iSupport-PD: a digital intervention for care partners of people with Parkinson's and cognitive impairment

(iSupport-PD)

Statistical analysis and Health Economics Analysis Plan

Version 1

Date: 10/11/2025

Contents

Section 1: Administrative Information

Title	
Trial registration number; registry	ISRCTN16483203 Prospectively registered on 07/06/2024
Source of funding	National Institute for Health Research – School for Social Care Research
Purpose of SAP/HEAP	To describe the planned statistical and health economic analysis for the ISupportPD feasibility RCT

Approvals

The following people have reviewed the Health Economics Analysis Plan and are in agreement with the contents.

Role	**Name**	**Signature**	**Date**
Economist/Statistician	**Andrew McCarthy**		10/11/2025
Chief Investigator	**Annette Hand**		10/11/2025

This statistical and health economics analysis plan deals with the statistical and economic analysis of the iSupportPD feasibility study. This analysis plan was prepared following recruitment but prior to completion of data collection and database lock.

2: Design

The iSupport-PD study is a parallel, two-arm, feasibility RCT with a 1:1 allocation ratio and includes an embedded pilot health economic analysis and mixed-methods process evaluation. Participants will be recruited in the UK, and the study runs for 20 months (1st July 2024 to 28th February 2026). The trial is registered ISRCTN16483203.

The two arms of this feasibility trial are:

- Intervention (access to iSupportPD)
- Control (usual care/no access to iSupportPD)

Full details of the background and design of the trial are presented in the protocol (version 9.0, dated 13th January 2025).

3: Trial Objectives

The primary research aim of this study is to determine the feasibility of conducting a powered randomised controlled trial (RCT) to investigate the clinical and cost effectiveness of the SPARC intervention. Specifically, to determine the following:

1. Recruitment, retention, and attrition rates of participants in the trial
2. Understanding the comparator (what does usual support look like?)
3. Potential effect sizes and variability to inform sample size calculations in an effectiveness trial
4. Feasibility of collecting outcome data
5. Engagement with intervention

Secondary aims include:

1. Conducting a prospective economic evaluation to develop and refine methods for a subsequent definitive trial
2. Conducting a mixed-methods process evaluation to explore intervention and trial acceptability

4: Randomisation

Randomisation will be performed on a 1:1 basis by computer using dynamic allocation, in particular minimisation, to ensure groups are balanced for carer age, relationship to person with PD, gender. Use of dynamic allocation will also protect against subversion of randomisation. Allocation will be hidden using the sealed envelope method whereby the information needed for randomisation, collected at baseline, will be placed in an opaque sealed envelope by a researcher and given to a separate researcher to conduct the randomisation independently.

5: Outcomes

5.1 Primary outcome

The primary outcome for this study is to determine the feasibility of conducting a larger powered RCT. This will include outcomes such as successful recruitment to target, data collection completeness, intervention engagement, study attrition rate.

Data on numbers of participants identified, recruited, commences and finished intervention will be collected during the trial and reasons for declining participation or withdrawal will be recorded where possible. Feasibility of outcome measures and data collection will be

measured as number of participants completing pre and post follow-up outcome measures.

5.2 Secondary Outcomes

Secondary outcomes include validated outcome measures, NHS and social care resource use and other cost data (health economics), participant demographics such as age, relationship to person with Parkinson's, gender.

Validated outcomes measures can be grouped into carer burden, mental health, process, and quality of life measures. Caregiver burden will be measured using the short form 12-item Zarit Burden interview (ZBI-12). Item responses range from 0 (never) to 4 (almost always), and higher scores indicate greater distress.

Mental health measures consisted of scales to capture depression and anxiety. Depression will be measured using the Center for Epidemiologic Studies Short Depression Scale (CES-D-10). The CES-D-10 consists of 10 questions each with 4 responses from 'rarely or none of the time (less than 1 day)' to 'all of the time (5-7days)'. Anxiety will be measured using the generalised anxiety disorder scale (GAD-7 scale) which consist of asking caregivers to respond to seven questions around different areas of anxiety they have felt over the previous two weeks, each with four possible responses from 'Not at all" to "Nearly every day".

