STUDY STATISTICAL ANALYSIS PLAN

c38568204-01

BI Study No.:	0352-2154
Title:	Proof of concept (proof of intervention principles) study assessing effects of Technology-Assisted Respiratory Adherence prototype version 3 (a Digital Behaviour Change Intervention, DBCI) on proximal clinical outcomes and mediators (psychological mediators, self-management behaviours) in individuals with COPD (IwCOPD)
Investigational Product(s):	NA
Responsible Study statistician(s):	[redacted]
Date of statistical analysis plan:	06-04-2022 SIGNED
Version:	1

1. TABLE OF CONTENTS

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2. LIST OF ABBREVIATIONS

Term	Definition / description
C-PPAC	Clinical Visits PROactive Physical Activity in COPD
CRQ-SAI	Chronic Respiratory Questionnaire – Self Administered Individualized
CSP	Clinical Study Protocol
IwCOPD	Individuals with chronic obstructive pulmonary disease
MCID	Minimal Clinically Important Difference
SSAP	Study Statistical Analysis Plan

3. INTRODUCTION

As per ICH E9 (1), the purpose of this document is to provide a more technical and detailed elaboration of the principal features of the analysis described in the protocol, and to include detailed procedures for executing the statistical analysis of the primary and secondary variables and other data.

This SSAP assumes familiarity with the Clinical Study Protocol (CSP), including Protocol Amendments. In particular, the SSAP is based on the planned analysis specification as written in CSP Section 7 “Statistical Methods and Determination of Sample Size”. Therefore, SSAP readers may consult the CSP for more background information on the study, e.g., on study objectives, study design and population, treatments, definition of measurements and variables, planning of sample size.

SAS® Version 9.4 will be used for all analyses.

4. CHANGES IN THE PLANNED ANALYSIS OF THE STUDY

As a result of the limited sample size (5 instead of the planned 50 individuals with chronic obstructive pulmonary disease (IwCOPD), the pre-planned analyses for this study will not be conducted. Instead, listings of participants' data will be generated for inclusion in an abbreviated study report.
The primary and secondary assessments will be listed for each participant, and from the further assessments, only the engagement with TARA will be listed. No subgroup analyses will be performed.

5. ASSESSMENTS

5.1 PRIMARY ASSESSMENT

Primary assessments are listed below and in CSP Section 2.1.2.

- Change from baseline in the Chronic Respiratory – Self Administered Individualized (CRQ-SAI) dyspnea domain score at 12 weeks.
- Increase from baseline in the CRQ-SAI dyspnea domain score at 12 weeks of at least 0.5, the minimal clinically important difference (MCID).

5.2 SECONDARY ASSESSMENTS

Secondary assessments are listed below and in CSP Section 2.2.2.

5.2.1 Activity Tracker ([redacted] device)

- Change from baseline in average number of steps measured by the activity tracker at Week 12.
- Change from baseline in average cadence (steps/min) measured by the activity tracker at Week 12.

5.2.2 Clinical Visit PROactive Physical Activity in COPD instrument (C-PPAC)

- Change from baseline in the difficulty domain of the Clinical Visits PROactive Physical Activity in COPD instrument (C-PPAC) at Week 12.

[redacted]

[redacted]

5.4 OTHER VARIABLE(S)

5.4.1 Demographics and baseline characteristics

Baseline is defined in Section 6.7.

Demographics and other baseline characteristics will include the following.

- Gender
- Race
- Ethnicity
- Age [years]
- English fluency
- State
- Time zone
- Smoking status
- Background Treatment

6. GENERAL ANALYSIS DEFINITIONS

6.1 TREATMENT(S)

Treatment specification is not applicable as there are no pharmacological treatments assigned nor administered as part of the study. Analyses will be performed separately by cohort, as different versions of TARA were used.

The following study periods will be defined with respect to safety analyses:

- Post-Informed-Consent: after informed consent

6.2 IMPORTANT PROTOCOL DEVIATIONS

The following table defines the different categories of important protocol deviations (iPDs) to be considered. Patients with iPDs will be excluded from analyses specified in Table 6.2: 1. In addition, the frequency of participants with iPDs will be summarized descriptively.

