Statistical analysis plan for MOBILIZE - A randomized controlled trial of personalized exercise therapy and self-management support for people with multimorbidity

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Statistical analysis plan

MOBILIZE - A randomized controlled trial of personalized exercise therapy and self-management support for people with multimorbidity

Section 1: Administrative information

Title & trial registration

- 1a: A randomized controlled trial of personalized exercise therapy and self-management support for people with multimorbidity
  (The MOBILIZE study)
  MOBILIZE is a pragmatic, parallel group, superiority, randomized controlled trial (RCT) investigating if personalized exercise therapy and self-management support is superior to usual care alone in improving quality of life at 12-months in people with multimorbidity.
- 1b: Trial registration: ClinicalTrials.gov ID: NCT04645732 (originally registered 02.11.2020)

Version

- 1: Version 1.0. Date: 10.04.2024

Protocol version

- 3: This statistical analysis plan (SAP) has been written based on the protocol approved by the Regional Committees on Health Research Ethics for Region Zealand (SJ-857; 28.05.2020) and the published study protocol for the RCT (18.01.2023).[1] This SAP adheres to the Guidelines for the content of statistical analysis plans in clinical trials.[2] The SAP was made publicly available before any outcome analyses commenced and before unblinding the data.

Revisions

- 4a: Revision history
- 4b: Justification for revision
- 4c: Timing of revision

Protocol version	Updated SAP version no.	Section number changed	Reason	Date changed

Roles and responsibility

- 5: Names, affiliations, and roles of SAP contributors

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Signatures

- 6a: SAP author:

  Date: 10.04.2024, 

- 6b: Statistician signature:

  Date: 04.04.2024, 

- 6c: Primary investigator signature:

  Date: 10.04.2024, 

Section 2: Introduction

Background

- 7: Synopsis of trial background

Background

Multimorbidity (two or more conditions in the same individual),[3] affects about one in three adults around the world[4] and is associated with decreased quality of life and physical function as well as increased health-care utilization.[3,5-11] The proportion of people with multimorbidity is increasing rapidly.[3,12] explained by changes in lifestyle factors and a population that is aging.[3] Altogether, this highlights the burden of multimorbidity and the need for global action.

However, little evidence on effective management strategies is available, challenging clinical practice.[3,13] Exercise therapy, supported by self-management support, represents a potentially effective management strategy of multimorbidity, which is safe and effective addressing functional limitations and improving outcomes in at least 26 individual chronic conditions.[3,14,15] This includes some of the most common chronic conditions, knee or hip osteoarthritis (OA),[16,17] chronic obstructive pulmonary disease (COPD),[18] heart failure (HF) or coronary heart disease (CHD),[19,20] hypertension,[21] type 2 diabetes mellitus (T2DM),[22] and depression.[23]

A recent systematic review suggested that exercise therapy is safe and effective in people with multimorbidity,[24] but the credibility of the evidence is low, which highlights the need for high-quality randomized controlled trials (RCT) on different combinations of chronic conditions.[24]

Objectives

- 8: Description of specific objectives and hypotheses

The aim of this RCT is to investigate the effects of a personalized exercise therapy and self-management support in addition to usual care, on self-reported, objectively measured, and physiological outcomes in people with multimorbidity (i.e. at least two of the following conditions: knee and hip OA, COPD, heart disease (HF or CHD), hypertension, T2DM, depression).

Hypotheses

We hypothesize that a personalized exercise therapy and self-management program in addition to usual care is superior to usual care in improving quality of life at the 12 months follow-up.

Section 3: Trial methods

Trial design

- 9: Brief description of design

This is a pragmatic, parallel-group (1:1 ratio), superiority RCT conducted at five intervention sites (two hospitals, a private practice physiotherapy clinic and two municipal rehabilitation centers) in Region Zealand, Denmark. A total of 228 persons with multimorbidity aged 18 years or older, were randomly allocated to one of two groups. These groups are 1) personalized exercise therapy and self-management support in addition to usual care or 2) usual care alone.

The primary outcome will be the between-group difference in change in EQ-5D-5L from baseline to the follow-up at 12 months. Secondary outcomes include objectively-measured physical function and physical activity, disease burden, anxiety, depression, self-efficacy, self-reported overall functioning and disability, self-rated health, adverse events and mortality, while a range of other outcomes are also assessed.