Process measurements include resilience, quality of relationship, self-efficacy, and carer burden. Resilience will be measured using the Resilience Scale (RS-14) which consist of 14 questions grouped into areas of self-reliance, purpose, equanimity, perseverance, and authenticity. Each question has a response between 1 (strongly disagree) to 7 (strongly agree). Quality of relationship will be measured using the Dyadic Relationship scale. This consist of 11 questions measuring the impact of the provision and receipt of family care. There are four levels of response to each question. Strongly Agree (0) to Strongly Disagree (3). Self-efficacy will be measured using the General Self-Efficacy scale(1) which consists of 10 questions with 4 responses to each question from 'not at all true' to 'Exactly True'. The positive aspects of caregiving scale (PACS) ((2)) consists of nine items related to positive aspects of caregiving each with a five response scored Likert scale from 'disagree a lot (1)' to 'agree a lot (5)'. An overall PAC score can be calculated (ranging from 9 to 45) with a higher score reflecting a more positive perception of the caregiving experience.

Quality of life measures include the Parkinsons Disease Questionnaire for carers (PDQ-C) will be used to measure quality of life of carers. The PDQ-C includes 29 questions covering different aspects of caring, with five response scale from 'never' to 'Always'. This is a validated measure for measuring quality of life for carers of persons with Parkinsonism and other related disorders. Health related quality of life will be measured using the EuroQol-5 Dimension EQ5D-5L(3). The EQ- 5D- 5L comprises five domains each assessing a specific dimension of health- related quality of life (mobility, self- care, usual activities, pain and anxiety and depression) with five response levels ('no problems', 'slight problems' 'moderate problems', 'severe problems' and 'extreme problems'). In addition, social care related quality of life will be measured using the ASCOT-Carer SCT4. This is a version of the Adult Social Care Outcomes Toolkit (ASCOT) designed for carers and consists of seven questions focused on areas of quality of life important to carers and sensitive to outcomes of social care services (occupation, control over daily life, self-care, personal safety, social participation and involvement, space and time to be yourself, feeling encouraged and supported). Each question consists of for response options (ideal, no needs, some needs, high-level needs).

5.3 Follow-up

Online questionnaires will be used as the primary mode of data collection. Participants will be sent a personalised link to self-complete questionnaires online using Qualtrics. Data will be collected at baseline (T0),), 3 months after baseline (T1), 6 months after baseline (T2), and 12 months after baseline (T3). Baseline measure will be collected prior to randomisation and will include demographic data such as age, gender, ethnicity, marital status, sexual orientation, socioeconomic status, education level, carer relationship, usual carer support, length of caring. Where data collection surveys are not completed a reminder will be sent via email to prompt participants to complete. After this, researchers will contact participants and collect data through interview via telephone or internet-based service. Although effort will be made to obtain follow-up data as close as possible to the relevant timepoints, it is anticipated that there may be some variation. T1, T2, and T3 follow-up will be acceptable up to 2 weeks early and 4 weeks late. Data will be stored on a secure password protected, purposely designed electronic database. Each participant will be randomly assigned a trial identify code at the point of their randomisation for use on CRF forms, electronic database, and other trial documentation. CRF data and electronic forms will be treated as confidential documents and held securely in accordance with regulations. The researcher will make an independent, separate, and confidential, record of participant name, age, date of birth, and trial number to permit identification of all trial participants as needed.