Table 6.2: 1 Important protocol deviations

Category / Code		Description	Requirements	Excluded from which analysis set
A		**Entrance criteria not met**		
	A1	Inclusion criteria not met	Inclusion criteria not met as specified in the protocol.	None
	A2	Exclusion criteria not met	Exclusion criteria not met as specified in the protocol.	None
B		**Informed consent**		
	B1	Informed consent not available/not done	Informed consent missing	All
	B2	Informed re-consent not available/not done	Informed re-consent missing	All

6.3 SUBJECT SETS ANALYSED

The following subject set will be used in the analysis:

- Entered set (ES):
  This subject set includes all enrolled subjects with informed consent who completed the baseline Survey (Survey 1).

  The ES will be used for all assessments.

[redacted]

6.5 POOLING OF CENTRES

This section is not applicable because center is not included in the analysis.

6.6 HANDLING OF MISSING DATA AND OUTLIERS

In general, the efficacy analyses as well as safety analyses will be evaluated by observed case analysis, i.e., using only available data without imputation.

6.6.1 Primary Assessment

For the primary assessment, imputation of missing values will not be performed, as per the CRQ-SAI manual.

6.6.2 Secondary and Further Assessments

For secondary and further assessments, imputation of missing values will not be performed.

6.6.3 Safety assessments

Missing or incomplete adverse event (AE) dates are imputed according to BI standards (refer to 2 and 3).

6.7 BASELINE, TIME WINDOWS AND CALCULATED VISITS

Generally, last assessment before day of TARA initiation (included) will be used as baseline. Time windows will not be used. Baseline will be defined as administration of Survey 1, and Week 12 as administration of Survey 5.

The following measurements will be included for analysis and in the calculation of average of the activity tracker tool scores.

- Survey 1: Baseline measure = 14 days before and up to (including) baseline
- Survey 5: Week 12 measure = 14 days before and up to (including) Week 12

7. PLANNED ANALYSIS

All the assessments (primary, secondary and further), as well as the demographics and baseline characteristics, will be presented as listings for participants, on the ES.

Customized listings will be developed for presenting the participant data, including participant identifier, cohort and specific measurement(s).

7.1 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Only listings are planned for this section of the report.

7.2 CONCOMITANT DISEASES AND MEDICATION

Not applicable due to limited data collected.

7.3 TREATMENT COMPLIANCE

This section is not applicable as there were no treatments administered nor assigned in this study. Instead of compliance, the engagement with TARA will be analyzed.

7.4 PRIMARY ASSESSMENTS

The primary assessments will be conducted on the ES.

For each participant, the CRQ-SAI dyspnea domain score will be calculated as the mean of numerical answers to the questions 1, 2, 3, 4, 5, excluding those questions not answered. The range for each numerical answer is 1-7 (with 1 being the worst and 7 the best). The primary endpoint is increase in dyspnea domain score from baseline to Week 12 of at least 0.5 (MCID), so Dyspnea-score-Week12 – Dyspnea-score-baseline >= 0.5 will be marked as Yes. The change from baseline in CRQ-SAI dyspnea domain score at Week 12 will also be reported. More details about the CRQ-SAI dyspnea domain score calculation appear in Section 10.1.

7.5 SECONDARY ASSESSMENTS

The secondary assessments will be conducted on the ES.

For each participant, the C-PPAC difficulty domain score is first calculated as a raw score by summing up the numerical answers to questions 3-12 (ignoring missing values); the range of raw score is 0-40. The raw score will then be scaled to a 0-100 Rasch scaled score (with 0 being the worst and 100 the best). The change from baseline in the scaled score of the C-PPAC difficulty domain at Week 12 will be reported. More details about the C-PPAC difficulty domain score calculation appear in Section 10.2.

The activity tracker ([redacted] watch) will record steps taken by the participants and time.

