Trials

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mHealth intervention delivered in general practice to increase physical activity and reduce sedentary behaviour of patients with prediabetes and type 2 diabetes (ENERGISED): statistical analysis plan

Tomas Vetrovsky[1,2*], Norbert Kral[2], Marketa Pfeiferova[2], Bohumil Seifert[2], Vaclav Capek[1], Katerina Jurkova[1], Michal Steffl[1], Richard Cimler[3], Jitka Kuhnova[3], Tess Harris[4], Michael Ussher[4,5], Charlotte Wahlich[4], Katerina Malisova[6], Jana Pelclova[6], Jan Dygryn[6], Steriani Elavsky[7], Iris Maes[8], Delfien Van Dyck[8], Alex Rowlands[9,10,11] and Tom Yates[9,10]

Abstract

Background Type 2 diabetes and prediabetes represent significant global health challenges, with physical activity (PA) being essential for disease management and prevention. Despite the well-documented benefits, many individuals with (pre)diabetes remain insufficiently active. General practitioners (GP) provide an accessible platform for delivering interventions; however, integrating PA interventions into routine care is hindered by resource constraints.

Objectives The ENERGISED trial aims to address these barriers through an innovative GP-initiated mHealth intervention combining wearable technology and just-in-time adaptive interventions.

Methods The ENERGISED trial is a pragmatic, 12-month, multicentre, randomised controlled trial, assessing a GP-initiated mHealth intervention to increase PA and reduce sedentary behaviour in patients with type 2 diabetes and prediabetes. The primary outcome is daily step count, assessed via wrist-worn accelerometry. The primary analysis follows the intention-to-treat principle, using mixed models for repeated measures. Missing data will be handled under the missing-at-random assumption, with sensitivity analyses exploring robustness through reference-based multiple imputation. The trial incorporates the estimand framework to provide transparent and structured treatment effect estimation.

Discussion This statistical analysis plan outlines a robust approach to addressing participant non-adherence, protocol violations, and missing data. By adopting the estimand framework and pre-specified sensitivity analyses, the plan ensures methodological rigour while enhancing the interpretability and applicability of results.

Conclusions The ENERGISED trial leverages innovative mHealth strategies within primary care to promote PA in individuals with (pre)diabetes. The pre-specified statistical framework provides a comprehensive guide for analysing trial data and contributes to advancing best practices in behavioural intervention trials for public health.

*Correspondence:
Tomas Vetrovsky
tomas.vetrovsky@gmail.com
Full list of author information is available at the end of the article

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Background

The rising prevalence of type 2 diabetes and prediabetes presents a major public health challenge globally [1]. Physical activity (PA) is a cornerstone in managing diabetes and delaying its onset in at-risk populations, offering significant benefits such as improved glycaemic control, reduced insulin resistance, and lower cardiovascular risk [2–4]. Despite these benefits, many individuals with (pre) diabetes remain insufficiently active [5–7]. Primary care settings, where most of these patients receive care, provide a valuable platform for implementing effective PA interventions [8, 9]. However, the integration of such interventions into routine practice is rare, often constrained by barriers such as limited time, resources, and scalability [10, 11]. These barriers highlight the need for innovative, scalable interventions that can be integrated into routine care to address the insufficient PA levels in patients with (pre)diabetes.

The ENERGISED trial seeks to bridge these gaps by introducing an innovative mHealth intervention delivered in primary care. Combining the credibility and accessibility of general practitioners (GPs) with the scalability of mHealth technologies, the intervention uses wearable devices and just-in-time adaptive interventions (JITAI) to facilitate behaviour change. By integrating brief advice delivered by GPs with an automated text-messaging program, initially supported with phone counselling, the trial aims to address traditional barriers and promote sustained patient engagement and adherence to PA goals [12, 13].

Objectives

We designed the ENERGISED randomised controlled trial to evaluate the effectiveness of a GP-initiated mHealth intervention aimed at increasing physical activity (PA) and reducing sedentary behaviour. The trial assesses changes in physical behaviour and clinical outcomes over 12 months in adults with prediabetes and type 2 diabetes, comparing this intervention to an active control involving self-monitoring with an activity tracker. The trial was designed as a pragmatic trial to ensure that, if effective, the intervention could be seamlessly integrated into routine clinical practice [12].

The ENERGISED trial design has been described in detail in a published protocol [12]. While the protocol briefly outlines the planned statistical analyses, detailed primary statistical analyses must be pre-specified to ensure transparency, prevent data-driven decisions, and minimise the risk of selective reporting of outcomes [14]. This article presents the statistical analysis plan (version 1.0) for the ENERGISED trial, finalised in January 2025, prior to the conclusion of data collection in April 2025. No preliminary analyses were conducted before finalising the statistical analysis plan to ensure that its development was not influenced by any trial data.

In addition to detailing the statistical analyses, this paper introduces updates to the published protocol and their justifications to reflect changes that occurred during the trial. These updates include the incorporation of the estimand framework [15], which provides a clear definition of the treatment effect of interest, consistent with the study objectives and enhancing the interpretability and robustness of the planned analyses [16].