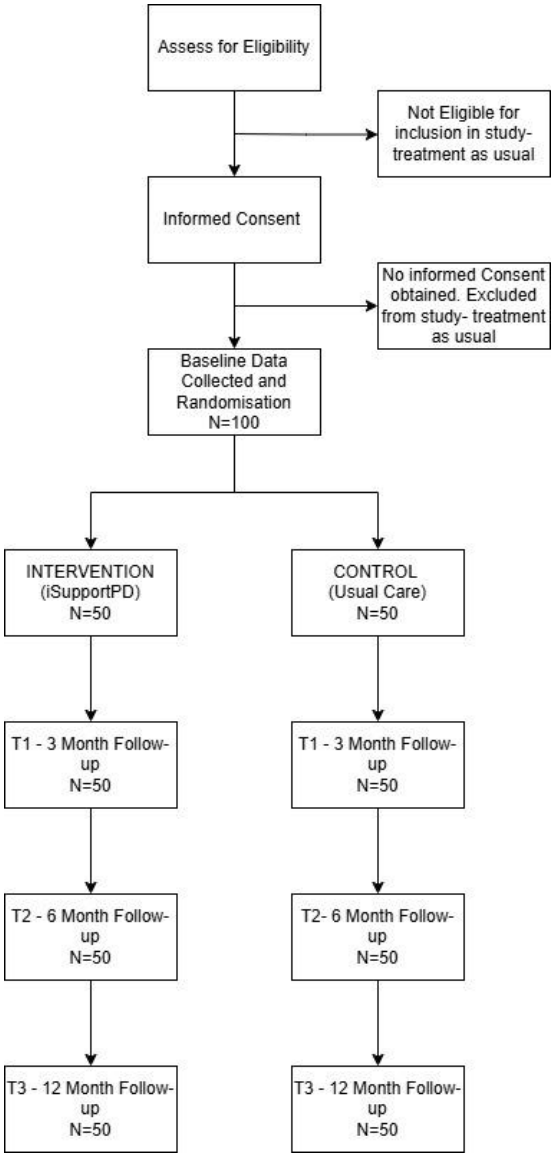

Figure 1: Planned flow of participants through trial

6: Data

6.1Data monitoring

Trial processed and data will be monitored throughout the trial with updated provided monthly at the trial management group meetings. Data collected during the course of the trial will be checked during the trial to offer quality assurance. As this is a feasibility trial, quality assurance will also allow the team to assess issues such as incomplete data collection forms, which may suggest misunderstanding, unwillingness to complete certain questions, or misunderstanding of data collection forms. This will contribute to the findings of the feasibility study and allow flexibility and changes to trial processes during the trial (with changes to the protocol noted and ethical approval for adjustments sought where necessary.

All study documentation will be retained in a secure location during the conduct of the study. Personal identifiable details such as names and contact details will be retained on a password protected database until required and then destroyed. All electronic data will be stored on secure network systems, to which only the relevant study personnel will have access. The dataset will be anonymised and stored securely

6.2 Sources of data

The Questionnaires (CRFs) consist of:

-Screening form

- Baseline questionnaire

-3 Month Follow-up questionnaire

-6 Month Follow-up questionnaire

-12Month Follow-up questionnaire

6.3 Management of datasets

The CRF forms are completed online. These online completed questionnaires are then downloaded and stored on a secure database. Each questionnaire will undergo a comprehensive data validation including: checks for completeness, appropriate data formatting, range checks. At the end of the trial follow-up, the dataset will be 'softlocked' and data quality will be checked across the whole dataset to check for consistency and any requested queries/amendments recorded. Once resolved, the database will be 'hard locked' where no further changes to the database will be allowed. Any further data changes/assumptions will be documented.

7: Analysis

All analyses will be conducted in STATA v15, under the principles of intention to treat (ITT) according to participant randomisation. The trial will report according to The Consolidated Standards of Reporting Trials (CONSORT) extension for reporting feasibility trials

7.1 Screening, eligibility, recruitment and follow-up data

For each time point, the number of questionnaires due and returned will be summarised, by arm and overall. This will detail how many were skipped, and for what reason.

Participants in this trial can withdraw from:

- Follow-up
- Fully (including death of the participant).

The number of withdrawals will be detailed by arm, by type. Additionally, the point at which the withdrawal occurred will be summarised.

7.2 baseline data

All participant baseline data will be summarised descriptively by trial arm both as randomised and as analysed in the primary analysis. No formal statistical comparisons will be undertaken. Continuous measures will be reported as means and standard deviations and categorical data will be reported as counts and percentages.

7.3 Statistical Analysis

Descriptive statistics will be used to determine the feasibility of conducting a larger powered randomised controlled trial. Analysis of outcome data will be conducted using an intention to treat approach, with patients analyses according to their treatment assignment. It will not be possible to collect outcome data for those who discontinue participation in the study. The data collected from outcome measures will be presented using summary statistics and differences

between intervention and control calculated at each follow-up points along with 95% confidence intervals. This data will help inform treatment effect estimates and sample size requirements for a larger powered RCT.

Progression criteria has been designed according to The Consolidated Standards of Reporting Trials (CONSORT) extension for reporting feasibility trials (4) and will enable interpretation of the findings of the feasibility study and inform whether a larger powered RCT is possible. Progression criteria will be assessed on a traffic light system of green/amber/red zones. Successful outcome of the feasibility trial would be to have all criteria assessed as green zones, suggesting no adjustments would be required for a future RCT. It is anticipated that progression to a future RCT would still be possible with a combination of amber and green zones but with potential adjustments implemented to mitigate risks highlighted in this feasibility study. Any red zone criteria would indicate that either the RCT trial design, or processes will need to be overhauled for any future RCT. All thresholds have been set based on levels that would enable completion of the trial objectives (Green without adaptation, Amber with adaptations to trial processes, Red/stop would not be possible to complete):

7.5 adverse events

It was not anticipated that any adverse events would occur in this trial. As such, no adverse events will be reported for this study

7.6 Protocol non-compliance/deviation

Any protocol deviations and instances of non-compliance will be summarised.