- A "valid day" is defined as a day where the activity tracker records at least 8 active hours during waking hours (7am to 10pm local time for the participant).
- Only activities between 7am to 10 pm local time will be analyzed. All times are collected in UTC and will have to be converted into local times.
- To calculate the average number of steps at baseline, the data from the prior 14 days is examined. At least 4 valid days out of the 14 days are needed for analysis, but they do not have to be consecutive days.
- If there are fewer than 4 valid days, the average number of steps at baseline will not be calculated.
- The number of steps taken is summed up for all the valid days, then averaged over the number of valid days, and that represents the average number of steps measured by the activity tracker at baseline.
- The same process is repeated for Week 12, to calculate the average number of steps at Week 12 (if there exist at least 4 valid days in the 14 days prior to Week 12).
- The change from baseline in the average number of steps measured by the activity tracker at Week 12 will be reported for each participant.
- The "walking duration" (in minutes per day) will be calculated from the start and stop times of the activity tracker's recorded activity for each valid day.
- The cadence (in steps/min) for a valid day will be calculated as the number of steps per day divided by the walking duration.
- The average cadence (in steps/min) measured by the activity tracker at baseline will be calculated as the average of cadence for all valid days 14 days prior to baseline.
- The average cadence (in steps/min) measured by the activity tracker at Week 12 will be calculated as the average of cadence for all valid days 14 days prior to Week 12.
- The change from baseline in the average cadence (steps/min) measured by the activity tracker at Week 12 will be reported.

[redacted]

[redacted]

7.7 EXTENT OF EXPOSURE

Exposure will be calculated as the number of days between first and last login with TARA.

7.8 SAFETY ANALYSIS

Safety analysis will be performed as defined in the CSP. All safety analyses will be performed on the ES.

7.8.1 Adverse Events

Unless otherwise specified, the analyses of AEs will be descriptive in nature. All analyses of AEs will be based on the number of subjects with AEs and NOT on the number of AEs.

The analysis of AEs will be based on the concept of treatment emergent AEs. That means that all AEs that occurred after signing the informed consent until the end of study (Week 12) will be assigned to the treatment observed at baseline (background treatment). Non-treatment-emergent AEs will be assigned to "screening" or "follow-up" (after Week 12).

According to ICH E3 (4), in addition to Deaths and serious adverse events, 'other significant' AEs need to be listed in the clinical study report. These will be any non-serious adverse event that led to an action taken with study drug (e.g. discontinuation or dose reduced or interrupted). An overall summary of adverse events will be presented.

The frequency of subjects with AEs will be summarized by treatment, primary system organ class and PT. Separate tables will be provided for subjects with serious adverse events (SAEs), AEs leading to treatment discontinuation, AEs of at least moderate severity and related AEs.

The system organ classes (SOCs) will be sorted by default alphabetically, PTs will be sorted by frequency (within SOC).

7.8.2 Laboratory data

This section is not applicable as no laboratory data is collected.

7.8.3 Vital signs

This section is not applicable as no vital sign data is collected.

7.8.4 ECG

This section is not applicable as no ECG data is collected.

