Statistical Analysis Plan for: The iPACK-HD Pilot Trial

1 Administrative Information

1.1 Statistical Analysis Plan (SAP) Summary Table

TRIAL FULL TITLE	Inhibit Progression of coronary Artery Calcification with vitamin K in HemoDialysis patients: The iPACK-HD Study
TRIAL REGISTRATION	https://clinicaltrials.gov/ct2/show/NCT01528800
PROTOCOL PUBLICATION	Holden et al. *Canadian Journal of Kidney Health and Disease* (2015) 2:17 DOI 10.1186/s40697-015-0053-x[1]*
CURRENT PROTOCOL DATE	2021-05-28
TRIAL PRINCIPAL INVESTIGATOR	Dr. Rachel M. Holden
TRIAL SENIOR STATISTICIAN	Andrew G. Day
STATISTICIAN(S) PERFORMING ANALYSIS	Andrew G. Day and Patrick A. Norman
SAP AUTHOR(S)	Andrew G. Day and Patrick A. Norman
SAP CONTRIBUTOR PRIMARY AFFILIATIONS	AGD and PAN: Kingston General Health Research Institute, Kingston Health Sciences Centre, Kingston RMH: Queen's University, Kingston CSB: Queen's University, Kingston
SAP DATE	2021-06-21
SAP STATUS	Version 1.0 - Complete
SAP REVISION HISTORY	None from first finalized version 1.0
STATUS OF TRIAL AT TIME OF SAP FINALIZATION OF V1.0	Enrollment completed. Blinded data cleaning completed. Some pooled analysis generated, but no by arm outcome results produced yet.

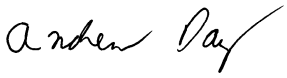
*The protocol publication describes the subsequent full study while this SAP is for the feasibility pilot study that was initially intended to be rolled into the full study.

1.2 Signatures

I have read and approve the enclosed SAP dated **2021-06-21** for the iPACK-HD trial:

Senior Statistician & SAP Author

Name: Andrew G. Day

Signature: 

Date: June 21, 2021

Statistician Performing Analysis (other than senior statistician) & SAP Author

Name: Patrick A. Norman

Signature: 

Date: June 22, 2021

Trial Project Leader

Name: Corinne S. Babiolakis

Signature: 

Date: June 21, 2021

Principal Investigator

Name: Dr. Rachel M. Holden

Signature: 

Date: June 22, 2021

1.3 Purpose, Usage and Target Audience of This Document

This document provides a detailed description of the analysis plan for the iPACK-HD trial. This document is meant to be used in conjunction with the study protocol. This document does not subsume the protocol, but several elements of the protocol, such as the sample size justification, are reproduced herein for completeness. This document has the following purposes:

1. Provides a written agreement between the Principal Investigator, lead study statistician and data analysts regarding exactly what analysis will be performed.
2. Provides a record of the analysis plan specified prior to unblinding treatment assignments that may be included as supplementary study documentation with the primary study publication.
3. Provides clear specifications for the analyst(s) performing the data filtering/transformation, variable derivations, statistical analyses, and report generation.

This document follows the guidance published in JAMA by Gamble et al (2017) and referenced at https://www.equator-network.org/reporting-guidelines/guidelines-for-the-content-of-statistical-analysis-plans-in-clinical-trials/.[1] The SAP checklist is completed in Appendix A.

1.4 SAP Contributors and Signatories

Andrew Day, Patrick Norman, and Dr. Rachel Holden drafted the SAP. Andrew Day drafted the statistical elements of the SAP, Patrick Norman edited the outcomes and statistical elements, and created the corresponding analysis dictionary, Corinne Babiolakis added details regarding the trial operation and data management, and Dr. Rachel Holden helped interpret the protocol and prioritize outcomes, analyses, and validation. All contributors provided critical review and editing to all parts of the SAP. The finalized version of the SAP was approved and signed off by all contributors.

