

STATISTICAL ANALYSIS PLAN (SUMMARY)

A cluster Randomised Controlled Trial of the effectiveness, usability and acceptability of a smart inhaler programme in asthma patients: the ACCEPTANCE study

Short title: ACCEPTANCE study
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This is a summary of the Statistical Analysis Plan version 1.0, dated 13 July 2022. The full Statistical Analysis Plan has been approved and signed by the principal investigator and reviewed by the subsidising party.

1. Statistical Analysis Plan

1.1. General principles

Unit of analysis will be patient level. Following the pragmatic goal of the study, the final analysis will be carried out on an intention-to-treat basis: patients will be analysed in the trial arm they are randomised to, regardless of whether or not they are exposed to the intervention (e.g. use of the Turbu+™ Insights application, switch of inhaler type) and regardless of compliance to the intervention by their HCP (e.g. use of the Turbu+™ Health care portal) or involvement of their HCP (e.g. general practices that do not participate). The exposure, delivery and result of the intervention (use of Turbu+™ health care portal in clinical decision-making) may depend on the clusters.

Therefore, the clustering of patients in the general practices will be taken into consideration in all analyses performed. In addition, a per protocol analysis will be performed for the primary outcome. A two-sided significance level of 0.05 will be used for the primary outcome, medication adherence. Due to the nature of the study, patients cannot be blinded to allocation. Furthermore, outcome assessors that perform visits with patients cannot be blinded as it is important to carefully instruct patients and practices on the use of the intervention app and portal. To reduce bias, validated questionnaires that are administered on paper or electronically will be used. Furthermore, the trial analyst that performs the data analyses will be kept blind to practice allocation until all analyses have been completed to avoid bias.

Data will be presented by intervention group. Continuous variables will be summarised as number of observed values, number of missing values, mean and standard deviation, median and interquartile range and minimum and maximum. Categorical data will be summarised as number of observed values, number of missing values, number and percentage in each category.

Analyses will be carried out using R version 4.1.1.¹, in the R Studio IDE version 1.3.1073² or higher versions of the programmes.

1.2. Study Populations

The intention-to-treat (ITT) population consists of all randomised clusters excluding clusters that were randomised in error (i.e. a cluster not containing participants that passed the T0 visit). Per protocol (PP) population consists of all participants who have any data available for the outcome of interest and do not have any other major protocol violation identified prior to database lock.

Reasons for exclusion from PP population will be summarised.

1.3. Study Status and Consort diagram

A consort diagram will be created to graphically depict the flow of practices and patients and the phases of the trial.

1.4. Visit Attendance

For each visit, the number and percentage who attended the visit, missed the visit, had withdrawn from follow-up or had died before the visit will be reported.

1.5. Baseline Characteristics

Baseline characteristics will be descriptively summarised overall and by treatment group to check for imbalances in randomisation and to provide an overview of the study population overall on practice level and patient level. The following characteristics will be presented:

- Practice level:
 - o GP participating clusters only: size of practice (continuous), number of HCPs employed (categorised)
 - o GP participating clusters and non-GP participating clusters: cluster size (categorised as 1/2/3/>3)
- Patient level:
 - o Age (continuous), sex (categorised), BMI (continuous), education level (categorised), smoking history including status (never, current, former) and pack years (number of cigarettes smoked per day/20*number of years smoked);
 - o Medical history: age of asthma onset (continuous), exacerbations in the year prior to the study (categorised as 0/1/2/>2), comorbidities (categorised), SABA prescription (yes/no), concomitant medication use (categorised as none/1/>1)
 - o Baseline medication adherence in % (continuous, adherence is defined as the number of adherent days as a proportion of the total number of days during the third and fourth week of the run-in period);
 - o Baseline asthma control (ACQ-5), asthma related quality of life (mini-AQLQ), level of self-efficacy regarding the patient's perceived ability to control asthma and attitude about asthma (KASE-AQ), medication beliefs about the necessity of prescribed medication and concerns about prescribed medication (BMQ-specific), illness perception (brief-IPQ) and eHealth literacy (eHLQ).

