UNIVERSITÄT BERN

Statistical Analysis Plan (SAP)

Transition cAre inteRvention tarGeted to high-risk patiEnts To Reduce rEADmission: A randomized controlled trial

TARGET-READ phase 2

Administrative Information

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Contents

1 Introduction

1.1 Background and rationale

This statistical analysis plan (SAP) serves to describe the methods and time points of the statistical analysis performed for the randomized controlled trial TARGET-READ phase 2 (transition care intervention targeted to high-risk patients to reduce readmission).

1.2 Objectives

The primary objective is to evaluate the effect of a transitional care intervention ("TARGET" intervention) prioritized to higher-risk medical patients on the composite of 30-day unplanned readmissions and death.

Secondary objectives are to evaluate:

- the effect of a targeted transitional care intervention to higher-risk medical patients on hospital utilization, medication adherence, patient's perspective on quality of transition of care and time to readmission or death (whatever comes first),
- the effect of a targeted transitional care intervention on the primary outcome in subgroup population of patients with intermediate (simplified HOSPITAL score of 4 or 5) compared to high risk of readmission (simplified HOSPITAL score ≥6), who suffer from common chronic diseases (diabetes, chronic heart failure, COPD or cancer), and according to living place, living status and health insurance,
- the cost-effectiveness of the transitional care intervention.

2 Study methods

2.1 Trial design

The study is a national multicenter single-blinded randomized controlled trial.

2.2 Randomization

Allocation of patients is done when all inclusion and exclusion criteria are satisfied. Patients are randomly assigned in a ratio of 1:1 to one of two treatment arms:

1) Transitional care (intervention) or

2) Usual care (control).

Allocation of patients is done with the data management system (REDCap™) that also hosts the electronic case report forms (eCRFs). Allocation is stratified by:

- Discharge site (Hôpital Fribourgeois, Centre hospitalier Bienne, CHUV Lausanne, Hôpital neuchâtelois)
- Readmission risk category according to the simplified HOSPITAL score (intermediate vs high risk, i.e. a HOSPITAL score of 4 or 5 vs ≥6)

The readmission risk category is documented on eCRF “Eligibility” by variable `strat_1`, the discharge site is coded via the patient ID. The random allocation is performed centrally within the data management system using permuted block with random block sizes of 2, 4 and 6. Investigators receive the allocation only after the eCRF “Eligibility” has been completed. The allocation is documented by variable `alloca_group` on eCRF “Eligibility”.

2.3 Sample size

Because we will target patients at higher risk of readmission, we hypothesize that the intervention could reduce the relative risk of readmission by 25%, i.e. more than the 18% reduction found in a recent meta-analysis where patients were mostly not at high risk for readmission. Based on previous findings, the expected 30-day readmission and death rate for patients at intermediate or high risk according to the simplified HOSPITAL score is around 27%. Allowing for 10% loss to follow-up, we determine that we will need 1,380 patients for the study to have 80% power, i.e. 690 in each arm.

The intervention phase (randomized controlled trial) will be restricted to the eligible patients who are at intermediate to high risk of 30-day readmission according to the simplified HOSPITAL score, i.e. ≥4/13 points. We estimate to have around 18,000 patients discharged during the 20-month study period, 30% of which (5,400) will be at higher-risk for a 30-day readmission or death. This should be enough to reach the targeted sample size within the study time frame.

2.4 Stratification

Unless explicitly mentioned, all primary analyses will be stratified for the factors used at randomization (section 2.4).

2.5 Statistical interim analyses and stopping guidance

There is no interim analysis planned, i.e. there are no stopping rules on the individual or trial level.

2.6 Timing of final analysis

All outcomes will be analyzed collectively after study completion. After completion of data entry, data validation and cleaning will be performed. Data analysis will start after database lock.

2.7 Timing of outcome assessments

Table 1: Timing of outcome assessments

	Index hospitalization[1)]		**Follow-up[2)] (post-discharge)**		
	Screening (before inclusion)	Visit 1 (inclusion, day 0)	Visit 2 (day3 ±1)	Visit 3 (day 14 ±1)	Visit 4 (day 30 ±15)
Assessment	**Pre-study screening**	**Baseline and pre- discharge intervention**	**Post-discharge intervention 1**	**Post-discharge intervention 2**	**Outcome collection**
Demography	X				
Eligibility	X				
HOSPITAL score	X				
Informed consent		X			
Randomization		X			
Baseline characteristics		X			
Medical history		X			
Medication		X			
Activity of daily living (ADL Katz score)		X			
Exposition to intervention		X	X	X	
Medication discrepancy			X	X	
Adverse drug event			X	X	
Primary outcome: unplanned readmission or death					X
Secondary outcomes:					
Number of unplanned readmission					X
Number of days of hospitalization within 30 days					X
Diagnoses at readmission or cause of death					X
Number of emergency department visits					X
Number of PCP visits					X
Discharge satisfaction (3-CTM)					X
Costs of readmission					X

1) Assessment based on electronic health record and/or in person.