2 Contents

3 Introduction to Study

3.1 Background and Rationale

Cardiovascular disease, which is due in part to progressive vascular calcification, is the leading cause of death among patients with end stage kidney disease (ESKD) on dialysis. A role for vitamin K in the prevention of vascular calcification is plausible based on the presence of vitamin K dependent proteins in vascular tissue, including matrix Gla protein (MGP). Evidence from animal models and observational studies support a role for vitamin K in the prevention of vascular calcification. A large-scale randomized controlled trial (RCT) is needed to investigate the effect of vitamin K supplementation on the progression of vascular calcification in patients with ESKD, a group at risk for sub-clinical vitamin K deficiency. But before undertaking a definitive large-scale RCT, a pilot study is required to assess the plausibility of the hypothesized intervention effect, and the feasibility of our group undertaking a large-scale RCT.

3.2 Overall Aim

The overall aim of this pilot trial is to assess feasibility and provide preliminary outcome results to support the design and funding application of a definitive phase II or III RCT to determine whether vitamin K treatment prevents coronary artery calcium (CAC) progression in hemodialysis (HD) patients.

3.3 Study Objectives

The **primary objective** of this trial is to pilot study procedures and assess the feasibility of implementing a larger scale definitive phase II or III trial assessing the same intervention in the same population as this trial.

The **secondary objective** of this trial is to explore the impact of vitamin K on CAC, clinical outcomes and vitamin K biomarkers.

The **tertiary objective** of this trial is to collect data that can be combined with the VitaVasK study to perform an individual patient data meta-analysis (IPD-MA). The IPD-MA is registered at PROSPERO (ID= 123104), and the analysis plan will be detailed in a separate document.

3.4 Study Hypotheses

We hypothesize that an adequately powered RCT to test whether vitamin K treatment inhibits the progression of CAC in patients with ESKD requiring HD treatment will be feasible (see section 7.1.1).

We hypothesize that vitamin K treatment will improve vitamin K biomarkers, reduce inflammation, prevent progression of CAC and valve calcification, reduce bone fracture, and improve body composition over 12 months.

4 Study Methods

4.1 Trial Design

The current iPACK-HD pilot trial is a prospective randomized parallel two-arm double-blind 3-centre feasibility and exploratory phase II trial in adults with ESKD requiring dialysis who have a baseline CAC score ≥30 Agatston units (AUs). Eligible patients were randomly assigned 1:1 to either the experimental treatment group (10 mg of phylloquinone thrice weekly) or to a control group (matching placebo thrice weekly). The initial plan was to roll patients from this pilot feasibility trial into a full definitive phase II RCT. However, due to pragmatic considerations including challenges obtaining Canadian Institutes of Health Research (CIHR) funding, this study is now a stand-alone pilot feasibility and exploratory phase II trial. If the results of this trial suggest that a large scale definitive RCT is warranted, then the feasibility and preliminary results will be used to help support the design and funding application for the definitive trial.

The protocol for the planned definitive RCT is published in the Canadian Journal of Kidney Health and Disease.[2] The protocol for this pilot feasibility trial is a successful grant application from the March 2015 CIHR RCT committee.

4.2 Randomization

Randomization was performed using web-based Central Randomization System (CRS) at the Clinical Evaluation Research Unit (CERU) at Kingston Health Sciences Centre (KHSC) - Kingston General Hospital (KGH) site. Randomization was concealed and stratified by site and diabetes mellitus using permuted blocks of random sizes disclosed as 2, 4 and 8 after enrollment completion. The prevalence of CAC is significantly higher in patients with diabetes mellitus; therefore, it was critical that the groups be balanced for this risk factor. Research Coordinators screened patients requiring HD. A de-identified log of screened patients was kept, recording inclusion and exclusion criteria. Reasons for being eligible but not enrolled were recorded. Once a Research Coordinator determined that a patient was eligible, they were approached for informed consent which was obtained either directly from the patient or their substitute decision maker. After obtaining informed consent, the Research Coordinator arranged for a CT scan to determine the CAC score. After the date of the CT scan results, the study drug had to be initiated within 4 weeks. This 4 week window provided sufficient time to arrange for the study treatment to be ordered, allocated, prepared, and dispensed. If the CAC score was <30 AUs, the patient received a letter that explained that they were ineligible for the trial based on minimal or no calcium present in the arteries in their heart. The Principal Investigator's contact information was contained in the letter in the event that a patient had further questions. If the CAC score was ≥30 AUs, the Research Coordinator contacted their local hospital pharmacy. A designated research pharmacist or pharmacy technician accessed the secure web-based CRS and obtained the patient's treatment allocation. The research pharmacist or pharmacy technician then prepared the study medication according to the assigned treatment allocation. The blinded medication was transported to the dialysis unit for administration to the patient.

