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EU PAL-COPD

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Evaluation of the ICLEAR-EU intervention to integrate palliative care in the treatment of people with advanced COPD and their family caregivers: An international stepped wedge cluster RCT in six European countries

Deliverable 4.3

Study Protocol

WP 4 – Development of protocol, ethics, questionnaires & piloting of data collection

Version 1.0

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Contents

Revision history ... 2
Partner short names ... 4
Abbreviations ... 4
Executive summary ... 5
1 Introduction ... 6
1.1 Objectives ... 6
2 Methods ... 7
2.1 Trial design ... 7
2.2 Study setting ... 8
2.3 Eligibility criteria ... 8
2.4 Participant timeline ... 9
2.5 Intervention and control ... 11
2.5.1 Control wedges ... 11
2.5.2 Intervention wedges ... 11
2.6 Measurement ... 14
2.6.1 Demographics ... 14
2.6.2 Primary outcome ... 14
2.6.3 Secondary outcomes ... 14
2.6.4 Health economic evaluation ... 16
2.6.5 Process evaluation ... 16
2.7 Sample size ... 19
2.8 Recruitment ... 19
2.9 Randomization and allocation ... 19
2.9.1 Masking/blinding ... 20
2.10 Data collection procedures ... 20
2.11 Data management ... 20
2.12 Statistical methods ... 21
2.12.1 Primary outcome ... 21
2.12.2 Secondary outcomes and subgroup comparisons ... 21
2.12.3 Health economic evaluation ... 21
2.12.4 Process evaluation ... 21
2.13 Monitoring ... 22
2.13.1 Data and trial monitoring ... 22
2.13.2 Potential harms ... 22
3 Ethical Considerations ... 22
3.1 Research ethics approval ... 22
3.2 Protocol amendments ... 23
3.3 Confidentiality and privacy ... 23
3.4 Access to data ... 23
3.5 Financial and competing interests ... 23
3.6 Ancillary and post-trial care ... 23
3.7 Dissemination ... 24
4 References ... 24

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Abbreviations

Abbreviation	Term
CONSORT	Consolidated Standards of Reporting Trials
RCT	Randomised Controlled Trial
SPIRIT	Standard Protocol Items: Recommendations for Interventional Trials
WP	Work Package

Executive summary

Background

The deliverable D4.3 is part of Work Package 4: Development of protocol, ethics, questionnaires & piloting of data collection. This work package is closely linked to WP5, where the two-year stepped wedge cluster-randomised controlled trial of the EU PAL-COPD project is conducted, by developing the protocol that forms the foundation of the planning and conduct of the study.

Objectives

The objective of the deliverable is to communicate key information regarding the design and conduct of the international stepped wedge cluster-randomised controlled trial. This study protocol presents the general framework of the trial; adaptations at the country level are possible for the purpose of meeting medical/research ethic committee requirements, but the core elements regarding design, eligibility criteria, study flow, outcomes, timing, and analysis as described below apply across all participating countries.

Methodology and implementation

Writing of the protocol was guided by the 2013 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement,[1] also cross-referencing relevant points specifically for stepped wedge designs from the Consolidated Standards of Reporting Trials (CONSORT) extension.[2] It received multiple rounds of feedback from all RCT partners (UGENT, ULANC, RUMC, UCPH, UPECS, UCP, KCL) who are responsible for carrying out the international trial and/or conducting data analysis for the trial. A first full draft was circulated in November of 2024, awaiting updates after pilot testing of the intervention. An updated version was created on April 1st, 2025 to enable RCT partners to prepare their submissions for ethics approval in a timely manner. Following partner feedback and revisions in June 2025, the latest version of the full protocol dates to 13 June 2025.

Outcomes

The outcome of D4.3 presents a description of the core elements of the main study protocol, based on the full study protocol which has been shared with all RCT partners to enable applications to relevant medical and research ethics committees and review boards at the national and/or hospital level. It describes core aspects of the study including its aims and rationale, the study design, the study population and recruitment procedures, outcome measures and their timing, methods for the analyses of outcomes, and ethical aspects of the study.

Impact

The main study protocol is a keystone in the project; guidance for conducting randomised trials emphasizes the importance of a comprehensive and robustly-designed protocol created a priori. The study protocol provides guidance for the procedures of the study which all scientific partners can refer to throughout the trial period, enables oversight by medical and research ethics committees, and specifies the aims of the study for which the collected data will be analysed.

Next steps

During the preparation and execution of the trial, the study protocol will be the main reference for conduct of the study procedures regarding design, timing, outcomes, and statistical methods. The full length study protocol will be updated following the updated SPIRIT statement which was published in January of 2025,[3] yielding a fully-detailed and comprehensive protocol for publication in a scientific journal. By publishing the protocol as an open-access scientific article, peer researchers, policy makers, clinicians and the public will be able to view a record of the study, to assess that the trial is conducted and analysed as prespecified. If amendments are proposed during the trial, the protocol will be

updated accordingly and submissions to medical/research ethics committees will be completed. A version history of the protocol will be kept.

1 Introduction

People with chronic obstructive pulmonary disease (COPD) experience significant symptom burden, leading to declining functional status and frequent hospitalizations in the advanced stages of the disease.[4] This population often experiences unmet needs, including physical, emotional, social, and existential care needs.[5] Exacerbations and hospitalisations for COPD are a risk factor for subsequent readmission;[6] data collected from COPD admissions in 13 European countries shows that 35% of patients discharged for an exacerbation were readmitted within 90 days.[7] This leaves patients vulnerable to rapid health deterioration after the first exacerbation and admission to hospital. Palliative care can improve the quality of life for patients with COPD by addressing needs across physical, psychological, social, or spiritual domains.[8] However, people with COPD are an underserved population in this regard: although the palliative care needs of people with COPD could be as high as those of people with (lung) cancer, referral and access to (specialist) palliative care are limited in comparison.[9–11]

A proactive approach to palliative care is needed, which integrates palliative care into routine care for COPD.[12] Integrated palliative care actively involves the patient, family, and multidisciplinary clinical teams who are trained in the palliative care approach, ensuring continuity between all services involved.[13] Early integration of palliative care is essential to reducing potentially preventable readmissions for patients with COPD.[14]