Participants were recruited from six general practitioners, three psychiatric facilities, and seven hospital departments in Region Zealand, Denmark as well as through self-referral. Recruitment strategies included direct consultations, targeted Facebook advertisements, articles in local newspapers, as well as various other advertising methods such as posters and handouts. The recruitment campaign commenced in November 2021 and ended May 2023.

See Section 5: Trial population for eligibility criteria.

Randomization

- 10: Randomization details

People willing to participate and fulfilling the eligibility criteria were randomized (1:1 allocation ratio) after baseline assessment. A priori, an independent statistician prepared a computer-generated randomization schedule in randomized, permuted blocks of four or six persons stratified by the number of chronic conditions the individual suffers from (2 or 3+) and recruitment centres (hospitals, general practitioners, and self-referrals). Allocation numbers were concealed in opaque sealed envelopes, which were only accessible by a study coordinator opening them after informed consent and baseline assessment.

Sample size

- 11: Full sample size calculation

The study is powered to detect a difference in change of 0.074 points between the two groups in the primary outcome (EQ-5D) from baseline to the follow-up at 12 months. This difference has previously been found to be the minimally important difference in persons with varying comorbidities.[25] To detect this difference, 95 participants in each intervention group are needed (assuming a common SD of 0.156, power=90%, alpha level=0.05). We planned to recruit a total of 228 participants to account for a potential loss to follow up of 20%.

Framework

- 12. Description of hypothesis testing framework

Both primary and secondary outcomes will be assessed using a superiority framework, expecting that participants undergoing personalized exercise therapy and self-management support will improve more than participants undergoing usual care alone. A confidence interval excluding 0.074 points or more in the EQ-5D index will be interpreted as a lack of a clinical meaningful difference.

Statistical interim analysis and stopping rules

- 13: Specification of planned interim analysis and/or stopping rules

Not applicable.

Timing of outcome assessments

- 14: Details of timing of all analyses

The primary follow-up (12 months) will be conducted 12 months after initiating treatment and all primary and secondary outcomes will be analyzed collectively by two independent statisticians (Prof. Thygesen and Dr. Møller). Data from all time points (baseline, 4, 6, and 12 months) will be included in this analysis. Outcomes presented under Primary or Secondary Outcome Measures at ClinicalTrials.gov (ID: NCT04645732) will be reported in the primary 12-month

RCT report, while outcomes presented under Other Outcome Measures will either be presented in the primary reported or in subsequent, secondary reports.

15: Timing of outcome assessments

Table 1 presents an overview of baseline characteristics and outcomes assessed and their timing. For a detailed overview of all outcome assessments, please refer to the published open access study protocol.[1]

Table 1. Overview of measures and outcomes in the MOBILIZE study

Outcome	Baseline	4-month follow-up	6-month follow-up	12-month follow-up
Participant characteristics				
Age (years), Sex, Height (cm), Educational level, Marital status, Cohabitation, Place of residence	X			
Work status	X	X	X	X
Smoking	X	X	X	X
Spirometry test (FVC, FEV1, FEV1%)	X			
Primary outcome				
EQ-5D-5L, the descriptive index	X	X	X	X
Secondary outcomes				
Objectively measured				
6-minute walk test (m)	X	X		X
30-second chair-stand test (number of chair stands in 30 sec)	X	X		X
Minutes/day spent being physically active with at least light intensity[1]	X	X		X
Steps/day[1]	X	X		X

Self-reported measures and other measures				
The Bayliss burden of illness measure	X	X	X	X
Personal Health Questionnaire Depression Scale (PHQ-8)	X	X	X	X
General Anxiety Disorder-7 (GAD-7)	X	X	X	X
Self-Efficacy for Managing Chronic Disease 6-item Scale (SEMCD6)	X	X	X	X
Overall functioning and disability. WHO Disability Assessment Schedule (WHODAS 2.0, 12 items)	X	X	X	X
Adverse events (self-reported and from medical record review)		X	X	X
EQ VAS	X	X	X	X
Mortality				X
Other outcomes				
Objectively measured				
Isometric knee-extension strength (Nm)	X	X		X
Sedentary activity[1]	X	X		X
Light physical activity[1]	X	X		X
Moderate physical activity[1]	X	X		X
Vigorous physical activity[1]	X	X		X
Moderate to vigorous physical activity[1]	X	X		X
Adherence to the WHO physical activity recommendations[1]	X	X		X
Vigorous intermittent lifestyle physical activity[1]	X	X		X