4.3 Sample Size Considerations

The original protocol sample size is quoted below:

> The multicenter pilot study will enroll a total of 50 patients from 3 Canadian Centers and 1 US site. We will combine these data with 30 patients from the single-center iPACK-HD pilot study at Queen's University for a total sample size of 80 patients. Table 1 [in appendix B] describes the probability of meeting feasibility outcome 1 to 4 under a range of true population values. With 80 patients, the overall rate of CAC progression will have at least a 63% and 95% chance of being estimated within ± 5% and ± 10% of the true population value respectively. Therefore, the total pilot sample size (n=80) should be adequate to reliably assess the feasibility of the fully-powered multi-center study. We believe a total sample size of 30 patients from Queen's University and 50 patients from 3 Canadian sites and 1 US site for a total of 80 patients will be adequate to thoroughly pilot the trial procedures and obtain acceptably accurate estimates for the study outcomes. The pilot study will not be used to determine effect size but will provide further information regarding the distribution of our primary outcome that will allow us to further refine a definitive sample size estimate. We anticipate that, to optimally power the definitive Phase II study, we need approximately 430 patients.

Since the original protocol did not anticipate that we would perform any by-arm comparisons, these are not addressed in the above sample size consideration quoted from the pilot protocol. Without adjustment for covariates or multiplicity of outcomes, a sample size of 40 per arm would achieve 80% power at a two-sided alpha=0.05 to compare means between groups using the two-sample t-test for approximately normal outcomes (regardless of equality of variance) if the population mean difference between arms was 63% of the within group standard deviation. If the Wilcoxon rank-sum test was used, we would achieve 80% power if the concordance index between the treatment arm and outcome value was 0.68. For binary outcomes (such as mortality or fracture), the sample size would achieve at least 80% power as long as the absolute difference in proportions between groups was 30%.

4.4 Framework

This pilot trial is both a feasibility trial and an exploratory superiority trial. Feasibility outcomes will be pooled by arm and compared to pre-established targets (with the exception of feasibility outcome #5). CAC, clinical outcomes and vitamin K biomarkers will be compared between arms using an exploratory superiority framework.

4.5 Statistical Interim Analysis

No statistical interim analysis was performed.

4.6 Timing of Final Analysis

All outcomes will be analyzed after all data is collected and cleaned and after finalization of this statistical analysis plan.

4.7 Timing of Outcome Assessments

For the purpose of this Phase II study, we will evaluate study exit outcomes and process measures. We will evaluate longitudinal outcomes (every 4 months) for certain biomarkers.

5 Statistical Principles

5.1 Confidence Intervals and P-values

Feasibility outcomes will be provided descriptively as rates or proportions. To meet the feasibility target, the point estimate of the observed feasibility metric simply needs to meet or exceed the target.

Most variables will be described within arm and compared between arms using two-sided p-values stratified by site and diabetes status. We will consider a p-value <0.05 to indicate statistical significance. In this exploratory phase II study, we will not formally adjust p-values for multiplicity of tests, but will consider the potential type I and type II errors in our interpretation of results. False discovery rates may be used to help interpret nominal statistical significance of the unadjusted p-values.

5.2 Analysis Populations

All analyses will use a modified intent-to-treat population using all available data. However, one patient who developed an exclusion criteria post-randomization but did not receive any study intervention will be excluded from primary analysis. Thus, all randomized patients will be analyzed in the arm they were randomized to regardless of treatment compliance or data completion.