The EU PAL-COPD project aims to achieve better quality of life and improved well-being for people with advanced COPD, by integrating palliative care into respiratory care via an innovative, non-pharmacological service-based intervention called ICLEAR-EU. The ICLEAR-EU intervention focuses on early identification of palliative care needs, multidisciplinary care integration including palliative, respiratory, and primary/community care, shared decision-making and advance care planning, and ongoing review of patient needs. The intervention is based on a model introduced in the United Kingdom (UK), where this multidisciplinary approach resulted in a reduction in hospital deaths.[15]

From the UK-based intervention, the consortium adapted the intervention through consultation meetings with clinicians and patients/patient representatives in six countries (Belgium, the Netherlands, the United Kingdom, Denmark, Hungary, and Portugal), then pilot-tested the intervention internationally.

The present protocol concerns the large-scale international trial of the adapted and pilot-tested ICLEAR-EU intervention. In this study, patients with advanced COPD who are admitted to the hospital for more than 48 hours due to an acute exacerbation of their COPD, are invited to participate and will be followed up for 90 days.

1.1 Objectives

We aim to compare the ICLEAR-EU intervention to current usual care (treatment as usual) with regard to its:

1. Effectiveness in healthcare systems, as indicated by:
   Primary Outcome Measure
   a. The percentage of patients who have respiratory-related hospital readmissions within 90 days from baseline (or until death if before 90 days from baseline)

Secondary Outcome Measures

b. **Patient outcomes**: illness perception, quality of life, mental wellbeing, existential wellbeing, presence of advance decisions to refuse treatment and documentation of advance care planning, preferred place of death
c. **Caregiver outcomes**: quality of life, mental wellbeing, existential wellbeing, family carer burden, bereaved caregiver views of quality of care and death,
d. **Healthcare utilisation outcomes**: Place of death, concordance between preferred and actual place of death, all-cause mortality, number of readmissions, length of hospital stays on readmission, referrals to specialist palliative care, ICU and emergency department admissions
e. **Cost-effectiveness:** Cost per quality-adjusted life year (QALY)
f. **Process and implementation evaluation:** We also aim to evaluate the **implementation processes** of the intervention: feasibility of integration into standard care, barriers and facilitators to implementation, and mechanisms involved in achieving outcomes in each participating country.

2. Effects on **subgroups**, including subgroups defined by characteristics known to affect health equity and equitable access:
    a. Comparison of outcomes **across participating countries**
    b. Effects on **subgroups** according to age, gender, socioeconomic status, cohabitation status, and hospital characteristics (e.g. urban vs. rural)

2 Methods

2.1 Trial design

We have chosen a stepped wedge cluster-randomized controlled trial design[16] for this study, which is a pragmatic design that allows every participating hospital the opportunity to receive the intervention.

The stepped wedge cluster-randomized controlled trial will proceed in a similar fashion across the six countries (Belgium, the Netherlands, the United Kingdom, Denmark, Hungary, and Portugal). Clustering is at the level of hospital sites. Each country will include three hospitals. A schematic representation of the trial design is shown in Figure 1.

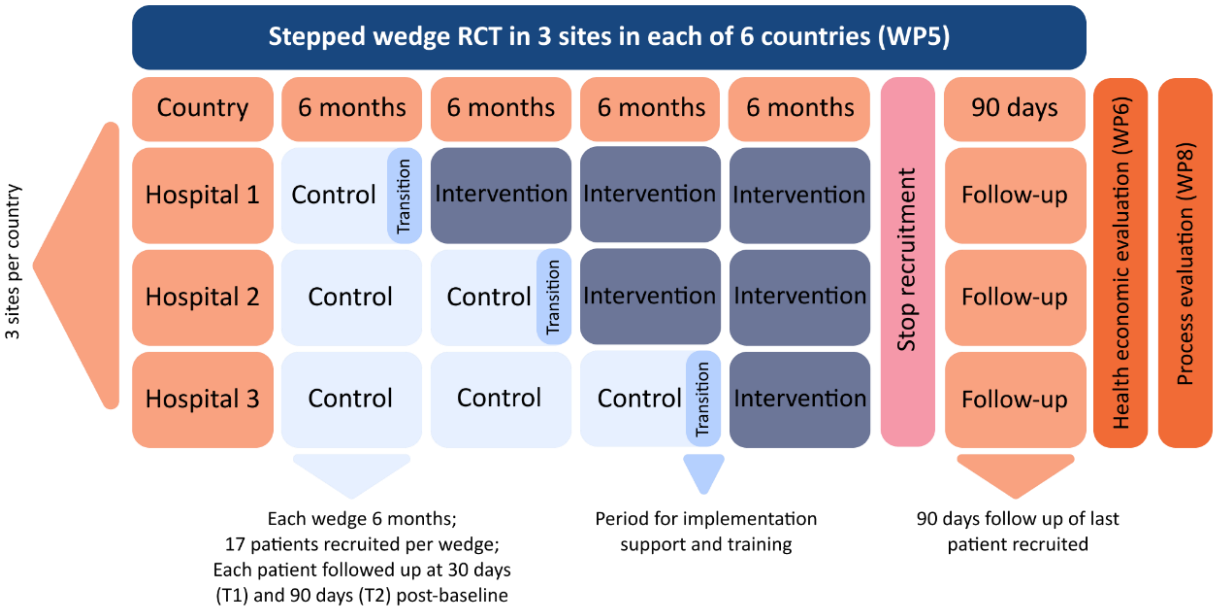

Figure 1. Stepped wedge design of the trial

Each hospital will go through four wedges, each wedge with a duration of six months, for a total of 24 months. Each hospital starts in control condition and crosses over to the intervention condition at 6, 12 or 18 months. The timing of cross-over will be randomly assigned at study onset. Before a hospital crosses over from the control condition to the intervention condition, a 30-day transition period will be integrated into the last control wedge, during which clinicians will receive the intervention training and implementation support will be provided.