Moderate-to-vigorous intermittent lifestyle physical activity[1]	X	X		X
Sleep[1]	X	X		X
Isometric handgrip strength (kg)	X	X		X
Weight (kg)	X	X		X
Guralnik 30-second balance test (score between 0-30)	X	X		X
Systolic and diastolic blood pressure after 5 minutes of rest	X	X		X
Cholesterol (HDL and LDL) and triglyceride	X	X		
Glycated haemoglobin (HbA1c) and fasting glucose and fasting insulin levels	X	X		
Inflammatory marker levels (hs-CRP, TNF, IL-6 and IL-1ra)	X	X		
Self-reported measures and other measures				
Left/right knee/hip pain + most affected joint if more than one	X	X	X	X
Only for persons with yes to knee/hip pain Knee/hip pain VAS for most affected joint (VAS 0-100)	X	X	X	X
Bodily pain, body chart	X	X	X	X
Perceived Stress Scale	X	X	X	X
Adapted Fried Frailty and pre-frailty criteria	X	X		X
Modified Karolinska Sleep Questionnaire + self-reported average sleep quantity	X	X	X	X
Fatigue	X	X	X	X

Global perceived effect		X	X	X
Patient acceptable symptom state		X	X	X
Treatment failure		X		X
Adherence to intervention protocol of the study		X		
Other treatment during follow-up		X	X	X
Multimorbidity Treatment Burden Questionnaire	X	X	X	X
Short form of Patient Activation Measure	X	X	X	X
Sedentary behavior and two items on physical activity	X	X	X	X
Individual items from the 12-item WHODAS 2.0	X	X	X	X
Falls and fear of falling		X	X	X

[1] Evaluated using combined wearable thigh and wrist accelerometers (Axivity AX3).
Abbreviations: cm: centimeters; FVC: Forced Expiratory Volume; FEV1: Forced Expired Volume in the first second; FEV1%: Percent predicted of Forced Expired Volume in the first second; Nm: Newton meters; kg: kilograms; HDL: High Density Lipoproteins-cholesterol; LDL: Low Density Lipoprotein-cholesterol; HbA1c: hemoglobin A1c; CRP: C-reactive protein; TNF: tumor necrosis factor; IL-6: Interleukin 6; VAS: Visual Analogue Scale; WHO: World Health Organization

Section 4: Statistical principles

Confidence intervals and p values

- 16: Level of statistical significance and confidence intervals

All statistical tests carried out to assess the between-group effects, will consist of two-sided tests with a 5% significance level (p=.05).

- 17: Adjustment for multiplicity

No correction for multiplicity will be carried out, but interpretation of all Other Outcome Measures will be with this in mind.

- 18: Confidence intervals

All confidence intervals presented will be 95%.

Adherence and protocol deviations

- 19a: Definition of adherence to the intervention

Adherence is considered satisfactory if participants attend at least 18 out of the 24 (75%) supervised self-management and exercise sessions, respectively. Enrolled persons participating in less than 18 sessions will be included in the intention-to-treat (ITT) analysis but excluded from the per-protocol analysis due to insufficient adherence.

- 19b: Description of how adherence will be presented

Adherence will be presented as the number and percentage of patients who participate in 18 or more self-management and exercise sessions, respectively.

- 19c & 19d: Definition of protocol deviations and how they will be reported

The following is defined as a major protocol deviation which may compromise the scientific value of the trial:

- More than 20% loss to follow-up (not providing data on the primary outcome at the primary endpoint, i.e. EQ-5D-5L index at the 12-month follow-up)
- Less than 50% of patients randomized to self-management and exercise participated in at least 18 of the self-management and exercise sessions, respectively.

- More than 25% of patients randomized to usual care alone participate in 12 or more supervised exercise therapy sessions for one of their conditions during follow-up.

All major protocol deviations will be reported in the primary report.

Analysis population

- 20: Definition of analysis populations

In the primary analysis of the trial outcomes and the safety analysis (serious and non-serious AEs), all participants will be included according to the treatment they were randomized to receive, following the Intention-To-Treat (ITT) principle.