6 Trial Population

6.1 Screening Data

Baseline patient characteristics of randomized patients will be compared using descriptive statistics only to help assess the representativeness of the sample. Continuous variables will be described as median [Q1 to Q3].

6.2 Eligibility Criteria

Published at https://clinicaltrials.gov/ct2/show/NCT01528800 and Holden et al. *Canadian Journal of Kidney Health and Disease* (2015) 2:17 DOI 10.1186/s40697-015-0053-x.

6.3 Screening, Recruitment, Patient Flow/Follow-up

A CONSORT style flow diagram will present the numbers of patients screened and all reasons excluded prior to randomization. The table will also include the number randomized to each arm and the number used in the primary analysis in each arm with reasons for the exclusion of randomized patients.

6.4 Baseline Characteristics

Baseline characteristics will be described by arm and overall using descriptive statistics only. Categorical variables will be described as counts (%). Continuous variables will be described as median [Q1 to Q3].

The following baseline patient characteristics will be described:

- Age, sex, ethnicity, CKD cause, number of comorbidities (0, 1, 2, >2), Charlson Comorbidity Index, weight, height, BMI, abdominal waist circumference, smoking history, parathyroidectomy, primary HD access site, primary HD access type, time from primary HD access installed to randomization, time from start of HD to randomization
- Baseline concomitant medication use
    - Calcium-based phosphate binders: calcium, calcium acetate, and calcium carbonate
    - Non-calcium-based phosphate binders: sucralfate, sevelamer hydrochloride (HCl), and lanthanum carbonate
    - Calcitriol
    - Vitamin D: ergocalciferol and cholecalciferol
    - Calcimimetic: cinacalcet HCl
    - HMG-CoA reductase inhibitors: atorvastatin calcium, fluvastatin sodium, lovastatin, pravastatin sodium, simvastatin, ezetimibe, rosuvastatin calcium, and amlodipine besylate/atorvastatin calcium
    - Angiotensin converting enzyme (ACE) inhibitors: benazepril HCl, captopril, perindopril erbumine, quinapril HCl, ramipril, enalapril, fosinopril sodium, lisinopril, and lisinopril/hydrochlorothiazide
    - Angiotensin II receptor blockers (ARBs): losartan potassium, irbesartan, candesartan cilexetil, telmisartan, eprosartan mesylate, and valsartan
    - Anti-platelet therapy: acetylsalicylic acid, clopidogrel bisulfate, and dipyridamole
- Baseline blood measures
    - Clinical lab values:
        - Hemoglobin, albumin, Kt/V, creatinine, and fibroblast growth factor-23 (FGF-23)
        - Lipid profile: high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, and total cholesterol
        - Parameters of mineral metabolism: phosphate, calcium, parathyroid hormone (PTH), and alkaline phosphatase (ALP)
    - Vitamin K status: protein induced by vitamin K absence or antagonist II (PIVKA-II), growth arrest-specific 6 (Gas6), phylloquinone/vitamin K1 (PK), vitamin K2 (MK4), osteocalcin Gla, osteocalcin Glu, osteocalcin Gla to Glu ratio, percent of osteocalcin undercarboxylated, and dephosphorylated-uncarboxylated MGP (dpucMGP)
    - Biomarkers of inflammation: c-reactive protein (CRP), interleukin 6 (IL-6), leptin, insulin, glucose, homeostasis model assessment-insulin resistance (HOMA-IR)
    - Vascular inflammation variables: myoglobin, calciprotectin, neutrophil gelatinase-associated lipocalin, matrix-metalloproteinase 2, osteopontin, myeloperoxidase, serum

