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Statistical Analysis Plan (SAP)

Impact of an INtervention TO increase MOBility in older hospitalized medical patients (INTOMOB): a cluster randomized controlled trial

INTOMOB

Administrative Information

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1. Introduction

1.1 Background and rationale

Patient confinement to bed is one of the top 5 low-value practices to avoid in hospitals according to *smarter medicine - Choosing Wisely Switzerland*, but it has been claimed to be an epidemic. While 80% of hospitalized patients could walk independently, 80% of their hospital stay is spent in bed, and only 3% ambulating or standing. Low mobility of hospitalized patients is associated with cascading problems, including persistent functional decline, institutionalization, and death. Higher hospital mobility is associated with better outcomes (e.g., fewer institutionalizations), but interventions to increase mobility have not succeeded to change clinical practice so far. Most studies did not actively involve the patients, required resources that are unavailable (e.g., more staff), or did not systematically address barriers to increase mobility (e.g., inappropriate catheters). A workable intervention must help healthcare professionals (HCPs) and patients change their behaviors and implement necessary changes in hospitals and healthcare systems.

The INTOMOB project included a pilot-study of the intervention preceding a cluster randomized controlled trial (RCT). This SAP focuses on the RCT part exclusively.

1.2 Objectives

The primary objective of the RCT is to evaluate the effect of a multilevel patient-empowering intervention targeting the patients, HCPs, and environment, compared to standard of care, on life-space level (i.e., the extent to which people can move from bedroom to outside town).

The second objectives are:

1) To evaluate the effect of the intervention, compared to standard of care, on functioning, quality of life, depression, pressure ulcer, delirium, mobility, muscle strength, fear of falling, fall-risk increasing drug (FRID) prescribing, falls, new institutionalization, discharge destination, emergency room visits, readmissions, death, and satisfaction with hospital stay.
2) To evaluate patient and HCP experience of the intervention (process evaluation) and characterize their perspectives on mobility after the intervention.

1.3 Timing of SAP writing

This SAP version was written and finalized before 50% of patients are enrolled.

2. Study Methods

2.1 Trial design

The INTOMOB RCT is a multicenter, cluster, randomized, controlled, superiority trial conducted in three hospitals in Switzerland, with a 180-day follow-up. The intervention is partially blinded. Outcome assessment and data analysis are blinded. Hospital wards are randomized in a 1:1 ratio to either intervention or control arm. Patients admitted to an intervention ward receive the intervention, while patients admitted to a control ward receive standard of care.

2.2 Randomization

Since the INTOMOB trial is a cluster RCT, only the wards (i.e., the clusters) have to be randomized. Ward randomization was done in a 1:1 ratio and generated shortly before start of the RCT by a statistician from CTU Bern (University of Bern, Mittelstrasse 43, 3012 Bern). The statistician only received identifiers and not the actual names of the hospitals and wards in order to stay blind. Randomization was blocked with block size two and stratified by hospital to have the same ratio of intervention and control wards in each study center. Randomization was also stratified by ward size (<30 beds or ≥30 beds). HCPs working on an intervention ward and participating patients admitted to an intervention ward receive the INTOMOB intervention. HCPs working on a control ward and participating patients admitted to a control ward receive the control procedure.

2.3 Sample size

See section 5.1 of the protocol, under “Sample size calculation for the RCT”. The calculated sample size includes a total of 274 patients (137 in each arm, and in 12 clusters in total).

2.4 Framework

All outcomes will be tested for superiority of the intervention arm compared to the standard of care.

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

There are four time points for the patients: visit 1 at day 0, visit 2 at discharge, visit 3 at 30 (+/-5) days and visit 4 at 180 (+/-5) days. The schedule of assessments is shown in the Appendix Table 1 of the protocol. In particular, the primary outcome is assessed at visit 3.

2.8 Blinding

The intervention is partially blinded. Complete blinding is difficult due to the nature of the intervention, the communication between colleagues working on different wards (i.e., the clusters) and the rotation of the personal (mostly the physicians) across different wards. HCPs are informed in the e-learning part of the intervention, and orally during a presentation of the study, that they should avoid speaking about the intervention with colleagues of other wards.