This statistical analysis plan follows the Guidelines for the Content of Statistical Analysis Plans in Clinical Trials [17] and adheres to the Principles and Recommendations for Incorporating Estimands into Clinical Study Protocol Templates [18], serving as a comprehensive reference for the planned analyses of the ENERGISED trial.

Methods

Estimands

The ENERGISED trial employs the estimand framework to clearly define the treatment effect of interest, ensuring transparency and robustness in the statistical analyses. The framework aligns with the trial's pragmatic nature and provides a structured approach to addressing intercurrent events and their impact on the interpretation of results.

Primary estimand

Population The population consists of adults with prediabetes or type 2 diabetes recruited through participating GP practices in the Czech Republic. Eligible patients are regular mobile phone users and able to walk independently. Notably, patients living in residential or nursing homes or those with co-morbid conditions that would seriously affect their ability to walk independently are not eligible for the trial. The full eligibility criteria are detailed in the Patient eligibility section.

Intervention A GP-initiated mHealth intervention integrating self-monitoring with an activity tracker, automated text messaging, and initial phone counselling, designed to promote PA and reduce sedentary behaviour. The intervention is described in detail in the Intervention and control groups section and in the previously published paper on intervention development [13].

Comparator A GP-initiated active control involving self-monitoring with an activity tracker alone, without additional text messaging or phone counselling.

Outcome The primary outcome is the daily step count, assessed via accelerometry over 7 consecutive days at the 12-month follow-up.

Intercurrent events and strategies:

(a) Treatment policy strategy: All intercurrent events (i.e. those occurring after treatment assignment and before primary outcome assessment), except for death, are handled using the treatment policy strategy. Under this strategy, the analysis proceeds as if participants continued with their assigned treatment, regardless of their adherence to the intervention or protocol violations. For example, events such as GPs failing to deliver the intervention as planned or participants discontinuing their involvement in text messaging or phone counselling do not warrant participant exclusions or adherence-based adjustments. This approach reflects real-world conditions and aligns with the pragmatic nature of the trial [19]. We recognise that missing data may be correlated with intercurrent events such as non-adherence, potentially introducing bias [20]. To mitigate this risk, GPs were trained to emphasise the importance of providing follow-up data, even when patients did not fully adhere to the intervention. The robustness of this strategy will be further assessed through sensitivity analyses, specifically by conducting analyses limited to adhering participants, to explore the potential impact of non-adherence on the results.
(b) Principal stratum strategy: Death is addressed using the principal stratum strategy, yielding an estimate of the survivor average causal effect. Under this approach, the analysis is restricted to participants who survive until the end of the follow-up period, excluding deceased participants from the dataset. This strategy enables the estimation of treatment effects within the principal stratum of survivors, offering a meaningful interpretation of outcomes in this subgroup. We acknowledge that this approach assumes that death is not influenced by the assigned treatment arm, an assumption necessary for the validity of the principal stratum estimand. In the context of our trial, this assumption appears plausible: the intervention promotes increased physical activity, which is unlikely to materially alter the risk of death over a 12-month period. Moreover, the 12-month mortality rate among adults with prediabetes and uncomplicated type 2 diabetes managed in primary care is very low, further supporting the appropriateness of the strategy. Given these considerations, the exclusion of deceased participants is considered preferable to imputing unobservable outcomes, enabling a clear and methodologically sound estimation of the treatment effect among survivors.

Summary measure The treatment effect is defined as the between-group mean difference in change from baseline to 12 months for the outcome of interest, estimated using a mixed model for repeated measures (MMRM).

Secondary estimands

Secondary estimands are defined similarly to the primary estimand, differing only in the outcome of interest, where secondary outcomes, as detailed in the Outcome definitions section, replace the daily step count. Furthermore, secondary estimands are specified for all outcomes with the summary measure reflecting changes from baseline to 3 months and baseline to 6 months, respectively.

These estimands ensure alignment between the study objectives and the statistical analyses, enhancing the interpretability and relevance of the trial results for real-world application [21].

Trial design

The ENERGISED trial is a 12-month pragmatic, multicentre, parallel-group, randomised, controlled, superiority trial [12]. The trial protocol was approved by the Ethics Committee of the General University Hospital in Prague (reference number: 49/20), and the trial is registered at ClinicalTrials.gov (identifier: NCT05351359, registered: 28/04/2022, https://clinicaltrials.gov/ct2/show/NCT05351359).

The trial recruited adults with prediabetes and type 2 diabetes through GP practices across multiple sites. Recruitment began in April 2022 and was initially expected to conclude in December 2023. However, slower-than-anticipated recruitment rates, partially due to the COVID-19 pandemic, led to a delay, with recruitment ultimately completed in April 2024.

Initially, 21 GP practices participated in the trial, but to limit further delays, additional practices were included during the trial period. In total, 28 GP practices participated in patient recruitment.

The 12-month follow-up is expected to conclude in April 2025, at which point the final analysis will be performed. No interim analyses were planned prior to this.