2) Assessment by phone call

2.8 Blinding

Most of the study personal including PI, study nurses, statistician and data manager will not be blinded. However, the study nurses collecting the outcomes or working on data cleaning will be blinded to the group allocation.

3 Data management

The CRFs in this trial are implemented electronically using a dedicated electronic data capturing (EDC) system (REDCap, https://www.project-redcap.org/). The EDC system is activated for the trial only after successfully passing a formal test procedure. All data entered in the CRFs are stored on a Linux server in a dedicated mySQL database. Responsibility for hosting the EDC system and the database lies with CTU Bern.

3.1 Data export

At final analyses, data files will be extracted from the database and imported into a statistical software package according to the SOP for data preparation and programming[2].

3.2 Data validation

First line data validation is performed by the online eCRF system at real-time as defined in the data dictionary. Second line data validation and cleaning will be performed after completion of data entry but before database lock according to the SOP for data validation[3].

All baseline characteristics (section 5.5), procedural characteristics (section 5.6) and variables used to derive the outcomes (section 6.2) will be checked for completeness and for outliers. Dates will be checked for consistency (e.g. sequence of date of discharge, intervention phone calls and outcome assessment). The time between discharge and intervention phone calls and outcome assessments will be calculated and values outside the visit windows will be checked.

4 Statistical principles

4.1 General

All recorded and derived variables will be presented by treatment group (and visits, if appropriate) using descriptive summary tables. Continuous variables will be summarized by mean and standard deviation, or median and lower and upper quartiles. Categorical variables will be summarized by absolute and relative frequencies.

In all summaries, the treatment groups will be displayed in the following order: transitional care, usual care. For all parameters, baseline is defined as the last available pre-treatment value (i.e. the last non-missing value available before randomization).

The data collected from patients who are not randomized will only be used for the patient's disposition.

4.2 Confidence intervals and p-values

A level of statistical significance of 5% will be used. All statistical testing will be two-sided. All tests will be accompanied by an effect measure (transitional care vs usual care) with a 95% confidence interval (95% CI).

4.3 Adherence and protocol deviations

Major protocol deviations are

- Violation of inclusion or exclusion criteria
- No informed consent signed
- Crossing-over to the other treatment arm
- Patients not discharged home or to nursing home
- Patients not discharged alive
- Change of HOSPITAL score risk group between inclusion and patient discharge
- Not receiving post-discharge component of the intervention and at least one of the follow-up phone calls (unless the patient was readmitted or died before the follow-up phone call).
- Blindness breach

These protocol deviations will be summarized by treatment group using absolute and relative frequencies.

Table 2: Derivation of protocol deviations.

Protocol deviation	eCRF sheet	Variable	Variable type	Derivation
Violation of inclusion or exclusion criteria				
Adult patient	Baseline Characteristics	patient_age	Continuous: years	patient_age<18
Planned discharge home or nursing home	Eligibility	discharged_alive_home	Binary: No, Yes	discharged_alive_home==No
Patient expected to be discharged alive?	Eligibility	discharged	Binay: No, Yes	discharged==No

Protocol deviation	eCRF sheet	Variable	Variable type	Derivation
Hospital stay of at least 24 hours	Baseline Characteristics	computed_nbdays	Continuous: days	computed_nbdays>=1
Patient at higher risk of 30-day readmission (HOSPITAL score ≥ 4)	Eligibility Baseline Characteristics	hosp_score_simple hospital_change hosp_score_simple_2	Integer: 0-12 Binay: No, Yes Integer: 0-12	hosp_score_simple<4 or hospital_change==Yes & hosp_score_simple_2<4
Previous enrolment into the current study	Eligibility	already_enrolled	Binay: No, Yes	already_enrolled==Yes
Not living in the country in the next 30 days	Eligibility	home_ch	Binay: No, Yes	home_ch== No
No phone to be reached at.	Eligibility	phone	Binay: No, Yes	phone== No
Not speaking French or German (depending on the site)	Eligibility	lang	Binay: No, Yes	lang== No
Informed consent	Eligibility	consent_signed	Binay: No, Yes	consent_signed==no
Crossing-over to the other treatment arm	Protocol Violation	category_interv_notdone category_interv_1funotdone category_interv_2funotdone category_interv_crossover	Binay: No, Yes	(category_interv_notdone==Yes & category_interv_1funotdone==Yes & category_interv_2funotdone==Yes) or category_interv_crossover==Yes
Not discharged home or nursing home	Baseline Characteristics	discharged_destination	Categorical: Home, Nursing home, Other acute care Hospital, Acute geriatric, Rehab, Palliative care, Other, Unknown	discharged_destination!=Home & discharged_destination!=Nursing home
Not discharged alive	Baseline Characteristics	discharged_alive	Binay: No, Yes	discharged_alive==No
Change of HOSPITAL score risk group between inclusion and patient discharge	Eligibility Baseline Characteristics	hosp_score_simple hospital_change hosp_score_simple_2	Integer: 0-12 Binay: No, Yes Integer: 0-12	hospital_change==Yes & hosp_score_simple==4 or 5 & hosp_score_simple_2 > 6 or hospital_change==Yes & hosp_score_simple>6 & hosp_score_simple_2==4 or 5
Not receiving post-discharge component of the intervention and at least one of the follow-up phone calls	Protocol Violation Follow-up calls	category_interv_notdone reach_phone_d3, reach_phone_d14	Binay: No, Yes Binary: No, Yes	category_interv_notdone==Yes or (reach_phone_d3==No & reach_phoned_14==No)
Blindness breach	Protocol Violation	description	Free text	Includes “blind”

