Division of Psychiatry
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Randomised control trial of a digital asthma management application: juli

Protocol and Analysis plan

Background
Each year, millions of people are diagnosed with asthma and seek additional support via digital applications. It can be overwhelming learning how to manage and unclear what can make symptoms better or worse. The digital health application juli, aims to support people with asthma via a number of evidence based approaches including symptom tracking, medication reminders, journaling, data visualisation of sleep, activity, exercise, oxygen saturation, external data including weather, pollen count and air quality, and heuristic behavioural change technique recommendations about how to improve these parameters (Denford et al., 2014; Jansen et al., 2009).

Trial design and methods
Patients with asthma who are interested in using a digital application for support and management will be individually randomised between use of the juli app and treatment as usual. The primary outcome will be the Asthma Control Test (ACT) questionnaire that measures asthma symptoms at 8 weeks (Nathan et al., 2004).

Trial Intervention

Use of juli app vs treatment as usual (plus attention placebo control app).

juli app: Participants will be prompted to open the app each day via an automated alert. They will be asked to rate how they are feeling on a scale using 5 emojis and track number of shortness of breath episodes, rescue inhaler usage and night time waking with shortness of breath. The app will gather information via Apple HealthKit; sleep, activity, workouts, oxygen saturation. It will present this data to the participant and show associations with asthma symptoms. It will make recommendations about these parameters to guide healthy behaviours and will use external data sources (weather, air quality, pollen count) to guide these recommendations. The app has a medication reminder function that can be set by the participants to improve medication adherence. Participants are also encouraged to engage in journaling via the app, especially in relation to exacerbating or reliving factors for asthma symptoms.

Attention placebo control app: Participants will be prompted to open the app each day via an automated alert and rate how they are feeling on a scale using 5 emojis.

Objectives
The primary objective is to investigate whether the juli app is effective in reducing the severity of asthma symptoms as measured by the ACT (compared to treatment as usual). The secondary objective is to investigate health related quality of life at 8 weeks using the SF-12.

Trial duration per participant
8 weeks.

Participant locations
Global.

Main inclusion criteria
1) asthma with ACT score<20 at baseline, 2) age 18 to 65 (inclusive), 3) English speakers, 4) have an iPhone.

Participant flow
Potential participants will be recruited via online advertisements and support groups. Interested participants will follow a link through to the online patient information sheet. If they wish to participate they will follow a link from the patient information sheet to the online consent form. Following consent they will be directed to download the application. After installing the app they will complete a baseline ACT and SF-12. If they score >19 on ACT they will not be entered into the trial, but can continue to use the app. If they score <20 on the ACT they will be randomised to use the juli app or the attention placebo control app.

Randomisation
Block randomisation will be conducted within the application using automated code, with random block sizes between 4 and 8.

Data collection
All outcome measures will be collected from within the juli app, there is no face-to-face or remote contact between the research team and the participant.

Concept	Measure	Baseline	Week 2	Week 4	Week 6	Week 8
sociodemographics	**Bespoke questionnaire**	**X**				
Asthma symptoms	**ACT**	**X**	**X**	**X**	**X**	**X**
Health related quality of life	**SF-12**	**X**		**X**		**X**
User experience	**MAUQ**					**X**
Sleep	**Time asleep each night**	**Daily**				
Sleep	**Time in bed each night**	**Daily**				
Activity	**Daily steps**	**Daily**				
Workouts	**Daily workout time**	**Daily**				
Heart rate variability	**Heart rate variability**	**Daily**				
Menstrual cycle	**Period and predicted fertile window**	**Monthly**				
Oxygen saturation	**O2**	**Daily**				
Shortness of breath	**Count of shortness of breath episodes**	**Daily**				

Rescue inhaler use	**Count of rescue inhaler use**	**Daily**
Wellbeing	**Likert scale**	**Daily**
Medication adherence	**Yes/no**	**Daily**
Journal	**Free text**	**Daily**
Weather	**Temperature/ cloud cover/rain**	**Daily**
Air pollution	**Air quality index**	**Daily**
Pollen count	**Weeds/trees/ grasses**	**Daily**

Abbreviations
ACT Asthma Control Test
SF-12 Short Form 12 item
MAUQ mHealth App Usability Questionnaire

Baseline measures
Participants will answer the following questions: age, gender, was asthma diagnosed by a physician? How long have you had asthma? Do you see a physician regularly about your asthma? Do you take regular medication?

They will compete the ACT and the SF-12.

Follow-up
Daily: wellbeing, shortness of breath episodes, rescue inhaler usage, medication adherence, journal (juli app only).

Week 2: ACT.

Week 4: ACT, SF-12.