Outcome assessment and data analysis is blinded. The primary outcome is assessed by phone by an investigator or one of her/his designees (study nurse, doctorand, PhD student, research fellow or medical student with completed GCP training) blinded to the intervention arm. The data analyst only receives identifiers and not the actual names of the hospitals and wards in order to stay blind. Moreover, the data analyst will be blinded to the randomization group.

3. Data Management

3.1 Data export

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 tor 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 Oracle database. Responsibility for hosting the EDC system and the database lies with CTU Bern.

At final analyses, data files will be extracted from the database via the database interface into statistical packages to be analyzed. After database lock, the status of the database is recorded in special archive tables.

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.

3.3 Data preparation

Data preparation will be performed according to the SOP for data preparation.

3.4 Data sharing

If required and budgeted by the sponsor, data sharing will be performed according to the SOP for data sharing.

4. Statistical Principles

4.1 Confidence intervals and *P* values

All effect measures will be accompanied by a two-sided 95% confidence interval. All applicable statistical tests will be two-sided and will be performed using a 5% significance level.

4.2 Analysis populations

4.2.1 Full analysis set (FAS)

The full analysis set (FAS) will include all randomized wards and all enrolled subjects. Following the intent-to-treat principle, wards and subjects will be analyzed according to the assigned intervention.

4.2.2 Per-protocol (PP)

The per-protocol population consists of all wards and subjects in the FAS that do not have any protocol deviations that could confound the interpretation of analyses conducted on the FAS. An eCRF dedicated to protocol deviations is implemented in the database. This will allow to determine the patients for whom such deviation occurred. Protocol deviations will be defined as at least one of the following:

- Discharge earlier than 3 days after enrolment
- Change from an intervention to a control ward or from a control to an intervention ward
- Any of the eligibility criteria not fullfilled

4.2.3 Safety population

Not applicable.

4.3 Estimands

4.3.1 Primary outcome on the FAS

Outcome of interest: life-space assessment at 30 (+/-5) days

Patient-set of interest: full analysis set

Handling of intercurrent events: if the primary outcome is missing in more than 5% of patients, we will employ multiple imputation in the primary analysis and additionally perform an available case analysis as sensitivity analysis disregarding missing data.

Population-level summary measure of outcome: absolute difference with 95% confidence interval, computed using generalized estimated equations (GEEs) with Gaussian distribution, exchangeable correlation structure and robust standard errors with small sample correction.

5. Trial Population

5.1 Screening data

The number of screened patients will be reported if available.

5.2 Eligibility

The inclusion criteria are:

- Admission to a general internal medicine (GIM) ward of a participating hospital,
- Age ≥ 60 years,
- Being ambulatory during the 2 weeks before admission (self-report),
- Living in the community (not in a nursing home or another institution) for at least the last 30 days prior to admission,
- Ability to understand French or German,
- Planned length of stay at least 3 days after enrollment.

The exclusion critera are:

- Medical contraindication to walk (e.g., wound not allowing loading weight),
- Wheelchair-bound,
- End-of-life,
- Severe psychiatric disorder (severe depression, schizophrenia, psychosis),
- Delirium (according to the Confusion Assessment Method [CAM]),
- Cognitive impairment making impossible to use study material (i.e., to implement the intervention) and to understand and sign informed consent, based on clinical judgement, except if a proxy can be actively involved in the study and provides consent,
- Severe visual impairment.

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 Baseline patient characteristics

Table 1 shows the list of baseline characteristics to be summarized. Continuous and count variables are presented as mean with standard deviation or median with quartiles, as appropriate. Categorical variables are presented as absolute and relative frequencies. Those variables will be presented by randomization group (intervention vs. control).

Table 1: Baseline table.

Description	Variable	Type
Age	age	Continuous [years]
Sex	sex	Categorical: female, male

Description	Variable	Type
Body mass index	weight_kg/height_cm	Continuous [kg/m^2]
Hospital	Hospital	Categorical: Inselspital, HFR, KSB
Number of hospitalizations in the last 180 days before admission	hosp_previous_n	Count
Support: home care	homecare	Binary: yes, no
Support: household help	household	Binary: yes, no
Support: mobility aid at admission	mobility_aid	Binary: yes, no
Life-space assessment		
Barthel Index (ADLs)	barthel_total	Continuous [range 0-100]
EQ-5D VAS	eq5d5l_vas2_uk_eng	Continuous [range 0-100]
DEMMI	demmi_score	Continuous [range 8-100]
Main diagnosis	hosp_cause	List of diagnosis categories
Number of medications at admission	med_n	Continuous

5.5 Adherence and protocol deviations

The occurrence of protocol deviations and non-compliance to the intervention (as defined in section 4.2.2) will be checked and reported in a table as well as in the flow chart (see paragraph 5.3).