4.4 Analysis populations

4.4.1 Full analysis set (FAS)

The full analysis set (FAS) will include all randomized subjects. Following the intent-to-treat (ITT) principle, subjects will be analyzed according to the treatment they are assigned to at randomization regardless of the treatment actually received.

4.4.2 Per-protocol set (PPS)

The PPS consists of all subjects in the FAS who received the allocated treatment and did not have any major protocol deviations (section 4.3).

5 Trial Population

5.1 Screening data

The number of screened, eligible, consenting and randomized patients will be presented.

5.2 Eligibility

Inclusion and exclusion criteria are defined in the study protocol[1]. The number and proportion of patients not fulfilling each criteria will be presented. The reasons for not obtaining an informed consent will be shown.

5.3 Recruitment

A CONSORT patient flow diagram will be drawn following the CONSORT 2010 standards (http://www.consort-statement.org/consort-2010).

5.4 Withdrawal/follow-up

All withdrawals and losses to follow-up will be listed with the time points and reasons (if available).

5.5 Baseline patient characteristics

Evaluations of the baseline characteristics will be based on the FAS. They will be presented in a descriptive summary table by treatment group—continuous variables as mean and standard deviation or median and quartiles, and categorical variables as absolute and relative frequencies. No statistical comparisons of patient characteristics at baseline will be performed.

5.5.1 Sociodemographics

Sociodemographics are collected on eCRFs “Baseline Characteristics”.

Table 3: Sociodemographics.

Description	Variable	Type
Age	patient_age	Continuous: years
Gender	gender	Binary: Male, Female
Nationality*	nationality	Categorical: Switzerland, Germany, France, Italy, Spain/Portugal, East Europe, Africa, Other, Unknown
Living status	living_st	Categorical: With spouse/partner, With another person, Alone, Unknown
Living place type*	living_type	Categorical: Home, Protected apartment, Nursing home, Other, Unknown
Nurse visits at home†	nurse_home	Categorical: No, Yes, Unknown
Support at home for cleaning†	support_home_cleaning	Binary: No, Yes
Support at home to buy grocery†	support_home_housing	Binary: No, Yes
Support at home for eating†	support_home_eating	Binary: No, Yes

Description	Variable	Type
Source of revenue	work	Categorical: Employed, Self-employed, Unemployed, Retired, Invalidity insurance, Social, Other, Unknown
Health insurance*	insur	Categorical: Base, Base+compl, Semi-private, Private, Other, No insurance
Patient left against medical advice	patient_left	Binary: No, Yes

**Further specifications are given as free text and will be listed only*

†Not applicable if living type is nursing home

5.5.2 Index admission and HOSPITAL score

Characteristics of index admission are collected on eCRFs “Baseline Characteristics” and “Costs at Index Diagnoses “. Components of the HOSPITAL score are collected on eCRF “Eligibility” and—in case of changes form screening to baseline—on eCRF “Baseline Characteristics”.

Table 4: Index admission and HOSPITAL score

Description	Variable	Type
Patient discharged alive	discharged_alive	Binay: No, Yes
Destination after discharge*	discharged_destinationr	Categorical: Home, Nursing home, Other acute care Hospital, Acute geriatric, Rehab, Palliative care, Other, Unknown
Length of stay	computed_nbdays	Continuous: days
Costs (in CHF) of the index hospitalisation	costs_indexhosp	Continuous: CHF
HOSPITAL score		
Last hemoglobin level available before discharge	hb_last or hb_last_2†	Continuous: g/l
Last sodium level available before discharge	na_last or na_last_2†	Continuous: mmol/l
Type of admission	adm_elect or adm_elect_2†	Binary: Elective, Non elective
Number of hospitalization at the same hospital in the last 12 months	prevhosp or prevhosp_2†	Integer
Length of stay of current hospitalization (in days).	los_index or los_index_2†	Continuous: days
Active cancer defined as under treatment, or if remission < 5 years	cancer or cancer_2†	Binay: No, Yes
Hospital score (simplified)	hosp_score_simple or hosp_score_simple_2†	Integer 0-12

**Further specifications are given as free text and will be listed only*

†The former is used if the HOSPITAL score did not change from screening to baseline, the latter if it did change. A change is documented by variable hospital_change on eCRF “Baseline Characteristics”

5.5.3 Index diagnosis

Information about the index diagnosis is collected on eCRF “Index Diagnosis”.