Patient eligibility

To be eligible for the trial, patients had to meet the following inclusion criteria at randomisation: (1) diagnosis of prediabetes or type 2 diabetes according to the Czech guidelines for GPs [22, 23], i.e. fasting plasma glucose 5.6–6.9 mmol/l, or 2-h plasma glucose of 7.8–11.0 mmol/l after ingestion of 75 g of oral glucose load for the diagnosis of prediabetes, and fasting plasma glucose ≥ 7.0 mmol/l, or 2-h plasma glucose ≥ 11.1 mmol/l after ingestion of 75 g of the oral glucose load for the diagnosis of type 2 diabetes; (2) age 18 years or older; (3) followed for prediabetes/diabetes by a participating GP practice. Of note, in the Czech Republic, only uncomplicated type 2 diabetes patients with glycated haemoglobin (HbA1c) ≤ 53 mmol/mol and not taking insulin are commonly followed by a GP; other type 2 diabetes patients are usually followed by a specialist-diabetologist; (4) regular users of a mobile phone (not necessarily a smartphone), able and willing to answer calls and read text messages as part of the study; (5) able and willing to wear and use a wrist-worn Fitbit activity tracker for the study duration; and (6) provided written informed consent before any assessment related to the study.

Patients were excluded from the trial if they were (1) unable to walk independently for any reason; (2) pregnant; (3) having a household member already recruited for this study to avoid contamination; (4) living in a residential or nursing care home where the imposed regime could interfere with the intervention; or (5) having any co-morbid conditions that would seriously affect their adherence to the trial procedures (e.g. active malignancy; recent (< 3 months) myocardial infarction, coronary artery bypass graft, or cerebrovascular accident; renal disease requiring dialysis; neurological condition (e.g. Parkinson disease); cognitive impairment, or significant hearing or visual impairment; hip or knee joint replacement within 3 months; major surgery planned within the next 12 months). Additionally, as all study materials and intervention tools were available only in Czech, patients were excluded if they lacked sufficient proficiency in the Czech language to comprehend and engage with the study procedures effectively.

Sample size

To detect a difference of 1000 steps/day at 12 months between groups, with a power of 80%, using a two-sided 0.05 significance level (alpha), and anticipating a standard deviation of 3000 steps/day [24–26], 143 subjects per group (286 in total) were needed. The sample size calculation was performed using G*Power software, version 3.1.9.6. To account for an expected attrition rate of approximately 15% [24–26], the trial aimed to recruit 340 patients. Ultimately, 343 patients were recruited into the trial, with 172 assigned to the intervention group and 171 to the control group.

Screening and recruitment

According to the published protocol, each of the original 21 GP practices was expected to recruit at least 17 patients, with a maximum of 24 patients to ensure balanced representation across practices. However, due to a smaller-than-expected number of recruits in some practices, adhering to this rule would have further delayed recruitment, even after the number of participating GP practices was expanded to 28. To address this, the maximum limit was increased to 30 patients per practice.

At the start of recruitment, GP practices were provided with a random selection of 24 patients, stratified by sex (female:male in a 1:1 ratio) and condition (prediabetes:diabetes in a 1:2 ratio), from the pool of all their prediabetes and type 2 diabetes patients. They were instructed to evaluate eligibility criteria, record reasons for ineligibility for those who did not meet the criteria, and introduce the study opportunistically to eligible patients during routine health check-ups. Once a GP practice exhausted this initial selection, they were offered a new random selection of 12 patients from their original pool, a process that was repeated as necessary.

Patients who agreed to participate signed written informed consent, while GPs documented reasons for refusal for those who declined.

Randomisation and blinding

Patients were randomly allocated in a 1:1 ratio to either the intervention or the active control group. The randomisation was performed centrally by the principal investigator using a computer-automated randomisation system within the REDCap electronic data capture tools [27] to ensure adequate allocation concealment. The trial used a randomisation scheme stratified by prediabetes/type 2 diabetes condition and sex to ensure equal representation in both groups.

Due to the nature of the study protocol, neither patients nor investigators could be blinded, as both were aware of the allocation due to their active roles in the intervention.

The statistician responsible for developing the statistical analysis plan was, however, blinded to group allocation. Participating GPs who conducted all assessments were also blinded to group allocation unless they specifically inquired about a patient's allocation (something they were discouraged from doing).

Intervention and control groups

At the start of the study, all patients received a wearable activity tracker, Fitbit Inspire 2 [28], from their GPs and were instructed to wear it for the duration of the study. All patients also received brief PA advice from their GPs, which included an educational leaflet on PA and exercise and a prescription outlining specific PA goals. Specifically, the GPs recommended that patients self-monitor their daily step count using the Fitbit and increase it by at least 3000 steps over their baseline (determined during the first week of Fitbit wear) through intentionally brisk walking, gradually over a period of at least 6 weeks [9, 29]. Additionally, patients were advised to interrupt prolonged sitting with short bouts of walking or exercise every 30 min [4, 30].