In addition, a per-protocol analysis will be conducted. In this analysis, the following participants will be excluded: 1) participants in the exercise and self-management group participating in less than 18 out of the 24 self-management and exercise sessions; 2) participants in both groups undergoing major surgery during follow-up affecting their ability to perform activities of daily living (e.g. joint replacement or open heart surgery); and 3) participants in the usual care group participating in 12 or more supervised exercise therapy sessions for one of their conditions during follow-up.

Section 5: Trial population

Screening data

- 21: Reporting of screening data

The duration of the recruitment period (start and end date) and the total number of subjects screened for eligibility throughout the recruitment period will be reported. See also item 23 & 24.

Eligibility

- 22: Summary of eligibility criteria

Patients were included if they had at least two of the following conditions: knee or hip osteoarthritis (OA), chronic obstructive pulmonary disease (COPD), heart disease (heart failure [HF] or coronary heart disease [CHD]), hypertension, type 2 diabetes mellitus (T2DM), or depression. Other comorbidities did not exclude participation. Furthermore, they had to be aged 18 years or older, capable of walking 3 meters unassisted, and have a score of at least 3 on the Bayliss Disease Burden: Morbidity Assessment by Self-Report scale[26] for at least one of the conditions above and a score of ≥ 2 for at least one of the other conditions. They should also be willing and able to engage in a 12-week supervised exercise therapy and self-management program twice a week.

Patients were excluded if they had participated in supervised systematic exercise therapy for one of their conditions within the past 3 months, had unstable health conditions or were at risk of serious adverse events (SAEs) as determined by a medical specialist. Furthermore, terminal patients and those with a life expectancy of less than 12 months, as well as individuals classified as Class IV on the New York Heart Association (NYHA) Functional Classification scale were excluded. Moreover, patients with psychosis disorders, post-traumatic stress disorder, obsessive-compulsive disorder, attention deficit hyperactivity disorder, autism, anorexia nervosa/bulimia nervosa, and/or dependency disorders were excluded. Finally, other reasons for exclusion included an inability to understand Danish or mental incapacity to participate.

Recruitment and withdrawals

- 23 & 24: Information to be included in the CONSORT flow diagram

The CONSORT flow diagram will consist of the following:

- All participants assessed for eligibility throughout the recruitment period
- All participants meeting one or more of the exclusion criteria, with reasons
- All participants eligible for inclusion in the trial
- All eligible participants not consenting, with reasons
- All participants randomized for both treatment arms
- All participants receiving and not receiving the allocated treatment for both treatment arms
- All participants with follow-up assessments at the 4, 6, and 12 months follow-up[1]
- Withdrawals/lost to follow-up with reasons and timing for both treatment arms
- Participants included in the ITT, per protocol and as treated analyses for both treatment arms

[1]Participants with complete primary outcomes (EQ-5D) will be summarized at each follow-up for both treatment arms.

Baseline participant characteristics

- 25a: List of baseline characteristics to be summarized

MOCK table 1 (below) presents an overview of baseline characteristics that will be presented in the primary report. For further details, please refer to the published open access study protocol.[1]

- 25b: Details on descriptive summary of baseline characteristics

Categorical and binary data will be summarized by absolute and relative frequencies. Continuous and count data will be summarized by mean, median, standard deviation, inter quartile range, 10% percentile, and 90% percentile. In case of only few different values observed or unusual shape of the distribution (e.g. bimodality, extreme skewness), also absolute and relative frequencies will be reported, potentially after a suitable categorization). Number of available measurements will be reported, too. No formal tests for significant differences between groups at baseline will be performed, as this is not recommended by CONSORT.[27]

Section 6: Analysis

Outcome definitions

- 26: Specification of outcomes and timing

Table 1 presents an overview of outcomes assessed and their timing. MOCK table 2 and 3 illustrate how the results of the primary and secondary outcomes and the safety analysis will be presented in the primary report. For a detailed overview of all outcome assessments, please refer to the published open access study protocol.[1]

Analysis method

- 27: What analysis methods will be used

Outcomes presented under Primary or Secondary Outcome Measures at ClinicalTrials.gov (ID: NCT04645732) will be reported in the primary 12-month RCT report, while outcomes presented under Other Outcome Measures will either be presented in the primary report or in subsequent secondary reports.