Table 5: Index diagnosis and comorbidities.

Description	Variable	Type
Main diagnosis category*	main_dx_at	Categorical: Heart failure, Acute ischemic heart disease, Arrhythmia, Venous thromboembolism, Stroke/TIA, COPD exacerbation, Pneumonia, Other infection, sepsis, Gastro-intestinal disorder, Liver disorder, Renal disorder, Nutritional or metabolic disorder, Adverse drug event, Neoplasm, Epilepsy, Other
Secondary diagnoses and comorbidities*		
Chronic heart failure	comorbidities___1	Binary: Unchecked, Checked
Coronary disease	comorbidities___2	Binary: Unchecked, Checked
Atrial fibrillation	comorbidities___3	Binary: Unchecked, Checked
Peripheral artery disease	comorbidities___4	Binary: Unchecked, Checked
Diabetes	comorbidities___5	Binary: Unchecked, Checked
Dementia	comorbidities___6	Binary: Unchecked, Checked
COPD	comorbidities___7	Binary: Unchecked, Checked
Active cancer	comorbidities___8	Binary: Unchecked, Checked
Chronic renal failure	comorbidities___9	Binary: Unchecked, Checked
Liver cirrhosis	comorbidities___10	Binary: Unchecked, Checked
Drug or Alcohol Abuse	comorbidities___11	Binary: Unchecked, Checked
Epilepsy	comorbidities___12	Binary: Unchecked, Checked
Any treated psychiatric disease	comorbidities___13	Binary: Unchecked, Checked
Letter of discharge has been collected	letter_disch_late	Binary: No, Yes

**Main and secondary diagnoses are also documented as free text (variables main_dx and dx_1_dx20), which will be listed only.*

5.6 Procedural characteristics

Procedural characteristic include the components of the transitional care intervention and are collected for the transition care group only. The pre-discharge component of the intervention is documented at baseline (visit 1) on eCRF “Pre-discharge component”, the follow-up phone calls (visit 2 and visit 3) on eCRFs “Follow-up call 1 (Day 3)” and “Follow-up call 2 (Day 14)”. Evaluations of the procedural characteristics will be based on the FAS. They will be presented in a descriptive summary table—continuous variables as mean and standard deviation or median and quartiles and categorical variables as absolute and relative frequencies.

Table 6: Procedural characteristics: pre-discharge components.

Description	Variable	Type
Basic information about her/his main diseases has been performed?	pat_info	Binary: No, Yes
Which information about those comorbidities have been given to the patient?		
Heart failure	inf_shee_giv___1	Binary: Unchecked, Checked
Coronary disease	inf_shee_giv___2	Binary: Unchecked, Checked
Peripheral artery disease	inf_shee_giv___3	Binary: Unchecked, Checked
Atrial fibrillation	inf_shee_giv___4	Binary: Unchecked, Checked
Chronic obstructive lung disease	inf_shee_giv___5	Binary: Unchecked, Checked
Stroke	inf_shee_giv___6	Binary: Unchecked, Checked
Gastrointestinal bleeding	inf_shee_giv___7	Binary: Unchecked, Checked
Chronic renal failure	inf_shee_giv___8	Binary: Unchecked, Checked
Liver cirrhosis	inf_shee_giv___9	Binary: Unchecked, Checked
Thromboembolism	inf_shee_giv___12	Binary: Unchecked, Checked
Diabetes	inf_shee_giv___13	Binary: Unchecked, Checked
Other*	inf_shee_giv___88	Binary: Unchecked, Checked
No listed comorbidity	inf_shee_giv___0	Binary: Unchecked, Checked
Medication reconciliation has been performed and explanation about medication list?	med_reco	Binary: No, Yes
Have you noticed any medication discrepency that needed to be transmitted to the medical team?	med_reco_disc	Binary: No, Yes
Patient education about general health recommendation has been performed?	pat_educ	Binary: No, Yes
Dependence Level: score of the Katz Index	katz_ind	Integer: 0-6
Post discharge follow-up visit to the treating physician has been planned?*	folup_plan	Binary: No, Yes
Discharge summary sent to the treating physician	dis_sumpcp	Binary: No, Yes
Barriers to a safe discharge, including patient's ability to carry out the discharge plan has been assessed	finalcheck	Binary: No, Yes

*Further specifications are given as free text and will be listed only.

Table 7: Procedural characteristics: follow-up call 1 (Day 3) and follow-up call 2 (Day 14).