Patients in the intervention group received an additional mHealth intervention incorporating JITAI principles [31], delivered through the HealthReact platform, which facilitated the integration of wearable data, just-in-time prompts, and automated messaging to support behaviour change [12, 13]. During the first 6 months, this intervention was initially supported with phone counselling (lead-in phase). For the subsequent 6 months, the intervention transitioned to being fully automated without human support (maintenance phase). The intervention was developed with input from (pre)diabetes patients following the mHealth development and evaluation framework, as previously reported [13]. In brief, the mHealth intervention delivered six types of text messages employing various behaviour change techniques: (1) Just-in-time prompts to increase walking pace, triggered when the patient was walking for 5 consecutive minutes. (2) Just-in-time prompts to interrupt sitting, sent after 30 min of prolonged sitting. (3) Personalised interim reviews of weekly step goals, delivered on Friday evenings. (4) Personalised weekly feedback and encouragement, provided on Sunday evenings. (5) Reminders of personalised action plans, tailored to each patient's goals. (6) Occasional short educational messages emphasising the importance of PA in (pre)diabetes management. Patients without smartphones or those unable to reliably sync their Fitbit data did not receive just-in-time or personalised messages. Instead, they were provided with an adapted mHealth intervention featuring static general messages, matched in the total number of text messages and the behaviour change techniques employed.

To facilitate adoption of the mHealth intervention, two trained counsellors, recruited from among university students, contacted patients by phone at the start of the intervention and at months 1, 2, 3, 4, 5, and after the 6-month assessment (seven calls in total, each lasting 10–20 min). The counsellors supported the implementation and personalisation of the mHealth intervention, employed various behaviour change techniques, and worked to enhance patients' adherence to the intervention.

Patients in the active control group also received brief PA advice, an educational leaflet, and a prescription with PA goals from their GPs at baseline. They were provided with a Fitbit tracker to self-monitor their daily steps and were encouraged to achieve the recommended goal of an additional 3000 daily steps. However, they did not receive the mHealth intervention, including text messaging or counselling support.

Progress through the trial

The progress of all participants through the trial, from the screening phase to the 12-month follow-up, will be summarised and reported using a CONSORT flow diagram [32]. The investigators will make every reasonable effort to ascertain the reasons for losses to follow-up and will summarise these reasons by trial group at each time point. In particular, the timing and level of consent withdrawal will be presented within the flow diagram. Consent withdrawal will be categorised as withdrawal from the intervention (further detailed as withdrawal from Fitbit wear, text messaging, or phone counselling), withdrawal from follow-up (specifically from accelerometry assessment), or complete withdrawal from the trial.

Statistical analysis

Baseline patient characteristics

Baseline patient characteristics will be presented both overall and separately for the two randomised groups. These characteristics will include age, sex, condition (prediabetes/type 2 diabetes), marital status, education level, employment status, smoking status, alcohol intake, anthropometric measures (height, weight, body mass index, waist circumference), fasting plasma glucose, glycated haemoglobin, blood pressure, lipid profile (LDL, HDL, total cholesterol, triacylglycerides), performance in the 30-s sit-to-stand test, patient-reported outcomes (symptoms of anxiety and depression assessed using the Hospital Anxiety and Depression Scale (HADS) [33], health-related quality of life using the 12-Item Short Form Health Survey (SF-12) [34], chronotype using the Morningness-Eveningness Questionnaire (MEQ) [35], and health literacy using the European Health Literacy Survey (HLS-Q12) [36]), accelerometry-assessed physical

behaviour (daily step count, peak 30-min cadence [37], daily minutes of moderate-to-vigorous physical activity (MVPA), sedentary time, time in sedentary bouts > 30 min, average acceleration, and intensity gradient [38]), accelerometry-assessed sleep metrics (sleep time, sleep window, sleep onset, wake time, and sleep efficiency [39]), comorbidities, and current medications.

Categorical data will be summarised using numbers and percentages. Continuous data will be summarised using mean and standard deviation (SD) for normally distributed data and median and interquartile range (IQR) for skewed data. Statistical significance tests will not be performed for baseline characteristics.

Adherence

Adherence to the intervention will be assessed based on the percentage of participants who were non-adherent by either (1) refusing or being unable to use the Fitbit activity tracker, (2) refusing or being unable to receive text messages, or (3) failing to engage in at least 4 out of the 7 planned phone counselling sessions.

Additionally, the number of participants without smartphones or those unable to reliably sync their Fitbit—who therefore received the adapted intervention using static general messages instead of just-in-time personalised messages—will be reported for each month of the intervention. However, this is not considered non-adherence, as the adapted intervention is provided in accordance with the protocol (see the Intervention and control groups section).

Protocol violations

The pre-defined major protocol violations include (1) failure to randomise eligible and consenting participants, (2) GPs' failure to provide participants with the activity tracker and brief advice, (3) investigators' failure to deliver text messages or provide phone counselling to participants in the intervention group, (4) erroneous provision of the intervention to participants in the control group, and (5) failure to collect baseline and 12-month accelerometry data or collecting 12-month data more than 6 months after the scheduled term (these will not be used and will be treated as missing data).

The pre-defined minor protocol violations include but are not limited to (1) enrolment of ineligible participants, (2) variations in the timing of the intervention, with delays of up to 6 weeks post-randomisation tolerated, (3) variations in the timing of assessments, with assessments conducted within 6 weeks of the scheduled date tolerated, (4) non-adherence to the intervention as defined in the Adherence section, (5) erroneous provision of text messages, (6) non-compliance with data collection procedures, and (7) failure to complete any of the assessments.