2.2 Study setting

The intervention will be implemented in the hospital setting and will also involve community/primary care.

2.3 Eligibility criteria

Hospitals: Hospitals that typically admit 100–500 patients annually for COPD-related causes and indicate a willingness to implement ICLEAR-EU meetings will be included in the study. Hospital sites have in-patient respiratory beds.

Patients and family caregivers: Patients with advanced COPD living at home, who are admitted to the hospital for more than 48 hours because of an acute exacerbation of COPD and who will potentially benefit from an integrated palliative care approach, are eligible for participation. For data collection purposes, patients who are enrolled during a control wedge will not be re-enrolled for data collection in the intervention wedge.

Patients may also indicate a family caregiver for participation. We consider the family caregiver to be "any relative, friend, or partner who has a significant relationship and provides assistance (physical, social, and/or psychological)"[17] to the patient. Not including a family caregiver does not exclude the patient from eligibility.

Inclusion and exclusion criteria for patients and family caregivers are described in Table 1.

Table 1. Patient and family caregiver inclusion and exclusion criteria

Patient	Family Caregiver
Inclusion criteria	
• Have a diagnosis of advanced COPD* • Admission to the respiratory ward of the hospital that lasts ≥ 48 hours (or likely to be admitted for ≥ 48 hours) for an acute exacerbation • Live at home	• Identified by the patient as the person who gives him or her the most help and support at home on a regular basis • Age 18 years or over
Exclusion criteria	
• Currently receiving care from a formally recognised specialised palliative care team • Cognitive impairment preventing informed consent as judged by treating respiratory physician and by the researchers. In case of doubts, the researcher will consult the corresponding treating respiratory physician. • Not able to speak or understand the language in which measurements are conducted, these being: ○ English ○ Dutch ○ Danish ○ Portuguese ○ Hungarian • Patients can be included in the study only once and cannot be re-enrolled during the overall duration study, even if at a different wedge.	• Cognitive impairment preventing informed consent as judged by treating respiratory physician and by the researchers. In case of doubts, the researcher will consult the corresponding treating respiratory physician. • Not able to speak or understand the language in which measurements are conducted

***Advanced COPD**

1. Spirometry (FEV1):
   a. Severe COPD: 30% ≤ FEV1 < 50% predicted **OR**
   b. Very severe COPD: FEV1 < 30% predicted

OR

2. High symptom burden:
   a. Modified Medical Research Council (mMRC) > 2 **OR**
   b. COPD Assessment Test (CAT) > 20

OR

3. High-risk exacerbation history:
   a. ≥ 1 exacerbation leading to previous hospitalisation in the past year **OR**
   b. ≥ 1 exacerbation leading to previous ICU admission in the past year

2.4 Participant timeline

The timeline for each patient (and family caregiver, if included) participant is shown in Figure 2. Participants fitting the eligibility criteria will be in the intervention or control condition, based on whether the hospital site is in a control or intervention wedge at the moment of the participant's informed consent and baseline assessment.

