334	0.008	0.035	0.021	0.036	0.069	0.049	0.013	0.125	0.005
FB: [-0.5, 0.5]	0.372	-0.269	-0.294	0.134	0.006	-0.487	0.010	0.087	-0.037	0.032	-0.164	0.093	0.018	0.310	0.008
FV: [-0.5, 0.5]	0.387	0.208	0.224	0.204	0.143	0.472	0.151	0.264	0.226	0.292	0.296	0.271	0.187	0.292	0.126
FAC2: > 0.8	1.000	1.000	1.000	1.000	1.000	0.917	1.000	1.000	1.000	1.000	0.917	0.917	1.000	1.000	1.000
2013															
Total	PC Doctor Centre	PC Doctor Home	PC Doctor Telephone	PC Nurse Centre	PC Nurse Home	PC Nurse Telephone	Card.	Endo.	Int. Med.	Nep.	Neu.	Psych.	Resp.	ED	Hosp.
R: > 0.8	0.883	0.885	0.886	0.877	0.887	0.887	0.874	0.882	0.879	0.860	0.859	0.882	0.880	0.884	0.881
NMSE: < 0.5	0.104	0.230	0.067	0.011	0.057	0.220	0.017	0.035	0.102	0.028	0.153	0.034	0.017	0.053	0.005
FB: [-0.5, 0.5]	0.276	-0.395	-0.228	-0.041	-0.199	-0.402	-0.070	-0.155	-0.241	-0.047	-0.311	-0.148	-0.094	0.193	-0.009
FV: [-0.5, 0.5]	0.295	0.332	0.192	0.168	0.170	0.375	0.191	0.164	0.331	0.255	0.345	0.142	0.150	0.226	0.131
FAC2: > 0.8	1.000	0.833	1.000	1.000	1.000	1.000	1.000	1.000	0.917	1.000	0.917	0.833	1.000	1.000	1.000
2014															
Total	PC Doctor Centre	PC Doctor Home	PC Doctor Telephone	PC Nurse Centre	PC Nurse Home	PC Nurse Telephone	Card.	Endo.	Int. Med.	Nep.	Neu.	Psych.	Resp.	ED	Hosp.
R: > 0.8	0.885	0.871	0.886	0.881	0.883	0.884	0.878	0.884	0.882	0.849	0.870	0.882	0.877	0.875	0.858
NMSE: < 0.5	0.062	0.156	0.005	0.032	0.054	0.165	0.028	0.073	0.168	0.052	0.184	0.080	0.040	0.028	0.021
FB: [-0.5, 0.5]	0.216	-0.319	-0.046	-0.149	-0.189	-0.354	-0.126	-0.230	-0.330	-0.093	-0.354	-0.212	-0.164	0.127	-0.012
FV: [-0.5, 0.5]	0.228	0.298	0.082	0.174	0.182	0.314	0.189	0.218	0.379	0.333	0.359	0.225	0.188	0.202	0.263
FAC2: > 0.8	1.000	0.833	1.000	1.000	1.000	1.000	1.000	1.000	0.833	1.000	0.917	0.833	0.917	1.000	1.000

R: correlation coefficient; NMSE: normalized mean square error; FB: Fractorial Bias; FV: fractorial variance; FAC2: fraction of predictions within a factor of two

Table 221: Goodness of fit test for different resources from 2015 to 2017.