Week 6: ACT.

Week 8: ACT, SF-12, MAUQ.

Statistical analyses

We will follow the Consolidated Standards of Reporting Trials (CONSORT) guidelines in reporting and analysing our data (Schulz et al., 2010).

Flow of participants through the trial
CONSORT diagrams will be produced illustrating the case-finding process and participant throughput in the follow up phase of the study. We will report the following information:

Number of participants recruited via different sources (Google advert, Facebook advert, Twitter, Instagram, Reddit, patient support groups)
Number accessing patient information form
Number completing consent form
Number completing baseline ACT

Number who met eligibility criteria
Number who dropped out after completing baseline information
Number who dropped out after randomisation
Number completing outcome measures at 2, 4 and 8 weeks
Number actively using the app and completing outcome measures at 2, 4 and 8 weeks
Number withdrawing from the trial at 2, 4 and 8 weeks
Number continuing to use the app after 8 weeks

Comparability of groups at baseline
Participants in the two treatment groups will be described separately on the following variables:

Age
Gender
Asthma duration
Physician contact
Asthma medication
Asthma severity (ACT)
Health Status (mental and physical component scores of SF-12)

Numbers (%) will be given for binary and categorical variables, and means and standard deviations (SD) or, medians and inter-quartiles ranges (IQR) for continuous variables, as appropriate. There will be no tests of statistical significance or confidence intervals calculated between randomised groups on any baseline variable.

Description of losses to follow up
The number (%) of participants lost to follow-up at 2, 4 and 8 weeks post-randomisation will be reported for both treatment groups and compared using a chi-square test. Factors associated with 'missingness' of key trial outcomes (e.g., ACT score) within the dataset at all follow-up points will be explored and described.

Analysis of primary outcome
Within our overall objective, we wish to test the hypotheses that severity of asthma episodes can be reduced using juli. The primary analysis will concentrate on severity of asthma.

We have chosen the ACT at 8 weeks as the primary outcome. The ACT is a widely used self-completed asthma symptom scale which has high reliability and validity and is responsive to change (Nathan et al., 2004; Schatz et al. 2006). The ACT is preferred in clinical practice to other measures such as the Asthma Control Questionnaire (Jia et al., 2013).

The primary outcome is the ACT score at 8 weeks. The primary analysis will therefore be the difference in total ACT score at 8 weeks between control and intervention groups. This will be estimated with a linear regression model in which the baseline ACT will be an adjustment.

We will also carry out a sensitivity analysis using linear regression with adjustment for any variables that are not balanced at baseline (age, gender, asthma duration, physician contact, asthma medication, SF-12, ACT). We will investigate how robust the findings are to the model specification by testing whether the results are consistent with those produced by a Poisson model.

Analysis of secondary outcomes

The following secondary analyses will be conducted adjusting for the baseline measure of the outcome variable. We will also adjust for any variables that show imbalance at baseline as a sensitivity analysis:

- ACT score as continuous outcomes at 2, 4, 6 and 8 weeks in a repeated measures analysis
- ACT score as a binary outcome where remission is defined as scoring >19 on the ACT at 2, 4, 6 and 8 weeks in a repeated measures analysis
- Difference in SF-12 physical and mental component scores at 8 weeks
- SF-12 physical and mental component scores at 4 and 8 weeks in a repeated measures analysis

Choice of regression model will depend on the outcome. Distributional assumptions appropriate for positive continuous outcomes will be investigated including the log-normal or Poisson distributions. The SF-12 is usually modelled using linear regression as this is often a good fit to the data. Logistic regression will be used for the analysis of binary outcome data.

Approach to dealing with missing outcome data

We will carry out sensitivity analyses to investigate the possible impact of missing data (White et al., 2011). The main approach will be to adjust for baseline variables associated with missing outcome data. We will of course be making strenuous efforts to minimise the amount of missing data, and in our power calculations have estimated that there will be up to 23% missing data at 8 weeks, based on meta-analysis of trial data of existing digital treatments for asthma (Morrison et al., 2014).

Power calculation

The best estimate of a minimum clinically important difference in ACT is 3.0 points (Schatz et al. 2009), this may be as small as 2.2. The standard deviation in ACT ranges from 3.1 to 4.7. In order to provide 80% power at the two sided 5% significance level a total sample size of 146 will be required. Allowing for 23% attrition, we will aim to recruit 90 participants per arm. Power calculations were carried out using Stata 16.

Minimum clinically important difference	Standard deviation	Total sample size	Allowing for 23% attrition
3.0	3.1	36	44
2.2	3.1	66	82
3.0	4.7	80	98
2.2	4.7	146	180

References

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