Description	Variable	Type
Patient reached by phone	reach_phone_d3 or reach_phone_d14†	Binary: No, Yes
Reason why the patient wasn't reached*	reas_pat_notre_d3 or reas_pat_notre_d14†	Categorical: Death, No answer, Other
Death source of information*	death_sourceinfo_d3 or death_sourceinfo_d14†	Categorical: Next of kin, Treating physician, Hospital, Death certificate, Other
Death was due to an accident/trauma?	trauma_death_d3 or trauma_death_d14†	Categorical: No, Yes, Unknown
Cause of death (according to certificate of death if possible)	cause_death_d3 or cause_death_d14†	Free text
Condition improved since discharge	cond_impr_d3 or cond_impr_d14†	Categorical: No, or rather no, Yes or rather yes, Stable, New symptom
Since your discharge of the hospital, do you have more pain?	morepain_d3 or morepain_d14†	Binary: No, Yes
How does the mobility/walking distance change since discharge?	red_wal_dis_d3 or red_wal_dis_d14†	Categorical: Mobility/walking distance improved, Mobility/walking remained about the same, Mobility/walking decreased, Not able to evaluate
Capacity to prepare meals alone?	cap_meal_d3 or cap_meal_d14†	Binary: No, Yes
Weight trend over the last days/weeks	wei_tren_d3 or wei_tren_d14†	Categorical: Increased, Reduced, Stable, Unknown
Glucose values most often‡	glu_val_tre_d3 or glu_val_tre_d14†	Categorical: Between 4-10, >10, Between 10-15, >15, Unkown
Do you take your medication as prescribed?	medicasprescribed_d3 or medicasprescribed_d14†	Binary: No, Yes
Is there any medication discrepancy between current list and list of discharge?	med_discr_d3 or med_discr_d14†	Binary: No, Yes
Presence of any of those medications?	pre_med_d3 orpre_med_d14†	Categorical: Anticoagulants, Narcotics and opiates, Sedatives, Insulin
Did any of these Adverse Event occur since discharge?		
Dizziness	adv_dru_ev_d3___1 or adv_dru_ev_d14___1†	Binary: Unchecked, Checked
Bleeding	adv_dru_ev_d3___2 or adv_dru_ev_d14___2†	Binary: Unchecked, Checked
Hypoglycemia	adv_dru_ev_d3___3 or adv_dru_ev_d14___3†	Binary: Unchecked, Checked
Delirium	adv_dru_ev_d3___4 or adv_dru_ev_d14___4†	Binary: Unchecked, Checked
Lethargy / Oversedation	adv_dru_ev_d3___5 or adv_dru_ev_d14___5†	Binary: Unchecked, Checked
Nausea / vomiting	adv_dru_ev_d3___6 or adv_dru_ev_d14___6†	Binary: Unchecked, Checked
Fall	adv_dru_ev_d3___7 or adv_dru_ev_d14___7†	Binary: Unchecked, Checked

Description	Variable	Type
None	adv_dru_ev_d3___0 or adv_dru_ev_d14___0†	Binary: Unchecked, Checked
Patient had doctor's office visit since discharge	pcp_visit_d3 or pcp_visit_d14†	Categorical: No, Yes as planned, Yes as new appointment
Reason why the patient didn't have any treating physician visit since discharge*	reas_no_pcp_d3 or reas_no_pcp_d14†	Categorical: Visit is planned, Patient didn't want/ couldn't, Treating physician couldn't/not available, Other, Unknown
Suggestion to see the treating physician was necessary during this follow-up call	sug_see_pcp_d3 or sug_see_pcp_d14†	Binary: No, Yes
Patient education about her/his diseases has been refreshed	patient_education_d3 or patient_education_d14†	Binary: No, Yes

**Further specifications are given as free text and will be listed only*

†For follow up call 1 and 2, respectively.

‡Only for patients with diabetes

6 Analysis

6.1 Outcome definition

6.1.1 Primary outcome

The primary outcome is the number of patients who have an unplanned readmission or die within 30 days after discharge.

6.1.2 Secondary outcomes

- Number of deaths within 30 days after discharge
- Number of patients with unplanned readmission within 30 days after discharge
- Time to first unplanned readmission or death within 30 days
- Main cause of readmission or death
- Post-discharge health care utilization within 30 days after discharge from index hospitalization:
    - number of unplanned hospital readmissions
    - number of planned hospital readmissions
    - total number of unplanned days of hospitalizations
    - total number of planned days of hospitalizations
    - number of emergency room visits
    - number primary care provider visits
- Patient's perspective (satisfaction) on quality of transition of care between hospital and home assessed by the three-item care transition measure (CTM-3) at 30 days
- Costs of readmission at 30 days

6.2 Outcome derivation

Table 8: Derivation of primary and secondary outcomes.