5.6 Withdrawal/follow-up

Number and percentage of withdrawal and lost to follow-up will be presented in the flow chart.

6. Analysis

6.1 Outcome definitions

Table 2: Derivation of primary and secondary outcomes.

Outcome	eCRF sheet	Variable	Variable type	Derivation	Outcome type
Primary outcome: Life-space level or Life-space level for institutional setting at D30 [range 0-120]	Life-Space Assessment or Life-Space Assessment for institutional setting (note: LSA and LSA-IS can be merged; same coding except with "_is" in addition [e.g., "ls1_yn_fu_is_d30"])	ls1_yn_fu_d30	Binary: No, Yes	ls1_yn_fu_d30 * ls1_frequency_fu_d30 * [(2 if equipment=No and personhelp=No) OR (1.5 if equipment=Yes and personhelp=No) OR (1 if personhelp=Yes)] + 2 * ls2_yn_fu_d30 * ls2_frequency_fu_d30 * [(2 if equipment=No and personhelp=No) OR (1.5 if equipment=Yes and personhelp=No) OR (1 if personhelp=Yes)] + … + 5 * ls5_yn_fu_d30 * ls5_frequency_fu_d30 * [(2 if equipment=No and personhelp=No) OR (1.5 if equipment=Yes and personhelp=No) OR (1 if personhelp=Yes)]***	Continuous
		ls1_frequency_fu_d30	Categorical: 1: <1x/week, 2: 1-3x/week, 3: 4-6x/week, 4: daily		
		ls1_equipment_fu_d30	Binary: No, Yes		
		ls1_personhelp_fu_d30	Binary: No, Yes		
		(Same variables with numbers from 2 to 5)			
Secondary outcomes					
1) Life-space level at D180	Same as primary outcome, with _d180 instead of _d30				
2) Activities of daily living (ADLs) at D30 and D180	ADLs (Barthel Index)	barthel_total_d30 / barthel_total_d180	Continuous [range 0-100]		Continuous
3) Instrumental activities of daily living (IADLs) at D30 and D180	IADLs (Lawton scale)	iadl_total_d30 / iadl_total_d180	Continuous [range 0-8]		Continuous

4) Quality of life at D30 and D180 (EQ-5D-5L VAS)	EQ-5D-5L	eq5d5l_vas2_uk_eng	Continuous [range 0-100]		Continuous
5) Depression at D30 and D180	Depression (PHQ-2)	depression_phq_2_d30/_d180	Binary (Yes/No)		Binary (yes/no)
6) Pressure ulcer at hospital discharge	Pressure ulcer	ulcer_yn_discharge	Binary (Yes/No)		Binary (yes/no)
7) Delirium during hospitalization	Delirium (Confusion Assessment method)	delirium_discharge	Binary (Yes/No)		Binary (yes/no)
8) Mobility at hospital discharge (DEMMI score)	Mobility: DEMMI	demmi_score_discharge	Continuous [range 0-100]		Continuous
9) Lower-limb muscle strength at hospital discharge	Muscle strength	strength_knee_discharge	Continuous 0-5 (from no activity to complete range of motion)		Continuous
10) Hand-grip muscle strength at hospital discharge	Muscle strength	strength_dynamo1_discharge, strength_dynamo2_discharge, strength_dynamo3_discharge	Continuous	Best of three attempts	Continuous
11) Level of activity during hospitalization (% in light, moderate, [very] vigorous)	Accelerometer output	accelero_activity_level [% in light activity], accelero_activity_level_2 [% in moderate activity], accelero_activity_level_3 [% in (very) vigorous activity]	Continuous		Continuous
12) Level of activity during hospitalization (intensity of movement: vector magnitude CPM)	Accelerometer output	Accel_vm_cpm	Continuous		Continuous
13) Fear of / concerns about falling at discharge, D30 and D180	Falls Efficacy Scale – International	fes_i_total_d30/d_180	Continuous [range 16-64]		Continuous
14) FRID prescribing at hospital discharge	Medication classes at discharge	med_frid_discharge	Binary (Yes/No)		Binary (yes/no)
15) FRID prescribing at hospital discharge, D30 and D180	Medication classes at D30-D180	med_frid_discharge_fu_d30, med_frid_discharge_fu_d180	Binary (Yes/No)		Binary (yes/no) and