1.6. Primary outcome

The primary outcome of this study is medication adherence over twelve months, as measured by electronic monitoring of inhalation actuations. The treatment effect of the intervention on medication adherence will be expressed as the mean absolute difference in medication adherence. Medication adherence is defined as the percentage of daily inhalations taken as prescribed (number of recorded inhalations/number of maintenance inhalations prescribed*100), corrected for dose dumping. Dose dumping is defined as ≥ 6 actuations within a 5-minute period. Daily adherence will be capped at 100% (i.e. to avoid falsely increased values). Adherence rates will be calculated for each week and recorded as a percentage. Medication adherence data of one week before and one week after (follow-up) visits (T0, T6, T12) and of one week after other follow-up moments (T3, T9) will be disregarded to minimize performance bias (i.e., caused by awareness of participation in trial around visits).

To test the effect of intervention condition on medication adherence and on changes in medication adherence over time a multilevel linear mixed-model analysis will be performed. The model will include weekly adherence rates per patient over 12 months. The mixed-model will include a random intercept on the level of general practices. A correlation structure will be chosen for the repeated measurements on the level of patients by selecting the best fitting variance-covariance matrix (e.g., autoregressive or exchangeable). The model will include fixed effects for treatment (intervention or control), time (i.e., week 1-52 as a continuous variable), their interaction, age and baseline adherence. Primary evaluation of the outcome will be based on comparing the estimated marginal means between the two treatment groups; we will further report on the other included variables in the model. Assumptions on mixed models will be investigated beforehand to check that these are met (i.e., normality of residuals and potential transformation of data to meet assumptions of

normality). The mixed-effect model will provide valid statistical inferences in the presence of missing outcome data, that can be explained by covariates in the model (i.e. treatment, age, time). A figure will be created in which mean adherence will be plotted against time in weeks, based on raw data.

1.7. Secondary Outcomes

To analyse the effect of intervention on secondary outcomes over time, a similar approach as for the primary outcome will be used. However, this data will not consist of daily/weekly observations, as they were obtained at several fixed time points (see Table 1 for an overview of measurements). In case of missing data, the participant will be expelled from the analysis, unless stated otherwise. In case of missing data at one or more follow-up moments, only the completed measurements will be included in the analysis, unless stated otherwise.

For continuous secondary outcomes, comparative analyses between the intervention and the control group will be performed as for the primary outcome. These outcomes are:

- Asthma control as measured by ACQ-5 (model will be adjusted for baseline ACQ-5).
- Asthma related quality of life as measured by mini-AQLQ (model will be adjusted for baseline mini-AQLQ).

Binary secondary outcomes will be analysed using a multilevel logistic regression model, allowing for the clustered nature of the data and repeated measurements. Binary secondary outcomes are:

- Proportion of patients with a change of ≤ -0.5 (MID) from baseline to T12 in ACQ-5 compared between treatment groups.
- Proportion of patients with a change of ≥ 0.5 (MID) from baseline to T12 in mini-AQLQ compared between treatment groups.
- Proportion of patients that shift in asthma control category as measured by ACQ-5 (<0.75 vs. ≥ 0.75) from baseline to T12 compared between treatment groups.
- Proportion of patients that shift from being adherent to non-adherent and vice versa, from baseline to T12, compared between treatment groups. Being adherent is defined as $\geq 80\%$ adherence.

Count data will be analysed using a Poisson regression model and will include a random intercept on the level of general practices. In case of zero inflated data, a negative binomial regression model will be used. These outcomes are:

- Total number of self-reported exacerbations from baseline to T12, as recorded every three months, compared between treatment groups.
- Number of exacerbations from baseline to T12, as retrieved from the general practices' electronic health records system at study end, compared between treatment groups.
- Number of prescribed reliever medication inhalers (SABA) from baseline to T12, as retrieved from the compared between treatment groups. The number of prescribed inhalers during the study period will be retrieved from the patient's main pharmacist.

Other secondary outcomes:

- Usability (as measured by the System Usability Scale (SUS) at T3 and T12) and acceptability (as measured by the Technology Acceptance Questionnaire (TAQ) at T3 and T12) of the Turbu+ Insights application (intervention patients) and Turbu+ Insights health care portal

(intervention general practices) will be summarised. Furthermore, scores at T3 and T12 will be compared, using a parametric (t-test) or nonparametric test (Mann Whitney U) depending on distribution of data. In case of missing data, the participant will be expelled from the analysis.

- Absenteeism, presenteeism, work productivity loss and activity impairment as measured by WPAI will be descriptively summarised for both groups. Scores will be compared between the two groups, using a parametric (t-test) or nonparametric test (Mann Whitney U) depending on distribution of data.
- Zero adherent days (when patients have taken no inhalations) and underuse days (when patients have taken less inhalations than prescribed) in both groups will be descriptively summarised.