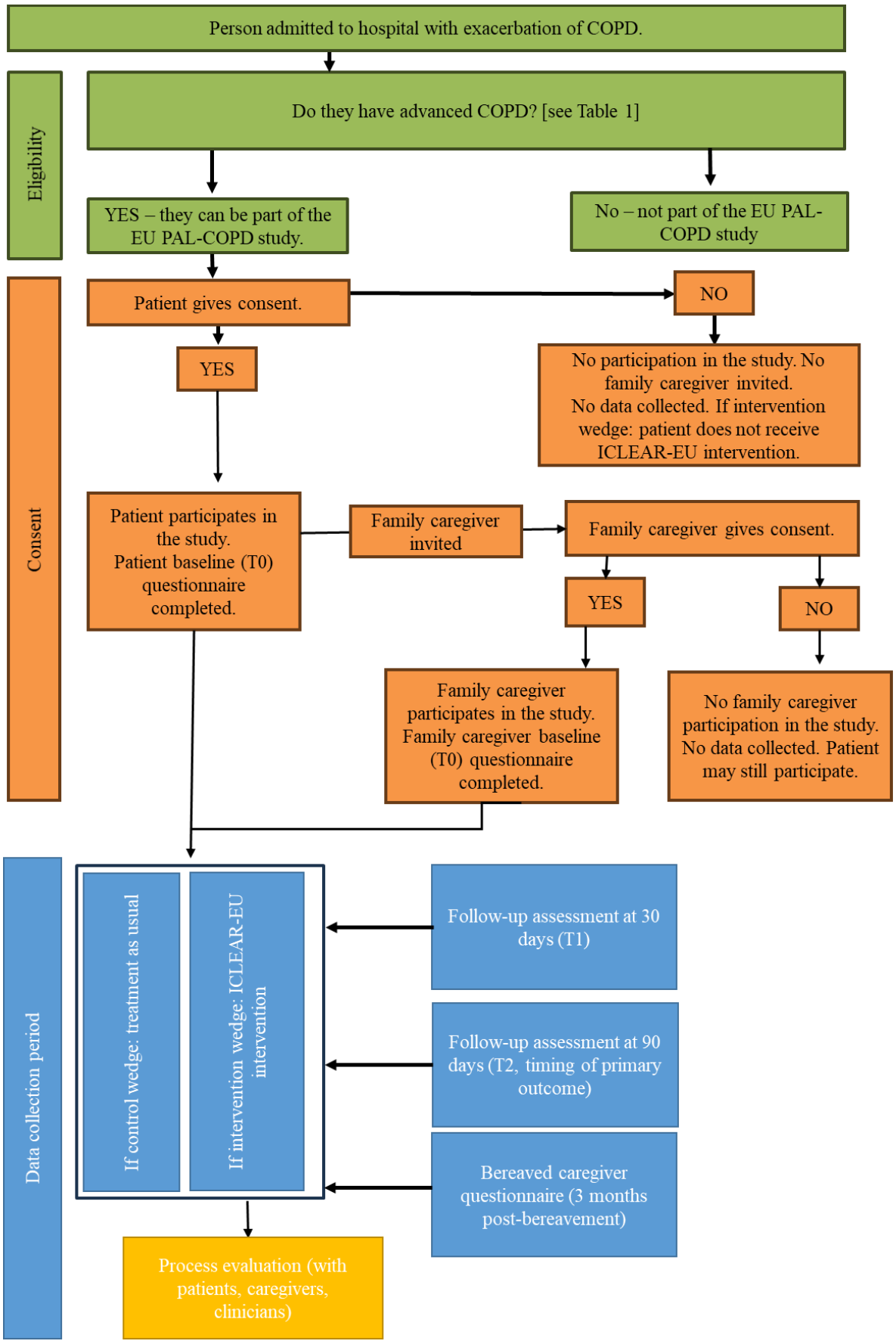

Figure 2. Participant timeline

2.5 Intervention and control

2.5.1 Control wedges

All sites start as control sites for 6 months. After the first 6 months, hospitals will cross over to the intervention at 6-monthly intervals (see Figure 1). During control wedges, sites will provide patients with treatment as usual according to the routine practice of each hospital, and in accordance with the practice of the healthcare system in each country.

2.5.2 Intervention wedges

During intervention wedges, the hospital sites will provide the ICLEAR-EU intervention. The developed Intervention Manual (Version 5, Post Pilot Clinical Manual; see Deliverable D2.6) contains the full intervention description, which will be provided for the clinicians delivering the intervention at the hospital sites.

The intervention consists of five core components supported by two implementation strategies, shown in Figure 3.

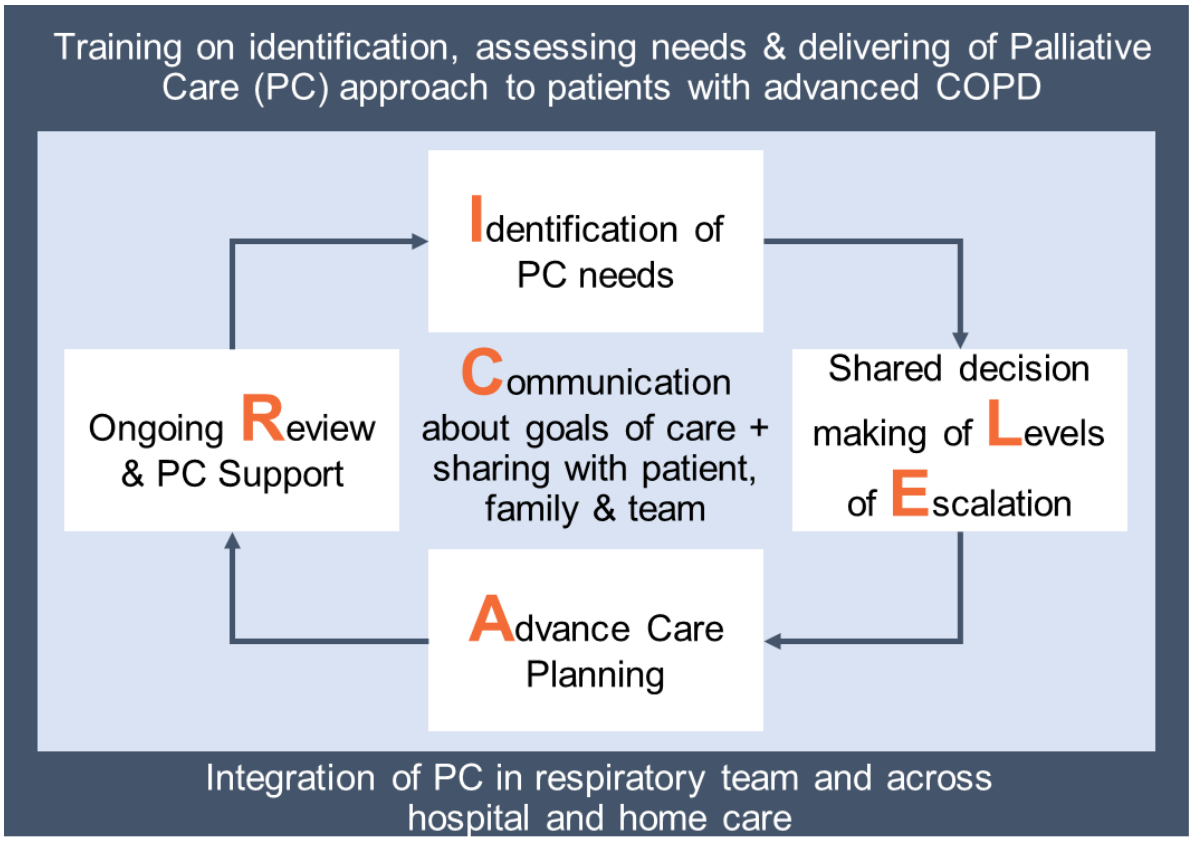

Figure 3. Overview of the ICLEAR-EU intervention

The five core components are:

1. **Identification** of unmet palliative care needs using assessment tools
2. **Communication** about goals of care and sharing with patient, family, and care team.
3. Shared decision-making regarding **Levels of Escalation**, contributing to a patient management plan for future care
4. Initiating **advance care planning** conversations with the patient and family (if present)
5. Ongoing **Review** and management of palliative care needs during follow-up visits with healthcare professionals, and revision of the patient management plan if or when necessary.

The implementation strategies consist of **training** for clinicians delivering the intervention, and overall **integration of palliative care** by improving inter- and multidisciplinary communication via shared reporting and outreach from hospital to community care. To achieve this, a weekly multidisciplinary ICLEAR-EU meeting will be implemented where the patients will be presented to discuss goals of care, levels of escalation and potential treatment plans. A form will be used to summarize the use of the intervention for each participant (the ICLEAR-EU form). The intervention is provided at the service level in each hospital. When hospitals are in the intervention wedge, they will apply the patient flow and deliver core components to patients with advanced COPD who are admitted for an exacerbation, as shown in Figure 4.