16) Falls during hospitalization and within D30 and D180	Falls	falls_yn_discharge1 / falls_yn_d301 / falls_yn_d1801 (1 => repeated instrument);	Binary (yes/no)	Sum the number of falls for the count analysis	Binary (yes/no) or count
17) New institutionalization at hospital discharge and within D30 and D180	New institutionalization	new_institutionaliza_v_11_d30/d180 institdate_d30/d_180	Binary (Yes/No) Date		Time- to event
18) Discharge destination	Index hospitalization – discharge data	Discharge_destination	Categorical [home, family (not own home), rehabilitation, nursing home permanent, nursing home temporary, other hospital, other institution, acute geriatrics, palliative ward, same hospital other ward, ICU, death, other]		Categorical
19) Emergency room visits within D30 and D180	Emergency room visits	er_visit_yn_30d1 (1 => repeated instrument); for between D30 and D180: same variable with "_180" instead of "_30" Date: er_visit_date_30d1 /_180d1	Binary (yes/no) Date	Sum the number of readmissions for the count analysis	Time-to-event or count
20) Readmissions within D30 and D180	Readmissions	readmission_yn_30_d1 (1 => repeated instrument); for between D30 and D180: same variable with "_180" instead of "_30" Date: readmission_30d1 /_180d1	Binary (yes/no) Date	Sum the number of readmissions for the count analysis	Time-to-event or count
21) Death within D30 and D180	SAE	death_date	Date		Time-to-event

22) Satisfaction with hospitalization evaluated at hospital discharge	Satisfaction with hospitalization	satis_nursing_1-5 satis_med_1-5 satis_physio_1-5 satis_info_1-3 satis_autonomy_1-2 satis_support_1-3	Ordinal (for each: dissatisfied, rather dissatisfied, neutral, rather satisfied, satisfied, not applicable)	Summary of all variables, and separately for each of the 6 domains	Continuous,

*** See the paper https://doi.org/10.1093/ptj/85.10.1008 for detailed explanation on this score calculation. LSA will range from 0 (totally bed bound) to 120 (traveled out of town every day without assistance).

6.2 Analysis methods

6.2.1 Primary analysis

The primary analysis will be an intention-to-treat analysis to compare the life-space assessment (LSA) between intervention and control groups at D30. LSA will be analyzed using GEEs with Gaussian distribution, exchangeable correlation structure and robust standard errors with small sample correction. This model accounts for the cluster design as well as for the small number of clusters and will be adjusted for the baseline LSA. The absolute difference between intervention group and control group will be presented with a 95% confidence interval (CI).

Continuous secondary outcomes will be evaluated likewise, adjusting for the baseline value if applicable. If outcome measures are non-normally distributed, we will apply an adequate distribution in GEE (e.g., gamma) or log-transform the outcome measure before analysis. Absolute differences between intervention group and control group will be presented with a 95% CI.

Binary outcomes will be analyzed using a GEE with a binomial distribution, a logit link, an exchangeable correlation structure and robust standard errors. Relative differences between groups will be presented as odds ratio with 95% CI.

Count outcomes will be analyzed using a GEE with a negative binomial distribution, a log link, an exchangeable correlation structure and robust standard errors. Relative differences between groups will be presented as rate ratio with 95% CI.

Time-to-event outcomes will be analyzed using a Cox regression model. To account for clustering, we will use shared frailties for clusters as well as cluster robust standard errors. Relative differences between groups will be presented as hazard ratio with 95% CI.

Categorical outcomes (discharge destination) will be analyzed using multinomial logistic regression with robust standard errors to account for clustering. Relative differences between groups will be presented as rate ratios with 95% CI.