Most major and minor protocol violations are considered intercurrent events and will be addressed using the treatment policy strategy in accordance with the trial's estimands. However, failure to randomise eligible and consenting participants (major violation 1) and enrolment of ineligible participants (minor violation 1) represent pre-randomisation events and are therefore not considered intercurrent events. Furthermore, protocol violations leading to missing data (major violation 5, minor violation 7) are not considered intercurrent events but will be handled through the predefined missing data strategy.

The number and percentage of participants with major and minor protocol violations will be summarised by treatment group, with details of the type of violation provided. No formal statistical testing will be undertaken.

Analysis population

The primary analysis for all trial estimands will follow the intention-to-treat principle, including all participants as originally assigned, regardless of protocol violations, adherence to the intervention, or withdrawal from the study (unless participants fully withdraw their consent for the use of previously collected data). Participants who die before the 12-month follow-up will be excluded from the analyses, consistent with the principal stratum strategy adopted for handling death within the defined estimand. Given that the MMRM, used in the analysis (see Analysis methods section), implicitly imputes missing values based on observed data, participants with missing data at any of the follow-up measurements (i.e. at 3, 6, or 12 months) will still be included in the primary analysis as long as they have at least one follow-up measurement. However, participants with no follow-up data (i.e. missing all outcome measurements at 3, 6, and 12 months) will not contribute to the model and will therefore be excluded from the analysis. The extent and distribution of missing data will be transparently reported.

Sensitivity analyses will include reduced populations, such as complete-case analyses, as described in detail in the Sensitivity analyses section.

Outcome definitions

Outcomes will be assessed at baseline and at 3, 6, and 12 months after randomisation. The primary outcome is the average daily step count, assessed via accelerometry over 7 consecutive days. All other outcomes are secondary.

The daily step count was chosen as the primary outcome because it directly reflects the main goal for study participants in both the intervention and control groups, who are recommended to increase their daily step count by at least 3000 steps above their baseline level (see Intervention and control groups section). Other physical

behaviour outcomes include the peak 30-min cadence, reflecting participants' goal to increase walking cadence, as well as total sedentary time and time spent in sedentary bouts > 30 min, reflecting the goal of interrupting prolonged sitting. Additionally, average acceleration and intensity gradient will be assessed. These metrics capture both overall activity levels and the distribution of activity intensities, thereby enabling a more detailed analysis of the intervention's impact on participants' activity behaviours [38]. Finally, minutes of MVPA will be evaluated for comparison with other studies, as this measure is frequently used as an outcome in PA interventions.

All these outcomes will be derived from accelerometry data collected using ActiGraph wGT3X-BT devices worn on the non-dominant wrist for seven consecutive days, 24 h a day. Data were collected at 100 Hz time resolution. Raw accelerometer data (gt3x) will be processed using the open-source R-package GGIR version 3.1–11 or newer, following standard procedures. These procedures include detection of non-wear periods and calculation of the average magnitude of dynamic acceleration corrected for gravity (Euclidean Norm minus 1 *g*) over 5-s epochs [40, 41]. Non-wear periods will be imputed using GGIR's default settings. Measurements will be excluded if the post-calibration error exceeds 0.01 *g* or if fewer than 3 days of valid wear (defined as > 10 h per day) are recorded [42]. Additionally, for the calculation of average acceleration and intensity gradient, measurements will be excluded if data lack coverage for each 15-min period of the 24-h cycle [38].

Minute-level step counts will be calculated using the revised Verisense algorithm within GGIR [43, 44]. For the daily step count, minute-level steps will be aggregated for each valid wear day, and the mean across all valid wear days will be calculated. For the peak 30-min cadence (expressed in steps/min), minute-by-minute step data will be rank-ordered from highest to lowest for each valid wear day; the highest steps/min for 30 min (not necessarily consecutive) will be selected and averaged for each valid wear day, and finally, the mean across all valid wear days will be calculated. Average acceleration and intensity gradient will be derived using GGIR, following the procedures described by Rowlands et al. [38]. Minutes of MVPA will be calculated using an acceleration threshold of 100 milligravity units (m*g*) [45]. To remove extraneous signals related to random wrist movement, only activities lasting > 1 min (where 80% of the activity was > 100 m*g* threshold criteria) will be classed as MVPA, in line with previous research using wrist-worn accelerometers [46, 47]. Total sedentary time and time spent in sedentary bouts > 30 min will be calculated using an acceleration threshold of < 40 m*g* [48], excluding sleep time determined using automated sleep detection [39].

Other secondary outcomes are detailed in the published trial protocol [12] and include anthropometric measures (body mass index and waist circumference), fasting plasma glucose, glycated haemoglobin, blood pressure, lipid profile (LDL, HDL, total cholesterol, triacylglycerides), performance in the 30-s sit-to-stand test, symptoms of anxiety and depression assessed using the HADS, and health-related quality of life measured with the SF-12.