8 Health Economics Analysis plan

8.1 Aims

Conducting a prospective economic evaluation to develop and refine methods for a subsequent definitive trial

8.2 Analysis

8.2.1 Costs

The use of health and social care services will be converted into costs by combining data on the use of each specific service with a unit cost for that service. For example, the cost of the GP appointments will depend upon how many appointments took place and the price per unit of that appointment. Costs will be estimated based on the data provided from “within the study” CRFs supplemented by information from the literature, data drawn routine UK health service databases, and social care services. At the end of the study, costs will be estimated for each participant in each treatment group. The specific resource use categories included in the cost-effectiveness analysis will be:

(1) Cost of iSupportPD. This will include the cost of hosting, running, and maintaining the website.

(2) Costs of resource use at follow-up. These will also include costs of resource utilization within primary, community, secondary and personal social service settings.

Costs, where relevant, will include the variable cost and a portion of the fixed cost related to the lifetime of the resource and how often it can be used(5). For each participant use of services will be multiplied by appropriate unit costs to calculate total cost for each participant. Unit costs for healthcare services will be obtained from standard sources such as NHS reference Healthcare Resource Group (HRG) tariff(6) or Unit costs of Health and Social Care(7) for contacts with primary care, community and social care. Costs will be estimated using 2021/22

prices. The most recent unit costs will be used where possible, with unit costs prior to 2021/22 being inflated using the relevant inflation index(7).

8.2.2 Health-related quality of life

Quality of life will be measured using EQ-5D-5L. Utilities values will be mapped to the EQ-5D-3L UK specific value set(3). Utility scores will be combined with length of life over the study follow-up to calculate QALYs, using an area under the curve approach and assuming linear extrapolation between time points(8). Specifically, the area under the curve equates to the total QALY value where QALYs are calculated by multiplying duration of time in a health state by the utility score (equation 1).

$$\text{Total QALYs} = \left(\frac{u1+u2}{2} * p1\right) + \left(\frac{u2+u3}{2} * p2\right) + \cdots (1)$$

Where u is the EQ-5D-5L utility value for each time period (1,2,3…) and p is the difference between the two time periods. In addition, the social care-related quality of life (SCRQoL) will be measures using the Adult Social Care Outcomes Toolkit (ASCOT) for carers.

8.3 Cost-effectiveness analysis

Both a cost effectiveness and cost utility analysis will be conducted from a personal health and social care services and a societal perspective. The cost utility analysis will be based on EQ-5D quality adjusted life years (QALYs) and both will estimate costs

Our analysis will take both an NHS and personal social services (PSS) and a societal perspective as we expect costs and savings will also accrue to family members. Incremental cost effectiveness ratios (ICER) and cost effectiveness acceptability curves (CEACs) will be produced comparing provision of iSupport-PD vs usual care. The economic analyses will follow CHEERS guidelines(9).

All health economic outcomes (resource use, costs, QALYs) will be described with the appropriate descriptive statistics. The continuous and count outcomes will be expressed as mean ± standard deviation or medians and inter-quartile range where appropriate and dichotomous and categorical outcomes will be presented as absolute numbers and percentages. Analysis of costs and outcomes (QALYs. SQALYs) will estimate the mean differences (with a bootstrapped 95% confidence interval) between the intervention and control groups(10). For each study participant a total cost and a QALY score will be estimated.

Total costs and total QALYs for each patient will be estimated using a pattern mixed linear regression model to estimate total costs and total QALYs. Each model will include the following predictors:

- Allocation: Intervention or Control
- Time
- Allocation x time interaction term
- Baseline utility score
- Correlation of observations within participants over time, modelled by a covariance structure – random effect.