Continuous outcomes (including the primary outcome) will be analysed using a repeated measures mixed-effects linear model with participants as random effect. Visit (baseline, 4, 6, and 12 months), treatment arm (Usual care, personalized exercise therapy and self-management program) and interaction between visit at time point 12 months and treatment arm will be included as fixed effects. The interaction term is the main test of effect. The model will be adjusted for the randomisation stratification factors (number of chronic conditions (2 or 3+) and recruitment centre (hospitals, general practitioners, and self-referrals)) by including them as fixed effects. This model assumes normally distributed residuals. Marked deviations from this assumption will be solved by appropriate transformations. For binary outcomes a repeated measures mixed-effects logistic regression model will be used including the same variables as mentioned above.

A confidence interval excluding 0.074 points or more in the treatment effect on the EQ-5D index will be interpreted as a lack of a clinical meaningful difference.

The distribution of the primary outcome at each time point (both raw values and change scores) will be visualized by box plots by error bar plots showing means and standard deviations, and by error bar plots showing means and 95% confidence intervals. The individual trajectories of the participants with respect to the primary outcome will be presented in a graph.

The occurrence of serious and non-serious AEs will be compared between groups at the 12-month follow-up using a Poisson regression model with a robust error variance.[28]

As described under item 20, the primary analysis of the trial outcomes and the safety analysis, will follow the ITT principle, while a secondary per protocol analysis will also be performed.

Primary and secondary analyses will be presented as illustrated in MOCK table 2.

Missing data

- 28: Handling of missing data

No imputation methods will be applied, as the repeated measures mixed model allows inclusion of all subjects as long as there is at least a baseline measurement or one follow up measurement.[29]

Loss to follow-up analysis

For each time point, the absolute and relative frequency of loss to follow-up in the primary outcome (EQ-5D) will be reported separated by treatment arm. In addition, these frequencies will be reported stratified by gender and age at baseline, EQ-5D at baseline, EQ-5D at the previous time point and change score at previous time point. The continuous factors will be categorized into three groups of equal size for these analyses.

Additional analysis

- 29: Details of any additional analysis

Other Outcome Measures at ClinicalTrials.gov (ID: NCT04645732) will be reported in subsequent, secondary reports.

Furthermore, a cost-effectiveness analysis, analyses of predictors of responders and non-responders to the personalized program, and of the working mechanisms behind the effects from the program, are expected to be published in secondary publications.

Further analyses will be conducted if found relevant.

Harms

- 30: Handling of adverse events

Participants were asked to self-report any non-serious AEs and serious AEs during follow-up using specific questions in the follow-up questionnaire. The physiotherapists delivering the intervention were also asked to report any AEs that they experienced among the participants. Furthermore, medical records will be inspected for any occurring during the follow-up period. An AE is defined as any undesirable experience during follow-up leading to contact with the health-care system. If an AE results in death, hospitalization, prolonged inpatient hospital care, permanent disability or damage, or if an AE is life-threatening, it will be categorized as an SAE.[30] If available, date of healthcare system contact, duration and potential consequences of SAEs will be registered and reported.

AEs will be assessed for severity, grouped into non-serious and serious AEs and categorized into sub-categories depending on the body system affected by a research assistant without accounting for whether the AEs are causally related with study treatments. Finally, an adjudication committee comprised by two experienced medical doctors from the study team (UB and PG) will evaluate the assessment independently for correctness. Any potential disagreements between the adjudication committee members will be resolved by consensus. To reach consensus, additional information can be requested from the recruiting hospitals.

AEs and SAEs will be presented as illustrated in MOCK table 3.

Statistical software

- 31: Details of statistical package used for the analysis

SAS 9.4 (or an updated version if applicable) (SAS Institute, Cary, North Carolina, USA).

Operating procedures

- 32: Data management

The procedures for data collection and management were approved by the Danish Data Protection Agency in Region of Zealand (REG-015-2020). Data entry and coding of the de-identified data will be conducted by trained staff. We will utilize secure, safeguarded, and authorized electronic platforms for both data collection and storage. This approach aims to minimize any instances of missing data while maintaining privacy and confidentiality of personal information.