amyloid A, insulin-like growth factor binding protein-4, intercellular adhesion molecule 1, vascular cell adhesion protein 1, matrix-metalloproteinase 9, and cystatin C
    - Vitamin D metabolites: 1,25-OH-D3, 25-OH-D2, percent 25D that is D2, Total 25D, 24,25(OH)2D3, 25D3:24,25D3, 24,25D3:25D3, 3epi25-OH-D3, 3epi25-OH-D3(%), 1,25(OH)2D3, 1,24,25(OH)3D3, 1,25(OH)2D3:1,24,25(OH)3D3, 1,25(OH)2D3:1,24,25(OH)3D3
- Agatston and volume calcium scores and abdominal aortic calcification (AAC) scores
- Thoracic and lumbar vertebral fractures
- Body composition:
    - Cross-sectional area (cm^2 or cm^2/m^2): muscle, normalized muscle, intermuscular adipose tissue (IMAT), visceral adipose tissue (VAT), subcutaneous adipose tissue (SAT) and total adipose tissue (TAT)
    - Radiodensity (HU): muscle, IMAT, VAT and SAT

7 Analysis

7.1 Outcome Definitions

7.1.1 Feasibility Outcomes (Primary)

The pre-specified primary outcomes are as follows:

	Outcome	Definition	Target
1	Recruitment rate	Number of participants recruited per month at each site (total eligible randomized patients per site divided by date of last randomized patient at that site minus date of first randomized patient at that site, with month defined as 30.4 days. This will exclude first phase of KGH enrollment), as well as an overall crude average of each site's rate.	>4.17 per month
2	Compliance with study medication	Proportion of prescribed doses received (divide received doses by prescribed for each patient to get a patient level measure before summarizing).	≥90% of prescribed
3	Dropout rate	Proportion of participants who dropped out from the trial (1-[% of randomized patients who either have a known date of death during the study period OR have a non-missing CAC value measured at least 6 months after randomization]).	<20%
4	Adherence to study protocol	Proportion of participants who adhered to the study protocol (90% study medication compliance and not dropped out) (all pooled).	≥80%
5	Rates of eligible patients consented and randomized	Proportion of eligible patients who were A) consented and B) randomized to the study.	No target

7.1.2 Secondary Outcomes

1) Coronary artery calcification progression:
a) the percent and absolute change of the Agatston and volume calcium scores (CT scan) will be assessed at study exit vs. baseline. Included measures will be: Total CAC, Left Main CAC, Right Coronary Artery CAC, Left Anterior Descending CAC, Circumflex CAC, and Posterior Descending Artery CAC.
b) the proportion of participants with a 15% or greater increase in Agatston and volume calcium scores will be assessed at study exit vs baseline.

2) Coronary artery calcification regression: the proportion of participants with a 10% or greater decrease in Agatston and volume calcium scores will be assessed at study exit vs baseline.

3) Aortic valve calcification progression: the absolute and percentage change of the Agatston and volume calcium scores (CT scan) will be assessed at study exit vs. baseline.

4) Mitral valve calcification progression: the absolute and percentage change of the Agatston and volume calcium scores (CT scan) will be assessed at study exit vs. baseline.

5) AAC score: the AAC score (mean score in L1-L4, mean number of positive segments, mean total severity using lateral lumbar spine radiographs) will be assessed at study exit vs. baseline.

6) Biomarkers of vitamin K status: Gas6, PK, MK4, osteocalcin Gla, osteocalcin Glu, osteocalcin Gla to Glu ratio, percent of osteocalcin undercarboxylated, and dpucMGP will be assessed at baseline, four, eight and study exit. PIVKA-II will be assessed at baseline and study exit.

7) Thoracic vertebral fractures: The prevalence and incidence of thoracic vertebral fractures (anterior and lateral radiographs) will be assessed at baseline and study exit.

8) Lumbar vertebral fractures: The prevalence and incidence of lumbar vertebral fractures (anterior and lateral radiographs) will be assessed at baseline and study exit.