Readmissions and emergency room visits will be analyzed as time-to-event outcomes, except if we notice that those outcomes often happen multiple times. In such case, we will analyze them as count outcomes.

Mortality and time to new institutionalization will be analyzed as time-to-event.

Falls will be analyzed as binary outcomes. If we notice that this outcome often happens multiple times, we will analyze it as a count outcome.

6.2.2 Secondary analyses

The secondary analyses will be analyses of primary and secondary outcomes on the PP set.

6.2.3 Sensitivity analyses

We will use generalized linear mixed-effects models instead of GEEs to account for clustering. For outcomes measured at D30 and D180, we will use a repeated-measures mixed-effects model. Should a GEE model not converge, we will use a mixed-effects model for that specific outcome as the primary analysis approach.

Because cluster randomization may lack the excellent balancing in characteristics between groups seen in individual-level randomization, we will adjust each model for additional pre-defined patient-level variables (age, sex, body mass index, LSA, number of ADLs/IADLs limitations, fear of / concerns about falling and muscle strength at baseline) to account for case-mix differences between groups in a sensitivity analysis. Moreover, we will assess imbalances of patient characteristics between groups. If we observe imbalances in covariates not considered in the sensitivity analysis, we will perform additional adjustments to assess the robustness of our results.

6.2.4 Subgroup analyses

We will perform subgroup analyses according to the following characteristics.

Table 3: Derivation of subgroups

Subgroup	eCRF sheet	Variable	Categorization
Age: 60-80 years old	Baseline form	age	age>=60 AND age<=80
Age: >80 years old	Baseline form	age	age>80
Sex: Female	Baseline form	sex	sex==1
Sex: Male	Baseline form	sex	sex==2
Length of stay below median	Discharge data form	discharge_date, start_date	generate los = discharge_date – start_date + 1 summarize los los < r(median)
Length of stay above median			summarize los los >= r(median)
Baseline ADL below median			
Baseline ADL above median			
Baseline IADL below median			
Baseline IADL above median			

Subgroup	eCRF sheet	Variable	Categorization
Number of comorbidities below median			
Number of comorbidities above median			

6.2.5 Additional analyses

Not applicable

6.2.6 Assessment of statistical assumptions

Model residuals will be inspected visually for normality using QQ-plots (Quantile-Quantile-plots).

6.3 Interim analyses

Not applicable.

6.4 Missing data

If the primary outcome is missing in more than 5% of patients, we will employ multiple imputation in the primary analysis and additionally perform an available case analysis as sensitivity analysis disregarding missing data.

Multiple imputation will be via chained equations assuming missing data to be missing at random (MAR). Where endpoints are missing, each will be imputed separately to ensure robust imputation models. We will use all baseline variables (see table 1 in section 5.4) and outcome measures at all time points as predictors in the imputation models. Indicators for intervention and treatment will be included in the imputation model(s). 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 be omitted from the predictors, levels of categorical variables with a frequency of less than 5% in one category will be combined with another level in a sensible way. Continuous variables will be log-transformed if it improves normality (checked by Shapiro-Wilks test and QQ plots). If predictors are too highly correlated among each other, we will only consider the predictor which is more strongly correlated with the outcome. We will impute values using predictive mean matching for continuous and ordinal variables, logistic regression for binary variables, and a multinomial regression model for categorical variables with more than two levels. In total, fifty imputed data sets will be generated, which will be analyzed as described using Rubin's rules (Rubin 1987).

6.5 Safety evaluation

Serious adverse events will be presented in a descriptive way, showing the number and proportion with 95% Wilson confidence interval in each group.

6.6 Subproject

Not applicable.

6.7 Statistical software

Stata version 18 (or higher) or R version 4.2 (or higher) will be used to carry out analyses.

6.8 Quality control

A data analyst from CTU will perform a double programming of the primary analysis as well as a quality control of the final statistical report.

7. Changes from the Protocol

The SAP is consistent with principle features of the statistical methods described in the protocol. Any deviation from the protocol is detailed hereunder with reason.

8. References

European Medicines Agency, Committee for Human Medicinal Products; Draft ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials, step 2b - Revision 1. 30 August 2017.

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SOP “Conducting Interim Analysis” CTU_STA_SOP-09, version 3.0.0, valid from 11.03.2022

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