Outcome values will be reported for each follow-up time point, separately for the intervention and control groups, as means and standard deviations, with transparent reporting of the number of participants contributing data at each time point. Additionally, changes from baseline to each follow-up time point will be presented as means and standard deviations, separately for the intervention and control groups, to ensure that the data can be easily utilised in future meta-analyses. However, the between-group differences will not be reported to avoid confusion with the treatment effects, which are addressed using MMRM as detailed in the Analysis methods section.

Analysis methods

The primary analysis for primary and secondary estimands will be conducted using mixed models for repeated measures (MMRM), where the outcome values at follow-up assessments at 3, 6, and 12 months will serve as the dependent variable. The model will include fixed effects for group (intervention vs. control), time point (categorical variable representing 3, 6, and 12 months), and their interaction (group*time point), as well as the baseline value of the outcome, age, sex, and condition (prediabetes or type 2 diabetes) as covariates. A random intercept and slope for time will be included at the GP practice level to account for clustering of patients within GP practices, and a nested random intercept for patients will be included to capture within-patient correlations. The model can be specified as:

$$\text{outcome} \sim \text{group} * \text{time point} + \text{baseline outcome value} + \text{age} + \text{sex} + \text{condition} + (1 + \text{time point} \mid \text{GP} / \text{patient})$$

This model structure accounts for the repeated-measures nature of the data, adjusts for baseline differences, and incorporates patient- and GP-level random effects to appropriately handle the hierarchical structure of the data. The interaction term (group*time point) provides estimates of the intervention effect at each follow-up time point, adjusted for the specified covariates. In other words, for each outcome, a single model will be fitted that incorporates all follow-up time points, with the intervention effects at 3, 6, and 12 months derived directly from this model. Model assumptions, including the normality

and homoscedasticity of residuals, will be evaluated using visual inspection (e.g. residual plots, QQ plots). If serious deviations from assumptions are observed, data transformations or alternative modelling approaches, such as generalised linear mixed models, will be considered.

All analyses will be performed under the missing at random (MAR) assumption, with missing outcome values implicitly handled by MMRM. This ensures that all participants with at least one follow-up measurement contribute to the analysis, enhancing robustness and validity.

Sensitivity analyses will be conducted using the same analytical approach but applied to reduced populations, as specified in the Sensitivity analyses section, to assess the robustness of the results under different assumptions.

The intervention effects will be reported as the mean difference between groups, with 95% confidence intervals (CIs), and the associated p value. All applicable statistical tests will be two-sided and performed using a 5% significance level. Adjustments for multiple testing will not be undertaken.

Missing data

Missing data will be handled implicitly by MMRM under the MAR assumption. This approach ensures that participants with partial data still contribute to the analysis by leveraging relationships between observed data points, covariates, and time points to estimate missing values. Missing baseline values of the outcome variables required for baseline adjustment in the MMRM models will be imputed using the mean baseline values calculated across the entire study population.

To assess the robustness of the MAR assumption, sensitivity analyses will be conducted for the primary estimand using reference-based multiple imputation. In this approach, missing data will be imputed under alternative assumptions about the missing data mechanism, focusing on deviations from MAR. Specifically, missing data in the intervention group will be imputed using the observed distribution in the control group, assuming that participants who discontinue the intervention behave like those in the control arm. Reference-based multiple imputation was selected because it provides a structured way to model plausible deviations from the MAR assumption, aligning with the trial's treatment policy estimand. Alternative approaches, such as retrieved dropout multiple imputation stratified by intercurrent event type, were considered but not pursued, as they would primarily operate under a MAR assumption within strata without explicitly modelling departures from MAR. Given the expectation that a substantial proportion of intercurrent events will result in missing outcome data, reference-based imputation offers an appropriate and recommended strategy in this context. Moreover, the expected number of intercurrent events is low, making reference-based imputation a better choice due to its greater stability compared to stratified imputation methods when event-specific sample sizes are small. In summary, reference-based imputation provides a transparent, interpretable, and straightforward approach for sensitivity analyses, avoiding unnecessary complexity in this trial context. The multiple imputation procedure is described as follows.

A chained equations approach will be used to generate $m=10$ imputed datasets, providing robust estimates of the missing values. The choice of $m=10$ imputations reflects common practice for moderate levels of missing data. Even with up to 50% missing information, an estimate based on $m=5$ imputations has a standard deviation that is only about 5% wider than one based on an infinite number of imputations, and there is no practical benefit to using more than five to ten imputations [49]. The imputation model will incorporate variables associated with missingness and the outcome, such as baseline values, age, sex, condition (prediabetes or type 2 diabetes), and any available follow-up measurements. After the imputation step, MMRM will be applied separately to each of the imputed datasets. The parameter estimates and standard errors from these analyses will then be combined using Rubin's rules, which account for the uncertainty introduced by the imputation process. Rubin's rules involve calculating a weighted average of the parameter estimates across the datasets and incorporating both within- and between-imputation variability to produce valid confidence intervals and p values.

Sensitivity analyses

Sensitivity analyses will be conducted to evaluate the robustness of the results to alternative assumptions and analytical decisions, ensuring that the primary findings are not unduly influenced by specific methodological choices. These analyses will align with the trial's estimands and address variations in the populations included, handling of missing data, and model specifications:

(A) A sensitivity analysis will be conducted for the primary estimand using reference-based multiple imputation, as described in the Missing data section. This approach imputes missing values in the intervention group based on the observed distribution in the control group, testing the robustness of the MAR assumption by exploring deviations aligned with plausible missing data mechanisms.