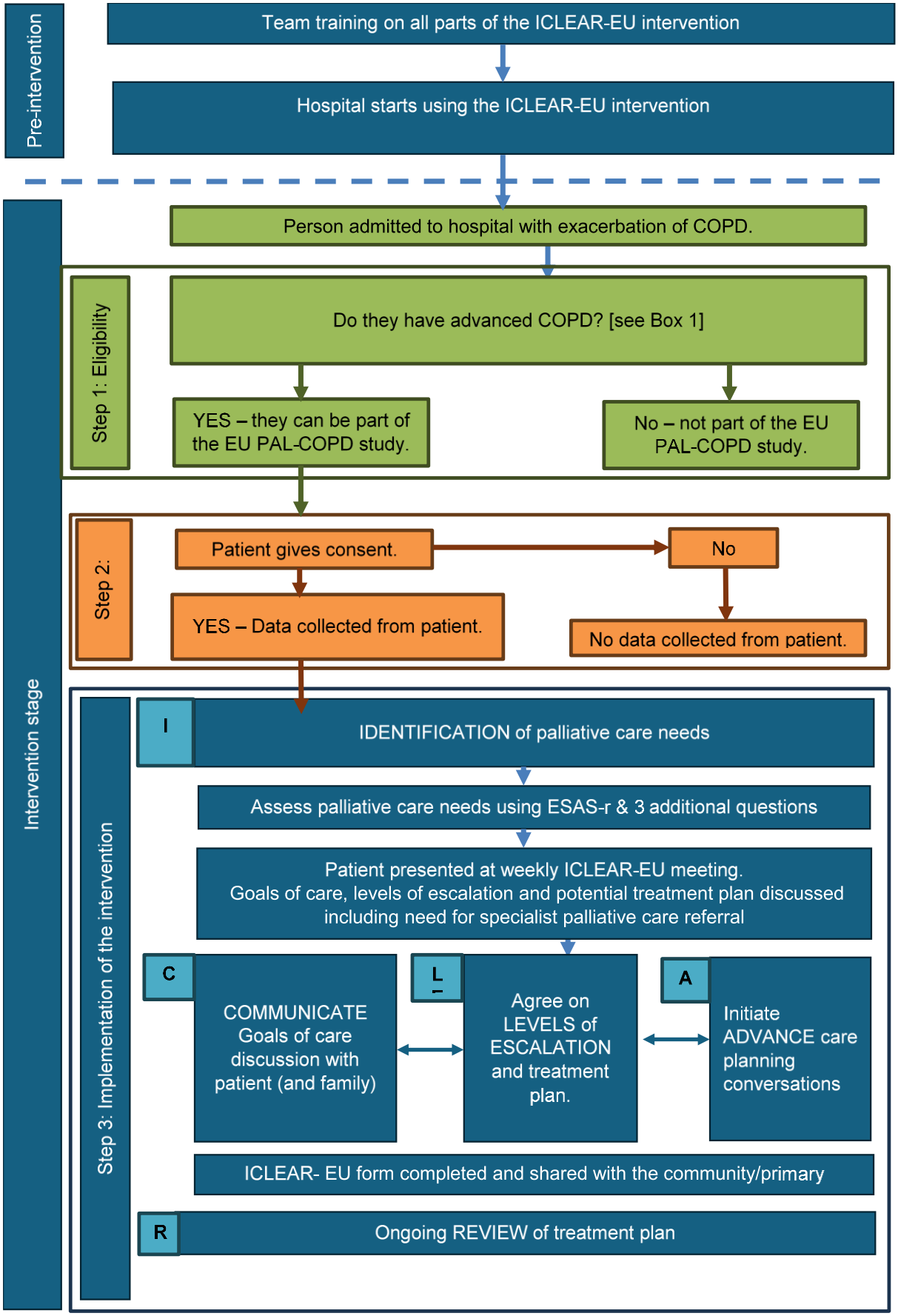

Figure 4. Diagram of pre-intervention steps and intervention procedures for hospitals in intervention condition

2.6 Measurement

2.6.1 Demographics

We will collect participant demographic data at baseline (T0), after completion of informed consent. Demographic characteristics collected can be found in Table 2 below.

2.6.2 Primary outcome

The primary outcome is the percentage of patients who have a respiratory-related readmission to the hospital within 90 days of baseline (or until death if within these 90 days). This is in line with outcomes reported in other studies across Europe, which will allow for comparison.[7] We hypothesize that fewer people in the intervention phase will require hospital readmission.

2.6.3 Secondary outcomes

Secondary outcomes measured during the study are shown in Table 2 below, along with the timing for data collection.

Table 2. Constructs measured in the study, corresponding instruments, scheduling

Construct	**Data collection measure**	**Completed by**	**Timing**		
			T0 (Baseline)	**T1 (30 days post-baseline)**	**T2 (90 days post-baseline)**
Patient outcomes					
Demographics	– Age – Sex – Marital status – Children – Cohabitation status – Hours of transit to hospital where recent hospitalization occurred – Highest level of education completed – Employment status – Comfort of living on household income – Financial difficulties due to physical condition or treatment – Country of birth + parent country of birth (if different from respondent birth country)	Patient	x		
Perception of illness	Brief Illness Perception Questionnaire[18]	Patient	x	x	x

Quality of life	SF-CRQ[19] EQ-5D-5L[20] ICECAP-SCM[21]	Patient	x	x	x
Mental wellbeing	PHQ-4[22]	Patient	x	x	x
Existential wellbeing	MQOL-R existential subscale[23]	Patient	x	x	x
Preferred place of death + whether this has been discussed with health care professionals	Questionnaire item	Patient	x	x	x
Presence of advance decisions to refuse treatment (ADRTs) and advance care plans (ACPs)	ICLEAR-EU form and medical notes	Physician/ researcher			x
[Bereaved] caregiver outcomes					
Demographics	– Age – Sex – Marital status – Children – Cohabitation status – Relationship to the person with COPD – Living with the person with COPD – Distance from home of person with COPD (hours) – Highest level of education completed – Employment status – Comfort of living on household income – Financial difficulties due to physical condition or treatment of family member with COPD – Country of birth + parent country of birth (if different from respondent birth country)	Caregiver	X		