7.8.5 Others

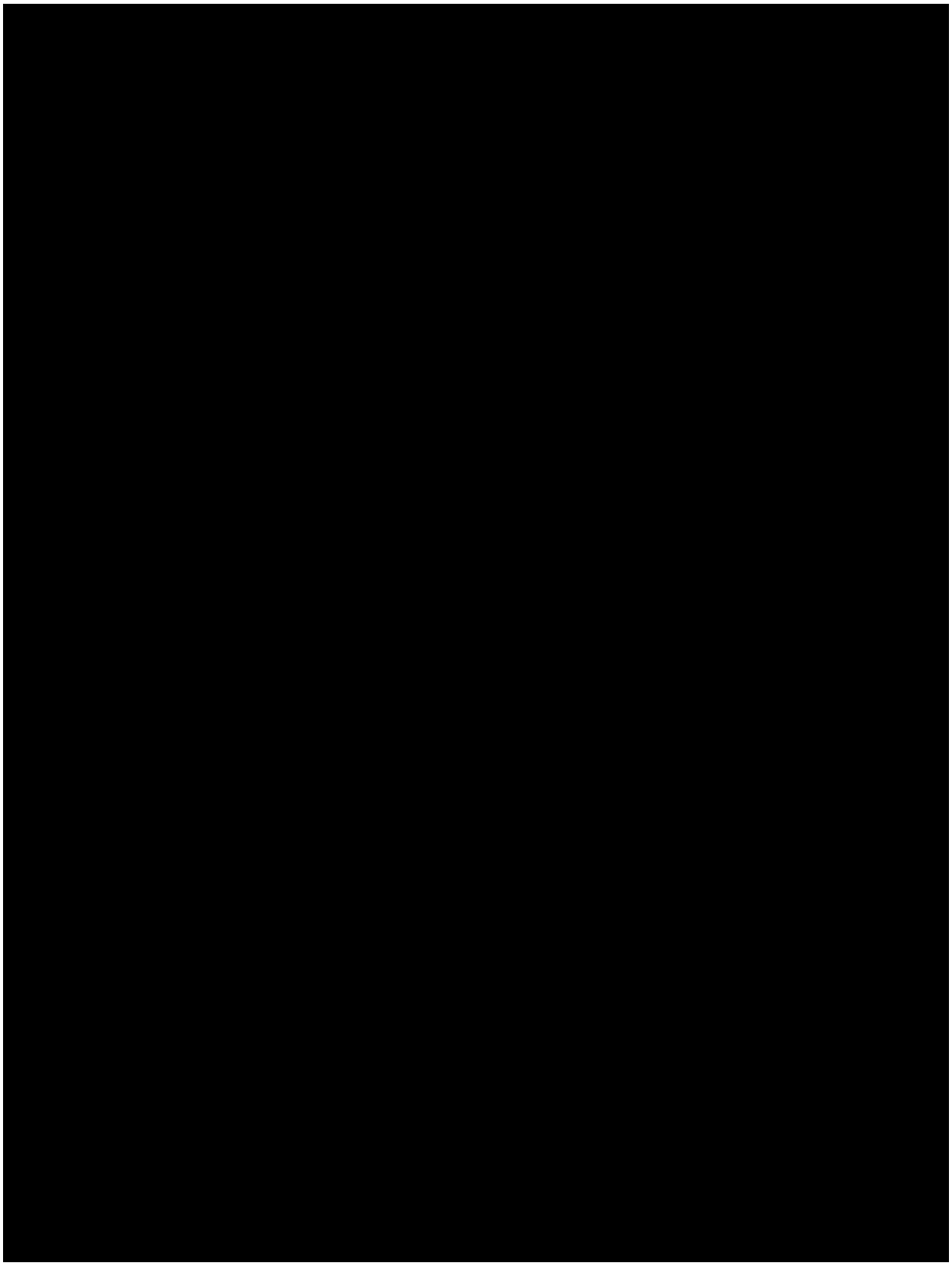
This section is not applicable as no other safety analysis is planned.