(B) A complete-case analysis will be performed with only the 12-month time point and including only

participants with complete data at this final assessment. Since this approach does not involve repeated measures, the analysis will utilise a simple linear model instead of the MMRM. This approach provides a straightforward estimate of the intervention effect at the primary time point, facilitating comparison with other studies that focus solely on final outcomes. By excluding participants with missing 12-month data, the analysis tests the robustness of the findings to potential biases introduced by missing data.

(C) Participants from each general practice will be excluded iteratively to conduct a leave-one-out sensitivity analysis for the primary estimand. This approach will assess whether the results are disproportionately influenced by any single practice. By refitting the main model for each subset of participants, the analysis will evaluate the consistency of the treatment effect estimates across practices, providing insights into practice-level variability and the robustness of the findings. This method ensures that the overall conclusions are not overly dependent on data from specific practices, strengthening the generalisability of the trial results.

(D) Alternative model specifications will be tested for the primary estimand, including simplified models without random slopes, to assess the impact of model complexity on the results.

Supplementary analysis

A supplementary analysis will be conducted to estimate the treatment effect among participants who adhered to the intervention, thus approximating a principal stratum estimand under strong assumptions, such as the existence of a well-defined subgroup of adherers, the stability of adherence behaviour across treatment arms, and the absence of unmeasured factors that jointly influence adherence and outcomes. This approach is conceptually related to a modified intention-to-treat analysis, which restricts the analysis to participants who initiate treatment, although in this trial, adherence is defined more broadly to include sufficient engagement with the allocated intervention. Adherence will be defined as (1) using the Fitbit activity tracker as instructed, (2) receiving text messages, and (3) participating in at least four out of the seven planned phone counselling sessions. By excluding non-adherent participants, the potential impact of adherence on the estimated treatment effects will be explored. A formal complier average causal effect (CACE) analysis was considered but not pursued, given the exploratory nature of this analysis, the complexity of the required modelling, and the strong assumptions needed regarding the relationship between adherence and outcomes.

Harms

Adverse events will be monitored and recorded throughout the study period. Data on falls, injuries, musculoskeletal problems, hypoglycaemic episodes, major cardiovascular events, and any other events potentially related to the study implementation will be collected at each assessment. The number and percentage of occurrences for each type of adverse event will be summarised by treatment arm, but no formal statistical testing will be performed. Information on severity, expectedness, or causality of adverse events will not be systematically collected, given the pragmatic nature of the trial and the anticipated low risk profile of the intervention.

Statistical software

All analyses will be conducted using R statistical software. The packages and their respective version numbers used for the analyses will be documented and reported.

Discussion

This paper presents the statistical analysis plan for the ENERGISED trial, detailing the methods for analysing its primary and secondary outcomes in accordance with the pre-specified estimands. It also reflects minor changes to the originally published protocol [12], which are summarised in the following section to ensure transparency.

Changes to the published protocol

Estimand framework: The present paper introduces the estimand framework to enhance the clarity and transparency of the trial's analytical approach. This addition provides a structured definition of the treatment effects of interest, aligning with current recommendations for modern clinical trial reporting and ensuring consistency in handling intercurrent events [18].

Patient eligibility: The eligibility criteria were modified to exclude patients who lacked sufficient proficiency in the Czech language. This change was necessary because all study materials and intervention tools were available only in Czech, ensuring that participants could fully comprehend and engage with the study procedures.

Recruitment: Several adjustments were made in response to delays in recruitment. The number of participating GP practices was increased from 21 to 28, and the maximum number of patients allowed per practice was raised from 24 to 30 to address slower-than-expected enrolment. Despite these measures, recruitment concluded 4 months later than planned, finishing in April 2024 instead of December 2023.

Outcomes: A new secondary outcome, the peak 30-min cadence, was introduced to align with one of the intervention's key goals—increasing walking pace. This metric has been recently shown to be associated with

all-cause and cardiovascular mortality [37] and provides a meaningful measure of PA intensity. Furthermore, the definition of a valid day was revised from > 16 h of wear to > 10 h, in line with recommendations for wake time-related measures [42] and consistent with large studies demonstrating associations between PA and health outcomes such as the NHANES study [50]. This change ensures that participants who remove the accelerometer at night are not unnecessarily excluded from the analysis. For the same reason, the condition of having coverage for each 15-min period of the 24-h cycle was dropped, and this requirement will now only apply to the calculation of average acceleration and intensity gradient, where it is necessary for the proper interpretation of these variables [38]. Additionally, the methods for deriving minute-level step counts from wrist-worn accelerometry data were defined using the revised Verisense algorithm, which offers robust and validated step-count calculations [43, 44]. The acceleration threshold of 100 m*g* and 40 m*g* were also specified for calculating minutes of MVPA and sedentary time, respectively [45, 48]. Conversely, metrics such as acceleration above which a person's most active 10, 30, 120, and 480 min are accumulated; time spent in light, moderate, and vigorous PA; and sleep measures at follow-up time points will not be reported. These measures are complex to analyse and interpret and will be reserved for exploratory analyses.