Quality of Life	EQ-5D-5L[20]	Caregiver	x	x	x
Mental wellbeing	PHQ-4[22]	Caregiver	x	x	x
Existential wellbeing	MQOL-R existential subscale[23]	Caregiver	x	x	x
Family carer burden	ZBI-12[24]	Caregiver	x	x	x
Bereaved caregiver views of quality of care and death	VOICES-SF[25]	Bereaved caregiver	3 months post-bereavement		
Healthcare utilisation of enrolled patients					
Place of death	Medical notes or phone GP	Researcher	As appropriate		
Concordance between preferred place of death and actual place of death	Questionnaire item Medical notes or phone GP	Researcher	As appropriate		
All-cause mortality	Medical notes	Physician/ researcher	As appropriate		
Number of readmissions to hospital	Medical notes	Physician/ researcher			x
Median length of hospital stays on readmission	Medical notes	Physician/ researcher			x
Number of referrals to specialist palliative care	ICLEAR-EU form and medical notes	Physician/ researcher			x
Intensive Care Unit (ICU) admissions	Medical notes	Physician/ researcher			x
Emergency Department admissions	Medical notes	Physician/ researcher			x

2.6.4 Health economic evaluation

We will use hospital data to quantify length and intensity of inpatient hospital stays. We will collect additional formal healthcare utilisation and unpaid family care using an adapted Client Service Receipt Inventory (CSRI), and estimate costs by combining reported frequencies with nation-specific unit costs. We will collect health-related quality of life using EuroQoL EQ-5D-5L, converting responses to quality-adjusted life years (QALYs) using nation-specific population preference weights and mortality data from the main trial.

2.6.5 Process evaluation

During this trial, we will conduct an embedded process evaluation in all sites. The full protocol for the Process and Implementation Evaluation can be found in the Project Deliverable D8.1.

To better understand current practices in the hospitals involved in the trial, which provide the context in which the trial is conducted and the intervention implemented, we will administer a questionnaire about current care practices at the end of each wedge, to be completed by the ICLEAR-EU coordinator or clinical champion.

Additionally, to assess current practices as they relate specifically to the ICLEAR-EU intervention model, we will also conduct a one-time interview in each hospital with the ICLEAR-EU coordinator or clinical champion. The interview will be conducted during the transition phase, prior to the intervention training.

2.6.5.1 PRISM/RE-AIM

We will use the PRISM/RE-AIM framework to evaluate the Reach, Effectiveness, Adoption, Implementation, and Maintenance domains of the intervention alongside key contextual factors. These will be qualitatively and quantitatively assessed as shown in Table 3.

Table 3. RE-AIM outcomes and measures

	Outcome	**Measure**	**Timing of measurement**	**Completed by**
Reach	Training attendance	Training attendance list: – Attendance numbers – Professions represented	After each ICLEAR-EU training	Coordinator/ data collector
	ICLEAR-EU Meeting attendance	ICLEAR-EU meeting attendance list: – Attendance numbers – Professions represented	After each ICLEAR-EU meeting	Coordinator/ data collector
	Total number of patients included vs.not included in study	– Admitted for acute exacerbation – Screened for study – Included in study	After every wedge	Coordinator/ data collector
Effectiveness	Effectiveness of training	Self-Efficacy regarding end-of-life communication (S-EOLC)[26] Palliative and end-of-life care-specific education needs (End-of-life Professional Caregiver Survey (EPCS))[27]	Pre: 1-4 weeks before training Post: 1-4 weeks after start first intervention wedge	ICLEAR-EU team members
	Experiences with ICLEAR-EU	Interview with patients, (bereaved) relatives, and clinicians	Patients: Approx. 4 weeks after hospital discharge Bereaved relatives: 3 months after bereavement	Local research team

			Clinicians: During follow-up period after last wedge	
Adoption	ICLEAR-EU meeting	Addendum ICLEAR-EU meeting form -How often? -Duration? -How many patients discussed? -How many patients not discussed? Why not?	After each ICLEAR-EU meeting	Coordinator
Implementation	Adherence	-Number of inclusions (calculated from inclusion log) -Fidelity checklist	After every wedge	Coordinator
	Ease of use	Interval scale	After every wedge	ICLEAR-EU team members
	Satisfaction with ICLEAR-EU training/trainer	Evaluation questionnaire	Immediately after training	ICLEAR-EU team members
	Satisfaction with the ICLEAR-EU intervention	Interval scale	After every wedge	ICLEAR-EU team members
	Fidelity	Core components ICLEAR-EU per patient: check based on ICLEAR-EU form or medical record	After every wedge	ICLEAR-EU coordinator for every patient
	Barriers and facilitators to implementation	Short questionnaire with text box Regular check-in with local research team by phone	After every intervention wedge	Local research team and coordinator
Maintenance	Intention for using ICLEAR-EU in the future	Interval scale	After last wedge	ICLEAR-EU team members, e.g. clinical champion and coordinator
	Organizational intention for long-	Interval scale	After last wedge	ICLEAR-EU team members, e.g.

	term implementation			clinical champion and coordinator
	Experiences with and recommendations for improving usability of intervention program	Interview with two clinicians from the ICLEAR-EU team	After last wedge	ICLEAR-EU team members, e.g. clinical champion and coordinator

2.7 Sample size

The sample size calculation is based on the approach described by Hussey and Hughes.[28] We specify a minimum clinically important difference of 15 percent in the number of patients readmitted to hospital within 90 days after baseline. Based on existing literature[6] and expertise of the research team, we estimate a proportion of 35% readmissions at baseline. We use a conservative estimate of the intracluster correlation coefficient (ICC) of 0.05 and apply a correction for 30% drop-out, such as due to withdrawn consent.

Sample size calculations based on these assumptions yield 18 hospitals to be included and randomized across six countries, with three hospitals per country and an average of 17 patients recruited per wedge (68 patients total per hospital, 204 per country, 1224 patients in total). This gives at least 90% power to detect a difference of 15 percent at $\alpha = 0.05$.