1.8. Sensitivity analyses

- To determine the robustness of our conclusions on primary outcome, a sensitivity analysis for the primary outcome will be performed following the same method as previously described, but using all measured medication adherence data, i.e. including medication adherence measured around follow-up moments.
- If substantial baseline imbalances are observed that have not already been adjusted for in the primary analysis, sensitivity analysis will be performed, by including the respective variable as additional covariate in the model, to assess the robustness of the primary analysis.
- A sensitivity analysis will be performed to assess the effect of intervention on the primary outcome including only those patients with doctor-diagnosed asthma.
- If more than 5% of the study population will be prescribed add-on therapy during the study (i.e. anti-IgE, anti-IL5, systemic corticosteroids), a sensitivity analysis will be performed to assess the effect of the smart inhaler programme on the primary outcome, including only those patients without add-on therapy.

1.9. Subgroup analyses

The interaction between intervention conditions (smart inhaler vs. control) and patient and disease characteristics on the dependent variables medication adherence and asthma control will be analysed using a linear mixed model (same approach as for the primary outcome), to assess whether the effect of the intervention on medication adherence and asthma control is modified by patient characteristics (i.e. self-efficacy, attitude, medication beliefs, illness perception and eHealth literacy). We will examine the effect of each interaction term (e.g. intervention condition * eHealth literacy) on the outcome, corrected for the main effects of the intervention condition, the respective moderator variable (e.g. eHealth literacy) and covariates. Separate analyses will be performed for medication adherence and asthma control and for the different interaction terms. A Bonferroni correction will be applied to correct for multiple testing,

1.10. Exploratory analyses

Medication adherence

- An exploratory analysis will be performed to test the effect of intervention condition on medication adherence and on changes in medication adherence over time, in which

medication adherence is defined differently than in the primary outcome analysis. Medication adherence will still be calculated as the percentage of daily inhalations taken as prescribed and corrected for dose dumping, but will be corrected for intervals between doses (i.e., correct time of use is twice a day, in a period of >6 hours and <18 hours between doses). Furthermore, a 24-hour period will be defined as 03:00-02:59. The same model as for the primary outcome will be used. As for the primary analysis, daily adherence will be capped at 100% (i.e. to avoid falsely increased values), adherence rates will be calculated for each week and recorded as a percentage and medication adherence data of one week before and one week after (follow-up) visits (T0, T6, T12) and of one week after other follow-up moments (T3, T9) will be disregarded to minimize performance bias.

Reliever use

- A subgroup of patients will have an EMD attached to their short-acting beta agonist (SABA) inhaler (i.e. reliever inhaler). An exploratory analysis will be performed on the effect of the intervention condition on electronically monitored SABA use, as a more accurate measure for reliever use. Reliever use defined as number of inhalations as measured by EMD, averaged over the monitoring period of twelve months, will be compared between the two groups, using a parametric (t-test) or nonparametric test (Mann Whitney U) depending on distribution of data.

Delivery and use of intervention

- Due to the pragmatic nature of the trial (i.e. patients and HCPs decide on how and how often they interact with the Turbu+™ Insights application and Turbu+™ HCP portal respectively), we expect that there will be differences in exposure to the intervention that may impact the magnitude of effect. In other words, we expect that use of the app (as measured by the log-rate) will be associated to medication adherence. Therefore, further exploratory analysis will be performed on the correlation between intervention use (single measure over the study period) and medication adherence. Medication adherence is defined as described for the primary outcome. Depending on distribution of data, a parametric (Pearson) or nonparametric test (Spearman) will be used.
- We also expect that there will be differences in intervention delivery, as participants in GP-participating clusters will receive the full intervention, whereas participants in non-GP participating clusters will receive only part of the intervention. This difference in delivery may impact the effect of the intervention. Therefore, further exploratory analysis will be performed on the correlation between intervention delivery (yes/no) and medication adherence. Medication adherence is defined as described for the primary outcome. Depending on distribution of data, a parametric (Pearson) or nonparametric test (Spearman) will be used.

1.11. Safety Outcomes

- Numbers withdrawn from the study and the main reasons for withdrawal will be summarised by treatment group.
- The number and characteristics of serious adverse events and adverse events will be summarised by treatment group.

2. References

1. R Development Core Team. *R: A language and environment for statistical computing*. (R Foundation for Statistical Computing, 2020).
2. Rstudio team. *Rstudio: Integrated Development for R*. (RStudio PBC, 2020).