These minor changes to the protocol are consistent with the trial's objectives and do not affect its overall integrity or validity.

Strengths and limitations

This statistical analysis plan demonstrates several strengths. First, the adoption of the estimand framework provides a structured and transparent approach to defining the treatment effects of interest, ensuring alignment with current methodological standards and enhancing the interpretability of the results [18, 51]. Second, it includes detailed handling of missing data, with the MMRM implicitly imputing missing values under the MAR assumption. To test the robustness of this assumption, sensitivity analyses will be conducted using reference-based multiple imputation, providing additional assurance about the validity of the findings [52]. Third, the plan outlines pre-specified sensitivity analyses to test the robustness of the findings under various assumptions and methodological choices, reducing the risk of bias from post hoc analytical decisions. Finally, the clear specification of statistical models, including the incorporation of random effects to account for hierarchical data structures, ensures methodological rigour and appropriateness for the study design.

Despite these strengths, the chosen methodological approach has several inherent limitations. First, the reliance on MMRM for handling missing data under the MAR assumption may not fully account for patterns of missingness that deviate from this assumption, particularly if unobserved factors influence dropout or non-compliance [20]. Although sensitivity analyses using reference-based multiple imputation are planned, these cannot fully eliminate uncertainty about the validity of the MAR assumption. Second, while the principal stratum strategy for addressing death provides a meaningful estimate within the survivor subgroup, it does not capture the treatment effect for the entire trial population, potentially limiting generalisability. Third, the pre-specification of a single primary analysis approach, while crucial for transparency, may limit flexibility in responding to unforeseen complexities in the data, such as unusual clustering or deviations from normality in outcome distributions. These limitations underscore the importance of sensitivity analyses to evaluate the robustness of the findings.

Conclusions

The statistical analysis plan for the ENERGISED trial demonstrates a strategic approach to addressing the complexities of pragmatic trials in real-world settings. By incorporating the estimand framework and advanced analytical methods, the plan ensures transparency and robustness while accommodating the challenges of missing data and intercurrent events. Beyond guiding the trial's final analysis, it offers an example for advancing best practices in the design and analysis of behavioural intervention trials in public health. While some methodological challenges remain, the pre-specified framework and comprehensive sensitivity analyses provide a solid foundation for interpreting the trial's findings and assessing their relevance for clinical and public health practice.

Abbreviations

GP	General practitioner
HADS	Hospital Anxiety and Depression Scale
HLS-Q12	European Health Literacy Survey Questionnaire
JITAI	Just-in-time adaptive intervention
MAR	Missing at random
MEQ	Morningness-Eveningness Questionnaire
MMRM	Mixed models for repeated measures
MVPA	Moderate-to-vigorous physical activity
PA	Physical activity
SF-12	12-Item Short Form Health Survey

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-025-08865-z.

Additional file 1: Statistical analysis plan checklist.

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Authors' contributions
Conceptualisation: BS, NK, MP, TV, TH, TY, MU, IM, DVD, SE, JP, MS, KJ, CW. Data curation: NK, VC, KM, JD, JK, TV, KJ. Formal analysis: VC, TV. Funding acquisition: TV, RC, BS. Investigation: KJ, MP, NK, KM, JK. Methodology: BS, NK, MP, VC, JK, AR, SE, DVD, IM, TH, JD, TY, TV, MU. Project administration: MS, BS, RC, TV. Resources: TV, JN, JK, MP, NK, JD, KM, RC, BS, JD. Software: JK, RC. Supervision: BS, TH, TY, AR, TV, MU, JP, SE, DVD. Writing—original draft: TV, TY. Writing—review and editing: all authors.

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Data availability
Not applicable.

Declarations

Ethics approval and consent to participate
The study protocol has been approved by the Ethics Committee of the General University Hospital, Prague (No. 49/20), and the study will be conducted in compliance with the principles of the Declaration of Helsinki. Informed consent to participate in the study will be obtained from participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Faculty of Physical Education and Sport, Charles University, Prague, Czech Republic. [2]Institute of General Practice, 1st Faculty of Medicine, Charles University, Prague, Czech Republic. [3]Faculty of Science, University of Hradec Kralove, Hradec Kralove, Czech Republic. [4]School of Health & Medical Sciences, City St George's University of London, London, UK. [5]Institute for Social Marketing and Health, University of Stirling, Stirling, UK. [6]Faculty of Physical Culture, Palacky University Olomouc, Olomouc, Czech Republic. [7]Department of Human Movement Studies, University of Ostrava, Ostrava, Czech Republic. [8]Department of Movement and Sports Sciences, Faculty of Medicine and Health Sciences, Ghent University, Ghent, Belgium. [9]Diabetes Research Centre, University of Leicester, Leicester, UK. [10]NIHR Leicester Biomedical Research Centre, University Hospitals of Leicester NHS Trust and the University of Leicester, Leicester, UK. [11]Alliance for Research in Exercise, Nutrition and Activity (ARENA), UniSA Allied Health and Human Performance, University of South Australia, Adelaide, Australia.

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