2.8 Recruitment

In each country, three eligible hospitals are being recruited, with clinical teams engaged to participate in the study and carry out the intervention. Informed consent will be sought from clinicians for the data collection as part of the process evaluation.

Patients admitted to hospital with an exacerbation of COPD will be flagged by hospital staff. Eligible patients will be approached concerning study participation by a member of the respiratory team. With the patient's agreement, the patient's contact details are provided to the local researcher, who will invite eligible patients for informed consent to participate in the study.

Family caregivers will be identified through eligible patients. Permission will be sought from the patient to approach this person for participation. Patients may still participate even if they do not identify a family caregiver or if the family caregiver does not wish to participate.

Informed consent will be obtained from patients and caregivers after providing information about the purpose of the study and data collection, using the Information Sheet.

2.9 Randomization and allocation

Hospitals will be randomized as to when they cross over from the control condition to the intervention, centrally by UGENT. The full list of 3 hospitals for each country will be randomized at study onset. At 4, 10, and 16 months, the next hospital in the list (Hospital 1, Hospital 2, or Hospital 3) to cross over is unblinded.

2.9.1 Masking/blinding

Hospitals are randomized according to their number (1, 2, or 3) only. However, participants and researchers cannot be fully blinded, as the intervention differs from treatment as usual and there is a training period for clinicians preceding the implementation.

2.10 Data collection procedures

The **primary outcome** (percentage of participating patients readmitted to hospital within 90 days of baseline, or until death if within these 90 days) will be collected via routinely-collected data regarding hospitalization in the patient (electronic) medical record. A data retrieval form will be used to collect data from the patient health record.

Patients and family caregivers enrolled in the study will be asked to complete questionnaires for **secondary outcomes** at baseline (T0, immediately following informed consent), and at 30 and 90 days post-baseline. If a patient dies during the trial, caregivers who consented will be contacted 3 months post-bereavement to complete the VOICES-SF questionnaire. Additional data regarding healthcare utilisation of enrolled patients will be collected through medical notes, consulting the patient's ICLEAR-EU form, and consulting with the general practitioner (GP) or other home/community care when possible and appropriate.

Data for the **cost-effectiveness evaluation** includes the CSRI and EuroQol (EQ-5D-5L) at 30 and 90 days, alongside other trial data collection through the participant interview. Unit costs will be identified first by literature search and, where necessary, by calculation by the research team. The economic evaluation will also utilize the hospital data to model intensity of hospital stay for a given patient profile.

For the **process evaluation**, both quantitative and qualitative data addressing the PRISM/RE-AIM domains will be collected throughout the study (see Table 3 for timing). Quantitative data will be collected using structured checklists, questionnaires, monitoring recruitment numbers, and short surveys; these will be conducted at set time points at the trial timeline and intervention timeline level, including pre-and post-training, after ICLEAR-EU meetings, and at the end of a wedge. Data will be collected via ICLEAR-EU team members attending the trainings and ICLEAR-EU meetings, and from the coordinator and/or clinical champion.

Semi-structured interviews for qualitative data collection will be conducted as follows:

- Per hospital: During the intervention phase, two patients will be selected by convenience sampling from the participants, to be interviewed approximately 4 weeks after discharge from hospital about their experiences with received care; although an individual interview is recommended, the patient can also opt for an interview with his/her relative present.
- Per hospital: During the intervention phase, 2 bereaved family caregivers will be selected by convenience sampling from the participants and invited to share their experiences with the care received, three months after bereavement .
- Per hospital: two clinicians (clinical coordinator and/or champion) will be interviewed about their experiences with the intervention and suggestions for maintenance after the last intervention wedge

2.11 Data management

Data collected during the project will be entered into REDCap, an internationally recognized system for data management and recording for clinical trials.[29,30] The Vrije Universiteit Brussel takes overall responsibility for data management throughout the project. A data management plan has been created and will be kept up to date throughout the course of the project, and a joint controller agreement will be in place to allow for transfer of data for analysis within the consortium.

The consortium additionally certifies that all research activities will adhere most strictly to all applicable legal, ethical and safety provisions of the individual states and of the EU. Participants will conform to relevant EU legislation including (1) The Charter of Fundamental Rights of the EU, December 2009 and (2) EU Regulation 2016/679 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (GDPR).

2.12 Statistical methods

A statistical analysis plan (SAP) will be developed to prespecify and guide analyses in this trial (Work Package 7 D7.1). All analyses will follow intention-to-treat (ITT). Participants will be assessed according to whether they entered the study during a control wedge or an intervention wedge.

2.12.1 Primary outcome

To determine the effectiveness of the ICLEAR-EU intervention, we will compare the primary outcome between control and intervention participants using a logistic mixed model approach. The model will include a random effect for the cluster, and fixed effects for the condition (control or intervention), country, and time. A fixed effect interaction between condition and time will capture whether effects change over time. A fixed-effect interaction term between country and time will be added to allow for varying secular trends between countries.[31] Gender will be added as a covariate in the analysis, as it has been shown to relate to outcomes in COPD.

2.12.2 Secondary outcomes and subgroup comparisons

Secondary outcomes will be analysed using modelling strategies similar to the primary outcome. Outcomes on a continuous scale will be analysed using linear mixed models, and binary outcomes will be analysed using logistic mixed models. For secondary outcomes which use repeated measurements (T0, T1, and T2), we will include a random effect to account for clustering of measurements within patients.

We will conduct pre-specified subgroup and cross-country comparisons of intervention effectiveness per subgroup analysed. A fixed effect interaction between condition and country will capture differences in effect sizes between country.

Missing values will be replaced according to a chained equations multiple imputations method.