9) Events of clinical interest:

   The presence or absence and total of the following events will be assessed across the study duration per patient:
   i) Hospitalizations
   ii) Cardiovascular events: acute coronary syndrome, congestive heart failure, stroke, transient ischemic attack, amputation, and cardiac (symptom-driven) (cerebral or peripheral) revascularization procedure, or cardiac arrest
   iii) Thrombosis: deep vein thrombosis and pulmonary embolism
   iv) HD access thrombosis. Fistula and/or graft thrombosis or dialysis catheter thrombosis
   v) Mortality: all-cause and cardiovascular cause

7.1.3 Exploratory Outcomes

1) Biomarkers of inflammation: these biomarkers (listed in Section 6.4) will be assessed at baseline, four months, eight months, and study exit.
2) Clinical lab values: Hemoglobin, albumin, Kt/V, creatinine, lipid profile (HDL, LDL, triglycerides, and total cholesterol), and parameters of mineral metabolism (phosphate, calcium, PTH, and ALP) will be assessed monthly. Serum FGF-23 will be assessed at baseline, four months, eight, and study exit.
3) Concomitant medication assessment: prescription of concomitant medications (listed in Section 6.4) will be assessed monthly. Average dosage and total exposure across the study duration will be assessed for calcitriol, other vitamin D drugs, and calcium-based phosphate binders.
4) Changes in body composition: body composition measures (listed in Section 6.4; L3 slice of ST scan) will be assessed for muscle atrophy and adipose tissue at baseline and at study exit.
5) Vascular inflammation variables: these variables (listed in Section 6.4) will be assessed at baseline, four months, eight months and study exit.
6) Vitamin D Metabolites: these metabolites (listed in Section 6.4) will be assessed at baseline, four months, eight months, and study exit.

7.2 Analysis Methods

The feasibility outcomes will be presented descriptively overall as rates or proportions. In addition, compliance with study medication, dropout rate, and adherence to study protocol will be compared by arm. Reasons for loss-to-follow-up and non-compliance will be tabulated.

For the binary outcomes, we will provide counts and percentages by arm and compare arms by the Mantel-Haenszel test stratified by site and diabetes (or Fisher's Exact Test for outcomes with less than 20 events or non-events).

This study has many continuous outcomes that are far from normally distributed. For all continuous outcomes, we will report medians and quartiles by arm and compare arms by the Van Elteren test stratified by site and diabetes. Selected continuous variables may be depicted by clustered boxplots comparing the two arms over time. Biomarkers assessed at multiple time points will have both absolute value and change from baseline compared by arm at each time point.

7.2.1 Assumption Checking

The statistical methods used will not require assessment of model assumptions or influence diagnostics. The primary feasibility outcomes, dichotomized CAC progression, and other categorical outcomes are simply proportions. The analysis of CAC progression as continuous, as well as all other continuous outcomes, will compare groups by the non-parametric rank-based Van Elteren (i.e., stratified Wilcoxon-rank sum test).

7.2.2 Subgroup Analysis

No subgroup analysis will be performed due to the small sample size.

7.3 Missing Data

The number of missing items will be presented by arm for each outcome. Imputation will not be performed for this feasibility/phase II pilot study.

7.4 Statistical Software

The analysis will be performed using SAS 9.4 TS level 1M6 and SAS/STAT version 15.1 under Microsoft Office Professional Plus 2010 version 14.0.7252.5000 (64-bit) and Microsoft Office Apps for Enterprise 365 (64-bit).

8 Quality assurance

8.1 Data Quality

Data was entered into REDCap by trained local site staff. Each user with access to REDCap had a unique username and password. Access to REDCap was secure and an audit trail was maintained to keep track of the username, time, and values of all data entry and modification. A custom secure randomization module was used to implement the randomization list and maintain concealment of future allocations. A custom query module was used to implement extensive value, range, and logical (including date sequence) data checks. Any violation of the pre-defined data checks triggered data queries that were tracked and required resolution (either correction or acceptance by central site staff) prior to data being marked as finalized.

We will also perform “back-end” checks on the SAS analytic database. We will identify any sequence of dates that is not sensible. For all continuous variables used in the analysis, we will use our outlier checking tool to generate boxplots by site with outliers labeled. This tool allows us to query and track all outliers so that we can perform one of three actions: 1) verify the outlier is true (these values will be included in the analysis), 2) correct the outlier, or 3) set the value to missing if it is truly incorrect but cannot be corrected.