Outcome	eCRF sheet	Variable	Variable type	Derivation	Outcome type
Primary: Unplanned readmission or death within 30 days after discharge	Baseline Characteristics	discharged_alive	Binary: No, Yes	discharged_alive==No or reas_pat_notre_d3==Death or reas_pat_notre_d14==Death or death_d30==Yes or unplanned>=1	Binary
	Follow-up calls	reas_pat_notre_d3, reas_pat_notre_d14	Categorical: Death, No answer, Other		
	Outcomes 30 days	death_d30	Binary: No, Yes		
		unplanned	Integer: 0-6		
Deaths within 30 days after discharge	Baseline Characteristics	discharged_alive	Binary: No, Yes	discharged_alive==No or reas_pat_notre_d3==Death or reas_pat_notre_d14==Death or death_d30==Yes	Binary
	Follow-up calls	reas_pat_notre_d3, reas_pat_notre_d14	Categorical: Death, No answer, Other		
	Outcomes 30 days	death_d30	Binary: No, Yes		

Outcome	eCRF sheet	Variable	Variable type	Derivation	Outcome type
Unplanned readmission within 30 days after discharge	Outcomes 30 days	unplanned	Integer: 0-6	unplanned>=1	Binary
Time to first unplanned readmission or death	Baseline Characteristics	disch_date_index, baseline_death	Date: dmy	Time: min(30, min[baseline_death, date_death_d3, date_death_d14, date_death_d30 unplanned_in_1, lcontact_date] – disch_date_index) Failure: Primary==Yes	Time-to-event
	Follow-up calls	date_death_d3, date_death_d14	Date: dmy		
	Outcomes 30 days	date_death_d30, unplanned_in_1	Date: dmy		
	End of Study	lcontact_date	Date: dmy		
Main cause of readmission or death	Follow-up calls	cause_death_d3, cause_death_d14	Free text	Tabulated free text fields will be manually categorized	Categorical
	Outcomes 30 days	dx_read30, cause_death_d30	Free text		
Number of unplanned hospital readmissions	Outcomes 30 days	unplanned	Integer: 0-6	-	Count
Number of planned hospital readmissions	Outcomes 30 days	planned_readmission	Integer: 0-8	-	Count
Total number of unplanned days of hospitalizations	Outcomes 30 days	unplanned_x_in, unplanned_x_out	Date: dmy	unplanned_x_out – unplanned_x_in	Count
Total number of planned days of hospitalizations	Outcomes 30 days	tot_rehosp_days_planned	Continuous: days	-	Count
Number of emergency room visits	Outcomes 30 days	nb_edvisits	Integer	-	Count
Number primary care provider visits	Outcomes 30 days	nb_pcpvisits	Integer	-	Count
Offset for count variables	Baseline Characteristics	disch_date_index, baseline_death	Date: dmy	min(30, min[baseline_death, date_death_d3, date_death_d14, date_death_d30 lcontact_date] – disch_date_index)	Continuous
	Follow-up calls	date_death_d3, date_death_d14	Date: dmy		
	Outcomes 30 days	date_death_d30	Date: dmy		
	End of Study	lcontact_date	Date: dmy		
Patient's perspective (satisfaction) on quality of transition of care between hospital and home (CTM-3)	Outcomes 30 days	ctm1, ctm2, ctm3	Binary: No, Yes	ctm1==Yes & ctm2==Yes & ctm3==Yes	Binary
Costs of readmission	Costs at Outcomes 30 days	costs_30d	Continuous: CHF	-	Continuous

6.3 Analysis methods

6.3.1 Primary analysis

The primary analysis will be based on the FAS. Missing data will be handled according to section 6.4.

6.3.1.1 Analysis of the primary outcome

The proportion of patients that have an unplanned readmission or die will be calculated in both groups with a 95% Wilson score confidence interval. For the comparison between the two groups, a Mantel-Haenszel risk difference stratified for the stratification factors used in randomization (section 2.4) will be shown (transitional care – usual care). A two-sided 95% CI will be calculated according to the procedure described by Klingenberg[4]. A stratified Cochran-Mantel-Haenszel test will be used to test for differences (e.g. using `emh` in Stata).

6.3.1.2 Analysis of secondary outcomes

The number of patients that die will be compared between treatment groups using a Mantel-Haenszel risk difference with a two-sided 95% CI[4] and a Cochran-Mantel-Haenszel test, both stratified for the stratification factors used in randomization.

The risk of 30 day unplanned readmissions in each group will be estimated using the cumulative incidence function with death as competing event calculated from flexible parametric survival models (e.g. using `stpm2` followed by `stpm2_standsurv` in Stata)[5,6]. Groups will be compared using the cumulative incidence difference with 95% CI and a z-test, based on delta method standard errors and a normal approximation. We will also report the cumulative incidence of the competing event (death without readmission) for each group and the risk difference between groups.

Time to unplanned readmission or death will be graphically depicted by Kaplan-Meier curves for each treatment group. Groups will be compared using a log-rank test stratified for the stratification factors used in randomization. As an effect measure, we will use the restricted mean survival time truncated at 30 days calculated using flexible parametric survival models with the group and factors used at randomization as covariates[7]. The restricted mean survival time for each group and the difference between groups will be reported with 95% CI and a p-value.

The main cause of readmission or death will mainly be analyzed with descriptive statistics. The number and proportion of patients in each category will be shown for both groups.

Count outcomes (number of hospital readmissions, number of days of hospitalization, number of emergency room visits, number of primary care provider visits) will be presented with number of patients, person-time and incidence rate with 95% CI. Groups will be compared using a negative binomial regression with the group and the stratification factors as covariates and the observation time as offset. An incidence rate ratio with 95% CI and p-value will be reported. In case of an excess of zeros and overdispersion that cannot be modeled by the negative binomial distribution we will consider zero-inflated negative binomial regression (e.g. using function `zeroinfl` from R package pscl).