The joint estimates of costs and effects from these models will be combined in an incremental analysis between intervention and control groups and will be presented as the point estimate of

mean incremental cost-effectiveness ratio (ICER) for intervention versus control. The ICER will be calculated as difference in costs divided by difference in effects (QALYs) between two interventions. Measures of variance for the joint incremental costs and effects will be obtained using non-parametric bootstrapping and presented graphically using the cost-effectiveness plane and cost-effectiveness acceptability curves.

To help identify the optimal approach, the net monetary benefit (NMB) framework will be used, where the NMB for a given strategy is equal to the accrued QALYs multiplied by the ceiling ratio (CR) of willingness to pay (WTP) per QALY, minus the strategy costs. Thus,

NMB = (QALYs * CR) - Costs

Although there are currently no agreed cost-effectiveness thresholds regarding social care interventions, values of £20,000 and £30,000 per QALY will be presented in the main results, alongside a cost-effectiveness acceptability curve presenting cost-effectiveness of values between £0 and £100,000 per QALY.

8.4 Missing data

Missing data will be quantified per data item (%). Ignoring small amounts of missing data (e.g., <5% of the observations) is acceptable if the amount and pattern of missing data are similar across treatment groups and a reasonable case can be made that doing so is unlikely to bias treatment group comparisons. As total cost is calculated as a sum of numerous components, if one component is missing then the total cost will be missing. Such complete case analysis may introduce bias if those with complete data differ from those with partial data. The method to handle missing data will be grounded in a plausible assumption regarding the missing data mechanism. Rubin's framework will be utilised for classifying missing data in order to define assumptions and choose an appropriate analysis method for the base case.(11) If *Missing At Random* (MAR) is suggested, we will incorporate multiple imputation with chained equations (MICE) to deal with missing cost and utility data. Data are missing at random (MAR) if the probability that data are missing is independent of unobserved values, given the observed data (including previous outcome measurements). Therefore, any systematic differences between the observed and unobserved values can be explained by differences in observed variables. Although the linear mixed effect model proposed for the cost-effectiveness analysis can also be used to deal with missing data under a MAR assumption, it has several limitations compared to multiple imputation(12). Firstly, as the linear mixed model is pre-specified, it is inflexible and cannot adjust for potential observed variables which impact missing data. This contrasts with multiple imputation in which missing data is imputed using a separate model, which can be adjusted for observed variables driving missing data. Secondly, multiple imputation allows further flexibility and potential sensitivity analysis to be conducted around the imputed missing data variables. Furthermore, combination of multiple imputation around a linear mixed model analysis has been identified as more efficient in trial-based cost-effectiveness analysis compared to just using linear mixed effects models alone(13).

A second consideration relates to the nature of costs, which as discussed previously is built up from numerous components. A balance needs to be struck between maintaining the data structure (hence imputing at more disaggregated level) and achieving a stable imputation model (which becomes more difficult as more variables with missing data are added(14). The choice of approach should be informed by the structure of the data, the pattern of missing data and by testing a variety of approaches. For costs, imputing at the total cost level is likely to be appropriate when the different types of resource use that make up the cost have the same pattern of missing data. We anticipate that analysis and imputation of costs will be conducted

at the aggregate level as this has been reported to be appropriate(12). We anticipate that missing EQ-5D data will not typically be domain specific and will be either reported or not in its entirety. Therefore, we anticipate, missing QALY data to be analysed and imputed at the aggregate score level(15).

Following analysis of the data sensitivity analysis will be conducted regarding methods for imputation. In particular, pattern mixture modelling will be used to conduct sensitivity analysis to allow potential plausible changes to missing data in order to investigate possible MNAR scenarios(12).

8.5 Sensitivity analysis

Sensitivity analysis will be conducted to explore uncertainty.Measurement uncertainty of costs and QALYs will be explored though deterministic sensitivity analyses. This is where one parameter is varied at a time and the impact on the ICER is quantified. Where missing data is limited and MCAR is assumed, parameter uncertainty will be explored through non-parametric bootstrapping of the model in the estimation of cost and QALY differences. Bootstrapping allows us to capture the second order uncertainty of cost and QALY estimates and subsequent ICERs estimates(16). Cost-effectiveness planes will present the uncertainty around the parameter estimates for Cost and QALY differences between intervention and control. Furthermore, cost-effectiveness acceptability curves will allow a graphical representation of the probability of an intervention being cost-effective across a range of cost-effectiveness thresholds. Where missing data is MAR, then multiple imputation will be used with sensitivity analysis will be conducted to explore potential MNAR through use of pattern mixture models.

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