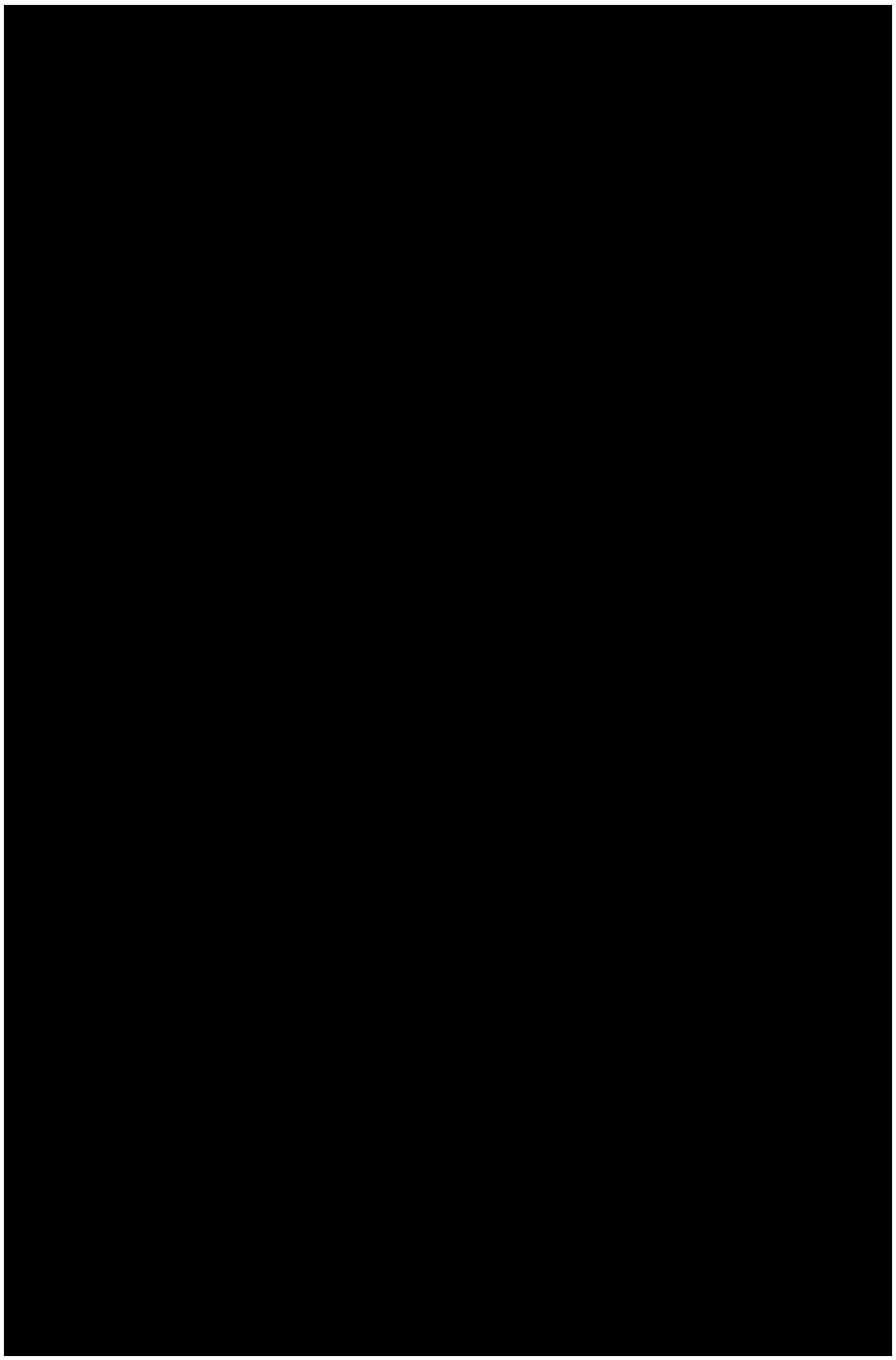
8. TIMEPOINT OF RELEASE OF TREATMENT INFORMATION

The information on cohort allocation for each participant will be entered into the study database at the time of first data transfer.

9. REFERENCES

1.	*CPMP/ICH/363/96:* "Statistical Principles for Clinical Trials", ICH Guideline Topic E9, Note For Guidance on Statistical Principles for Clinical Trials, current version.
2.	*001-MCG-156_RD-01:* "Handling of missing and incomplete AE dates", current version; IDEA for CON.
3.	*001-MCG-156*: "Handling and summarization of adverse event data for clinical trial reports and integrated summaries", current version; IDEA for CON.
4.	*CPMP/ICH/137/95*: “Structure and Content of Clinical Study Reports”, ICH Guideline Topic E3; Note For Guidance on Structure and Content of Clinical Study Reports, current version, EMA webpage.





11. HISTORY TABLE

Table 11: 1 History table

Version	Date (DD-MMM-YY)	Author	Sections changed	Brief description of change
1	**06-04-22**	[redacted]	None	This is the final SSAP

APPROVAL / SIGNATURE PAGE

Document Number: c38568204 **Technical Version Number:1.0**

Document Name: 8-01-tsap-core

Title: Proof of concept (proof of intervention principles) study assessing effects of Technology-Assisted Respiratory Adherence prototype version 3 (a Digital Behaviour Change Intervention, DBCI) on proximal clinical outcomes and mediators (psychological mediators, self-management behaviours) in individuals with COPD (IwCOPD)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Statistician	[redacted]	07 Apr 2022 14:05 CEST
Approval-Team Member Medicine		07 Apr 2022 15:05 CEST
Approval-Clinical Trial Leader		07 Apr 2022 17:00 CEST
Approval-Medical Writer		11 Apr 2022 12:37 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	**Signed by**	**Date Signed**