Each item of the CTM-3 score will be summarized by treatment group using relative and absolute frequencies. The number of patients with a yes on all items will be compared between treatment groups using a Mantel-Haenszel risk difference with a two-sided 95% CI[4] and a Cochran-Mantel-Haenszel test, both stratified for the stratification factors used in randomization.

The costs of readmission will be analyzed by linear regression with the treatment group and the stratification factors used in randomization as covariates. The treatment effect will be presented as

mean difference with 95% CI and a p-value. Model assumption will be checked visually using plots of residuals (residuals vs fitted values, QQ-plot). If model assumptions are violated, transformation of the outcome (e.g. log), more robust methods (e.g. robust standard errors or robust regression) or non-parametric methods (e.g. Wilcoxon-Mann-Whitney test or van Elteren's test) will be considered.

6.3.2 Secondary analyses

All outcomes will also be analyzed in the PPS. Only patients without missing value for the respective outcome will be considered (complete cases).

6.3.3 Sensitivity analyses

The following sensitivity analysis will be included for all outcomes:

1) Without early readmissions. The primary endpoint will be re-analyzed excluding the patients with unplanned readmissions up to the day after index discharge (i.e. unplanned_1_in - disch_date_index <=1)

2) No stratification: All outcomes will be analyzed in crude analyses not adjusting for stratification factors. Binary outcomes will be compared by chis-squared test, continuous outcomes by Student's t-test or the Wilcoxon-Mann-Whitney test, count outcomes using an exact Poisson-test and time-to-event outcomes by a log-rank test. Effects will be presented as non-stratified risk difference, mean difference or Mann-Whitney statistic (i.e. the probability that a random patient from the intervention group will have a higher value than a random patient from the control group), incidence rate ratio, and restricted mean survival time difference, respectively, with 95% CI.

3) Primary endpoint based on survival methods. The risk of readmission or death at 30 days for both groups and the risk difference between groups will be calculated with 95% CI and p-values from a z-test using a) a flexible parametric survival model for time to unplanned readmission or death with the group and stratification factors as covariates and b) from the Kaplan-Meier-estimator for time to unplanned readmission or death not using the stratification. CIs for the risk differences and the z-test will be calculated using delta method standard errors and a normal approximation.

4) Non-parametric unplanned readmissions: The risk of unplanned readmission at 30 days in the presence of the competing risk of death will be calculated for each group using the non-parametric cumulative incidence function estimator with 95% CI according to Choudhury et al[8]. Stratification will be ignored.

6.3.4 Subgroup analyses

The primary outcome will be analyzed for subgroups defined by the stratification factors for randomization:

- Risk for readmission (HOSPITAL score of 4 or 5 vs ≥6)
- Clinical site
- Diabetes
- Chronic heart failure
- COPD
- Cancer

- Living place (nursing home vs rest)
- Living status (alone vs rest)
- Health insurance (Semi-private and private vs rest)

Table 9: Derivation of subgroups

Subgroup	eCRF sheet	Variable	Categorization

HOSPITAL score	Eligibility
	Baseline Characteristics
		hosp_score_simple
		hosp_change
		hosp_score_simple_2
			if hospital_change==no:
			hosp_score_simple > 5
			else:
			hosp_score_simple_2 > 5

Clinical site	-	record_id	substr(record_id,1,3)
Diabetes	Index Diagnosis	comorbidities___5	comorbidities___5==checked
Chronic heart failure	Index Diagnosis	main_dx_at comorbidities___9	main_dx_at==Heart failure or comorbidities___9==checked
COPD	Index Diagnosis	main_dx_at comorbidities___7	main_dx_at==COPD exacerbation or comorbidities___7==checked
Cancer	Index Diagnosis	main_dx_at comorbidities___8	main_dx_at==Neoplasm or comorbidities___8==checked
Living place	living_type	Categorical: Home, Protected apartment, Nursing home, Other, Unknown	living_type==Nursing home
Living status	living_st	Categorical: With spouse/partner, With another person, Alone, Unknown	living_st==Alone
Health insurance	insur	Categorical: Base, Base+compl, Semi-private, Private, Other, No insurance	insur==Semi-private or insur==Private

Subgroups will be analyzed using regression models with the treatment group, the subgroup and their interaction and the stratification factors used at randomization as covariates. If possible, a binomial model with identity link function will be used and the effects will be reported as risk differences with 95% CIs. Otherwise, a Poisson model with identity link and robust standard errors (leading to risk differences) or a binomial model with logit link (leading to odds ratios) will be considered. Models with and without interaction will be compared using a likelihood ratio test and the p-value will be reported as p-value for interaction. Results will be presented in a forest plot.