This SAP will form the basis for all analyses of the primary and secondary endpoints, which will be carried out by the same independent statisticians, without any involvement from the investigators or study chairs (identical to the authors of the primary report from the study). A research assistant will code the two treatment arms into ‘Group A’ and Group B’ before handing the data over to the statisticians. This will help ensure that the statistical analyses will be performed blinded from treatment allocation.

In a first step the data will be passed to the statisticians without any information on the compliance and on adverse events to ensure blinding. The statistician will finalize the report about the ITT analysis before getting information on compliance and adverse events in the second step.

To reduce risk of interpretation bias,[31] blinded results from the ITT analysis (Group A vs. Group B) will be presented to all authors, who will agree on two alternative written interpretations, one where group A is exercise therapy and self-management support and one where Group A is usual care alone. After finalizing the blinded interpretation, the research assistant will unblind who is Group A and Group B.

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Mock tables

Mock Table 1. Baseline characteristics

Baseline characteristics	Self-management and exercise	Usual care alone
Women		
Age (years)		
Weight (kg)		
Body Mass Index		
Educational level		
Employment status		
Marital status/Cohabitation		
Smoking status		
Number of conditions		
Bayliss burden of illness measure		
EQ-5D Index		
EQ VAS		
6-minute walk test (m)		
30-second chair-stand test (number of chair stands in 30 sec)		
Minutes/day spent being physically active with at least light intensity[1]		
Steps/day[1]		
Personal Health Questionnaire Depression Scale (PHQ-8)		
General Anxiety Disorder-7 (GAD-7)		
Self-Efficacy for Managing Chronic Disease 6-item Scale (SEMCD6)		

Overall functioning and disability. WHO Disability Assessment Schedule (WHODAS 2.0, 12 items)

Mock Table 2. Outcome at 12 months

	Total no. of assessments (self-management and exercise/usual care groups)[1]	**Mean score at 12 months in self-management and exercise group**	**Mean score at 12 months in usual care group**	**Mean improvement in self-management and exercise group**	**Mean improvement in usual care group**	**Between-Group difference in mean improvement (crude)** (95% CI)	**Between-Group difference in mean improvement (adjusted)[2]** (95% CI)
Primary outcome							
EQ-5D-5L, the descriptive index							
Secondary Outcomes							
Objectively measured							
6-minute walk test (m)							
30-second chair-stand test (number							

of chair stands in 30 sec)							
Minutes/day spent being physically active with at least light intensity[1]							
Steps/day[1]							
Self-reported measures and other measures							
The Bayliss burden of illness measure							
Personal Health Questionnaire Depression Scale (PHQ-8)							
General Anxiety Disorder-7 (GAD-7)							

Self-Efficacy for Managing Chronic Disease 6-item Scale (SEMCD6)							
Overall functioning and disability. WHO Disability Assessment Schedule (WHODAS 2.0, 12 items)							
EQ VAS							
Mortality							

[1] There were XXXX possible assessments for each group (XXXX at baseline, 3, 6 and 12 months)

[2] The results will be adjusted for randomisation stratification factors, i.e. number of chronic conditions (2 or 3+) and recruitment centres (hospitals, general practitioners, and self-referrals).

Mock Table 3. Serious Adverse Events

Serious adverse events[1]	**Self-management and exercise**	**Usual care alone**	**P Value**
Number of participants affected			
	Number of events		
Overall			
Mental			
XXXX			
XXXX			
Pulmonary			
XXXX			
XXXX			
Musculoskeletal			
XXXX			
XXXX			
Endocrine			
XXXX			
XXXX			
Cancer			
XXXX			
XXXX			
Neurological			
XXXX			
XXXX			
Gastrointestinal			

XXXX
XXXX
Cardiovascular
XXXX
XXXX
Genitourinary
XXXX
XXXX
Sensory organs
XXXX
XXXX
Other
XXXX
XXXX

[1] This table includes all serious adverse events that occurred during the 12-month study period, but which did not necessarily have a causal relationship with the treatment administered. Serious adverse events include those that result in hospitalization, prolonged inpatient hospital care, result in re-surgery, or if an AE is life-threatening, result in death, permanent disability or damage.[30] The Supplementary appendix will present non-serious adverse events in a similar way.