2015														
Total	PC Doctor Centre	PC Doctor Home	PC Doctor Telephone	PC Nurse Centre	PC Nurse Home	PC Nurse Telephone	Card.	Endo.	Int. Med.	Nep.	Neu.	Psych.	Resp.	ED	Hosp.
R: > 0.8	0.886	0.873	0.886	0.882	0.879	0.886	0.880	0.875	0.881	0.817	0.882	0.883	0.871	0.880	0.864
NMSE: < 0.5	0.043	0.060	0.023	0.010	0.020	0.013	0.020	0.099	0.274	0.110	0.274	0.020	0.044	0.023	0.021
FB: [-0.5, 0.5]	0.178	-0.189	0.116	-0.068	-0.082	-0.101	-0.108	-0.257	-0.431	-0.183	-0.435	-0.101	-0.163	0.119	0.050
FV: [-0.5, 0.5]	0.205	0.208	0.161	0.134	0.154	0.098	0.166	0.277	0.465	0.442	0.440	0.115	0.218	0.182	0.258
FAC2: > 0.8	1.000	0.917	1.000	1.000	1.000	1.000	1.000	1.000	0.833	1.000	1.000	1.000	0.917	1.000	1.000
2016														
Total	PC Doctor Centre	PC Doctor Home	PC Doctor Telephone	PC Nurse Centre	PC Nurse Home	PC Nurse Telephone	Card.	Endo.	Int. Med.	Nep.	Neu.	Psych.	Resp.	ED	Hosp.
R: > 0.8	0.887	0.868	0.887	0.883	0.878	0.884	0.877	0.883	0.880	0.868	0.884	0.883	0.876	0.873	0.864
NMSE: < 0.5	0.038	0.044	0.049	0.004	0.019	0.008	0.034	0.102	0.197	0.067	0.291	0.019	0.033	0.025	0.020
FB: [-0.5, 0.5]	0.164	-0.137	0.167	-0.001	-0.062	0.008	-0.147	-0.273	-0.371	-0.179	-0.461	0.040	-0.145	0.114	0.063
FV: [-0.5, 0.5]	0.208	0.217	0.261	0.125	0.166	0.158	0.205	0.252	0.395	0.300	0.413	0.155	0.182	0.221	0.253
FAC2: > 0.8	1.000	0.917	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	0.833	1.000	0.917	1.000	1.000
2017														
Total	PC Doctor Centre	PC Doctor Home	PC Doctor Telephone	PC Nurse Centre	PC Nurse Home	PC Nurse Telephone	Card.	Endo.	Int. Med.	Nep.	Neu.	Psych.	Resp.	ED	Hosp.
R: > 0.8	0.888	0.863	0.887	0.886	0.869	0.879	0.881	0.874	0.886	0.882	0.886	0.884	0.882	0.871	0.863
NMSE: < 0.5	0.034	0.049	0.049	0.017	0.043	0.037	0.006	0.113	0.066	0.010	0.230	0.045	0.009	0.019	0.016
FB: [-0.5, 0.5]	0.157	-0.021	0.167	0.095	0.018	0.105	-0.035	-0.276	-0.221	-0.048	-0.410	0.115	-0.058	0.090	0.036
FV: [-0.5, 0.5]	0.195	0.308	0.261	0.176	0.287	0.294	0.131	0.298	0.232	0.143	0.388	0.211	0.125	0.224	0.253
FAC2: > 0.8	1.000	0.917	1.000	1.000	1.000	1.000	0.917	1.000	0.917	0.917	1.000	1.000	1.000	1.000	1.000

R: correlation coefficient; NMSE: normalized mean square error; FB: Fractorial Bias; FV: fractorial variance; FAC2: fraction of predictions within a factor of two

Table 232: Goodness of fit test for different resources from 2018 to 2019.

2018														
Total	PC Doctor Centre	PC Doctor Home	PC Doctor Telephone	PC Nurse Centre	PC Nurse Home	PC Nurse Telephone	Card.	Endo.	Int. Med.	Nep.	Neu.	Psych.	Resp.	ED	Hosp.
R: > 0.8	0.888	0.863	0.885	0.883	0.867	0.878	0.880	0.885	0.885	0.876	0.886	0.884	0.879	0.876	0.869
NMSE: < 0.5	0.028	0.064	0.075	0.053	0.070	0.043	0.006	0.105	0.027	0.011	0.180	0.182	0.012	0.016	0.011
FB: [-0.5, 0.5]	0.137	0.046	0.217	0.180	0.085	0.131	-0.013	-0.276	-0.123	0.004	-0.372	0.235	-0.063	0.084	0.029
FV: [-0.5, 0.5]	0.195	0.356	0.315	0.286	0.353	0.314	0.144	0.257	0.203	0.172	0.326	0.397	0.150	0.203	0.220
FAC2: > 0.8	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	0.917	1.000	1.000	1.000	1.000	1.000
2019														
Total	PC Doctor Centre	PC Doctor Home	PC Doctor Telephone	PC Nurse Centre	PC Nurse Home	PC Nurse Telephone	Card.	Endo.	Int. Med.	Nep.	Neu.	Psych.	Resp.	ED	Hosp.
R: > 0.8	0.888	0.867	0.884	0.882	0.866	0.878	0.882	0.881	0.881	0.881	0.882	0.876	0.880	0.877	0.860
NMSE: < 0.5	0.003	0.066	0.042	0.029	0.083	0.035	0.009	0.091	0.011	0.017	0.219	0.366	0.015	0.005	0.017
FB: [-0.5, 0.5]	0.038	0.062	0.152	0.118	0.126	0.118	-0.064	-0.257	-0.064	0.079	-0.405	0.308	-0.085	-0.005	-0.063
FV: [-0.5, 0.5]	0.088	0.358	0.279	0.250	0.378	0.295	0.136	0.240	0.152	0.169	0.382	0.449	0.144	0.166	0.257
FAC2: > 0.8	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	0.917	1.000	1.000

R: correlation coefficient; NMSE: normalized mean square error; FB: Fractorial Bias; FV: fractorial variance; FAC2: fraction of predictions within a factor of two