As a secondary analysis, subgroups will be categorized (according to Table 9) and analyzed using Mantel-Haenszel methodology. A risk difference will be shown for each subgroup with both a lower one-sided and a two-sided 95% CI. The p-value from a Mantel-Haenszel test of homogeneity will be presented. The Mantel-Haenszel subgroup analyses will not be stratified for the factors used at randomization.

6.4 Missing data

The number of patients with non-missing observations will be reported for each outcome.

Missing data may occur due to drop-outs or deaths. The former will lead the absence of all outcome information as outcomes are only assessed once. Since the follow-up is very short we do not expect a lot of drop-outs and it is unlikely that these patients did have a readmission or died. Therefore, we will assume that drop-outs did not have a readmission and did not die. For survival analyses they will be censored at one day. For count outcomes they will be assumed to have no observed event and an offset of one day. For patient satisfaction multiple imputations will be used (section 6.4.1). If the amount of drop-outs is larger than 5%, we will do a sensitivity analysis in which the primary outcome (unplanned readmission or death) will be multiply imputed as a binary variable (section 6.4.1).

Death will not lead to missing data for the primary outcome, 30-day deaths and time to primary outcome. For 30-day unplanned readmission, death is a competing event and the cumulative incidence at 30 days will be used (section 6.3.1.2). Count outcomes will be handled by including the observation time as offset in the Poisson regression. For patient satisfaction multiple imputations will be used (section 6.4.1). In a sensitivity analysis, the worst possible outcome will be assigned to deaths (i.e. a negative respond to all question of the CTM-3).

6.4.1 Multiple imputations

Multiple imputations will be based on the treatment group, and selected baseline and outcome variables (see next section). Since missing values in these variables are possible, chained equations will be used (e.g. with command `mi impute chained` in Stata). This procedure fills in missing values in multiple variables iteratively based on a sequence of univariate imputation methods with fully conditional specification of prediction equations. Predictive mean matching (`pmm`) will be used for continuous, logistic regression (`logit`) for binary and multinomial regression (`mlogit`) for categorical variables. Survival outcomes will be imputed by adding the log time and the censoring indicator to the imputation model.

Based on such chained equations, a total of 50 multiple imputations will be calculated. If it is not possible to impute all outcomes in one model, a stepwise approach will be considered.

The 50 imputed data sets will be analyzed using Rubin's rules[9] (e.g. with prefix `mi estimate` in Stata).

6.4.1.1 Selection of variables for multiple imputations

Baseline variable (section 5.5) and outcomes (section 6.1) will be considered for multiple imputations.

Variables with more than 50% missing values will not be used for the imputation model. Binary variables with a frequency of less than 5% in one category will also be omitted. If two binary variables have less than 5% or more than 95% discordant pairs only one of the two will be used (the one with less missings). Levels of ordinal variables with a frequency of less than 5% will be collapsed by adding the entries to the neighbouring category (i.e. next higher or lower level) with the higher frequency (if there are more than one). Categorical variables might generally be recoded if it improves the fit of the imputation model and does not lead to substantial loss of information. Continuous variables will be log-transformed if it improves normality (checked by Shapiro-Wilk tests and QQ plots).

From the remaining variables an imputation model will be constructed based on combined clinical and statistical reasoning. All variables that may provide information about the imputed variable will be included.

6.5 Evaluation of safety parameters

Since the intervention is of very low risk for the patient safety parameters will not be evaluated.

6.6 Statistical software

The statistical analysis will be performed using the statistical software packages Stata[10] and/or R[11].

6.7 Quality control

A second statistician will reproduce the analysis of the primary outcome (for both the FAS and the PPS) based on the exported data. The risk difference and the 95% confidence interval should not differ by more than 0.01, the p-value by 0.001. Otherwise, the reason for the difference will be determined and a consensus must be reached.

7 Changes from the protocol

The SAP is consistent with principle features of the statistical methods described in the protocol. The following deviations were made:

Table 10: Changes from protocol

Header	Change	Reason
Blinded analysis	Blinded analysis not implemented	The allocation can immediately be seen from the eCRFs because only patients in the intervention group have follow up phone calls. It would therefore need an extra statistician that carefully prepares the data so that it is not possible to see the allocation. Given the open-label nature of the study and the straightforward analysis this additional effort seems not to be justified.
Secondary outcome “Medication adherence: 4-item Morisky Medication Adherence Scale (MMAS-4)”.	Removed	High license fees would incur
Secondary endpoint “Number of planned hospital readmissions” and “Total number of planned days of hospitalizations”	Added	Information about the planned readmissions is of interest but was not considered in the protocol.
Test for the analysis of primary and binary secondary outcome	Stratified Cochran-Mantel-Haenszel test instead of simple chi-squared test	Stratification factor should be considered in the analysis
Subgroup HOSPITAL score	Categories 4 or 5 vs ≥6 instead of 5 or 6 vs ≥7	Categories correspond to stratification of the randomization
Subgroup clinical site	Added	Used as stratification factor in randomization
Subgroups cancer, living place, living status and health insurance	Added	Of interest, not mentioned in protocol

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