2.12.3 Health economic evaluation

Prior to conducting primary analysis of cost-effectiveness, we will examine: (i) baseline differences on characteristics associated with outcome and where necessary control for baseline variables in analysis; and (ii) skewness, kurtosis and heteroscedasticity in the cost data and fit an appropriate (most likely, nonlinear) model. We will account for correlated costs and effects using seemingly unrelated regressions, bootstrapping each set of regressions with 1000 replications, and combining these bootstrapped results in estimating cost-effectiveness acceptability curves. Recognising the uncertainty associated specifically with our trial design, we will employ a stratified two-stage nonparametric bootstrap resampling procedure for clustered data. We will model both costs and outcomes using multi-level models to cluster by country. We will express results in incremental cost-effectiveness ratios (cost per QALY), and cost-effectiveness acceptability curves (probability of cost-effectiveness for different willingness-to-pay thresholds).

2.12.4 Process evaluation

Quantitative data (e.g. attendance lists, answers to the S-EOLC and EPCS questionnaires, numbers of included patients, the ICLEAR-EU form and input on short surveys (interval scales on ease of use, satisfaction, etc.) will be analysed descriptively and using inferential statistics ((e.g., mixed methods models due to clustering) depending on the type of data and the analysis rationale. Analyses of qualitative data from the process evaluation will be coordinated by RUMC. Open coding of the qualitative data will be done locally in each country in the English language. A common codebook will

be developed by the RUMC and can be appended by the other research partners. Grouping codes into categories and themes will be done in English, in an international (online) research meeting led by RUMC. All other partners will be involved in the interpretation of findings.

2.13 Monitoring

2.13.1 Data and trial monitoring

The trial monitoring structure consists of monitors at the country and project level. In each country, a trial manager or PI will oversee the conduct of the trial, using a trial management and monitoring plan provided by the coordinators at Vrije Universiteit Brussel. In each country, an independent trial monitor (not involved in other EU PAL-COPD trial activities) should conduct a six-monthly check that the trial is properly documented and conducted. The report of this monitoring will be collected by VUB and will contribute to reports made to the Trial Steering Committee and Data and Safety Monitoring Board.

The Trial Steering Committee (TSC) has been established for trial oversight, monitoring trial progress against the proposed timeline, and adherence to protocol. The TSC is composed of project team members and independent members.

Additionally, the Data and Safety Monitoring Board (DSMB) has been established to safeguard the interest of participants, including privacy and data security. No formal interim analyses are planned.

2.13.2 Potential harms

Based on experiences with previous studies with similar interventions in the UK[15], the Netherlands[32] and Belgium[33], we do not anticipate serious adverse events related to the intervention or the trial procedures.

Adverse events will be addressed via a standard operating procedure (SOP) provided to all sites. Adverse events, if they occur, will be recorded in REDCap and should be reported to the country PI, the national/local ethics committee, and in the case of serious adverse events, to the coordinator. Serious adverse events will be expedited for reporting to the Data and Safety Monitoring Board (DSMB) and TSC. Non-serious adverse events will be included in six-monthly reports to the DSMB and TSC.

3 Ethical Considerations

All partners involved in the EU PAL-COPD consortium, and more specifically the partners in the six countries conducting this study, will comply with all the relevant European and National legislation and recommendations from appropriate authorities.

This study will also be conducted in full compliance with fundamental ethical principles, including those reflected in the Charter of Fundamental Rights of the European Union, the European Convention on Human Rights and its Supplementary Protocols, and the Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects.[34–36] Ethical principles and values in research, including the highest standards of research integrity as set out, for instance, in the European Code of Conduct for Research Integrity[37] will also be followed.

All partners will adhere as well to the legal and regulatory context concerning research involving human participants within their own country.

3.1 Research ethics approval

The full trial protocol will be used in each country for submission to national or local medical/research ethics committees, according to the requirements in each country. Each partner involved in conducting the trial will obtain ethics approval prior to trial start.

3.2 Protocol amendments

Any substantial modifications which may impact the conduct of the study or patient safety (e.g. changes in study objectives, inclusion criteria, sample size, trial procedures) in one country or across the project consortium will be agreed upon by the EU PAL-COPD consortium prior to submission as amendments to the relevant ethics committees.

Minor changes, which are not expected to impact the conduct of the study or patient safety, such as grammatical changes to the protocol or informed consent forms, are not regarded as substantial modifications and thus not cause for amendment.

3.3 Confidentiality and privacy

Project partners will take all necessary steps to guarantee compliance with the provisions of the EU Regulation 2016/679 on the protection of natural persons with regard to the processing of personal data, and on the free movement of such data (GDPR). A Data Protection Impact Assessment will be performed with the data protection officer (DPO) of the VUB. Additional Data Protection Impact Assessment might be required with the DPOs of the trial partners and/or hospitals participating in the trial. This will be monitored by the VUB and adjusted according to national and/or local requirements.

All data from participants will be handled in coded fashion and pseudonymised prior to analysis. No identifiable data will be transferred between partners.

3.4 Access to data

All members of the research team accessing the REDcap database will have their own login details. REDCap is accessed via a secure communication protocol (https – using a 256-bit encryption) to ensure data security in transit. The VUB is responsible for designating which persons have access to the data. Access to data will be granted to third parties upon reasonable request and upon signing of the necessary data sharing agreements (see Data Management Plan D1.3).

3.5 Financial and competing interests

The EU PAL-COPD trial investigators declare no competing interests.

EU PAL-COPD is funded by the European Union. Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or the European Health and Digital Executive Agency (HaDEA). Neither the European Union nor the granting authority can be held responsible for them [grant number 101136621]. This project is also supported by the UK Research and Innovation (UKRI) [grant numbers 10109731 and 10109782], the Ministry of Culture and Innovation of Hungary from the National Research, Development and Innovation Fund [grant number 2020-2.1.1-ED-2023-00260], and the Swiss State Secretariat for Education, Research and Innovation (SERI).

None of the funders have had a role in the design of this study and will not have any role during its execution, analyses, interpretation of the data and information, or decision to submit and disseminate its results.

3.6 Ancillary and post-trial care

Patients and caregivers in the trial are referred to existing hospital-based or community-based resources for ancillary and post-trial care, including continued integration of the ICLEAR-EU intervention in these settings as deemed appropriate.

3.7 Dissemination

Trial results will be disseminated through peer-reviewed publications in international academic journals, to which free access will be guaranteed either by paying (gold open access) or by placing the publication in an accessible repository (green open access).

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