8.2 Validation of SAS Database and Analysis

The study Principal Investigator and Project Leader will sense check all results to make sure they are not highly suspicious and that all counts are consistent with the patient flow diagram.

A second statistician who did not perform the primary analysis will independently verify the patient flow counts and re-analyze the main secondary outcome of CAC progression (measured by percent change in Agatston and percent change in the volume calcium scores), as well as the biomarkers of vitamin K status and inflammation.

9 References

1. Gamble C, Krishan A, Stocken D, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA 2017;318:2337-43.

2. Holden RM, Booth SL, Day AG, et al. Inhibiting the progression of arterial calcification with vitamin K in HemoDialysis patients (iPACK-HD) trial: rationale and study design for a randomized trial of vitamin K in patients with end stage kidney disease. Canadian Journal of Kidney Health & Disease 2015;2:17.

10 Appendix A: Statistical Analysis Plan (SAP) Checklist v 1.0 2019

Section/Item	Index	Description	Reported on page #
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Protocol Version	3	Reference to version of protocol being used	1
SAP revisions	4a	SAP revision history	1
	4b	Justification for each SAP revision	N/A
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	26a	Specification of outcomes and timings. If applicable include the order of importance of primary or key secondary end points (e.g., order in which they will be tested)	11-13
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	27b	Any adjustment for covariates	N/A
	27c	Methods used for assumptions to be checked for statistical methods	13
	27d	Details of alternative methods to be used if distributional assumptions do not hold, e.g., normality, proportional hazards, etc.	N/A
	27e	Any planned sensitivity analyses for each outcome where applicable	N/A

	27f	Any planned subgroup analyses for each outcome including how subgroups are defined	13
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Additional analyses	29	Details of any additional statistical analyses required, e.g., complier-average causal effect10 analysis	NA
Harms	30	Sufficient detail on summarizing safety data, e.g., information on severity, expectedness, and causality; details of how adverse events are coded or categorized; how adverse event data will be analysed, i.e., grade 3/4 only, incidence case analysis, intervention emergent analysis	12
Statistical software	31	Details of statistical packages to be used to carry out analyses	14
References	32a	References to be provided for nonstandard statistical methods	NA
	32b	Reference to Data Management Plan	NA
	32c	Reference to the Trial Master File and Statistical Master File	NA
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Taken from the paper: Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Doré C, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA. 2017;318(23):2337-43.

Abbreviations: CONSORT, Consolidated Standards of Reporting Trials; hbA1c, haemoglobin A1c; QoL, quality of life; SAP, statistical analysis plan.

11 Appendix B: Table 1 from the iPACK-HD Pilot Trial Protocol

Below we provide the probability of reaching the study's feasibility targets with 80 participants. We believe that a total of 80 participants are sufficient but not excessive to ensure that it is highly probable that the study's targets will be met if and only if they should be.

1. *Recruitment of trial patients in the multi-centre iPACK-HD pilot study: Successful recruitment in the multi-centre iPACK-HD pilot trial will be defined as enrolling 50 patients in 12 months from the 4 study sites in the multi-centre pilot study (average monthly accrual ≥4.17).* If the true accrual per month follows a Poisson distribution with a rate of 6 per month, as we expect based on recruitment rates in the iPACK-HD single-centre pilot study at Queen's University, then the chance of meeting the target will be 99.7%. On the other hand, if the true recruitment rate was an unacceptably low at 3 per month, then the chance of meeting the recruitment feasibility target will only be 1.6%.

2. *Compliance with study medication: Successful adherence will be defined as ≥90% of prescribed intervention being administered.* For true adherence rates of 80%, 85% and 95% the chance of meeting the target will be 1%, 13% and 98% respectively.

3. *Dropout rate: Successful rate of loss to trial completion will be defined as ≥ 80% of randomized patients completing the trial.* For true completion rates of 70%, 75%, 85% and 90% the probability of meeting the target will be 3%, 18%, 92%, and 99.8% respectively.