Statistical Analysis Plan (SAP)

Type 2 Diabetes Exemplar (T2DEx): An evaluation of a digital support service for North-West London

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Study Investigators:
Co-Principal Investigators: Professor Kausik Ray; Gianluca Fontana
Co-investigators: Dr Jack Halligan, Emanuela Falaschetti, Dr Victoria Cornelius

SAP Working Group:
Nicholas Johnson – Study Statistician
Emanuela Falaschetti – Senior Statistician

Version	Date	Author
0.2	11JULY2022	Nicholas Johnson

Approved by:

Name	Role	Signature	Date
Prof. Kausik Ray	Co-Principle Investigator		
Emanuela Falaschetti	Senior Statistician		
Nicholas Johnson	Study Statistician		

Type 2 Diabetes Exemplar (T2DEx): An evaluation of a digital support service for North West London (Protocol v4.0)

1. Contents

2. Abbreviations

ASCVD	**Atherosclerotic Cardiovascular Disease**
BP	**Blood Pressure**
CCG	**Clinical Commissioning Groups**
CRG	**Clinical Risk Groups**
DDS	**Diabetes Distress Score**
DP	**Decimal Place**
EPR	**Electronic Patient Record**
GP	**General Practitioner**
HCA	**Healthcare Assistant**
HCP	**Healthcare Providers**
NWL	**North-West London**
PN	**Practice Nurse**
PSM	**Propensity Score Matching**
SAP	**Statistical Analysis Plan**
SD	**Standard Deviation**
SUS	**System Useability Scale**
T2DM	**Type II Diabetes Mellitus**
VGC	**Video Group Consultation**
WSIC	**Whole of Systems Integrated Care**

3. Introduction & Study Summary

As the prevalence of Type 2 Diabetes Mellitus (T2DM) grows the burden on healthcare is increasing in the form of additional consultations, hospital outpatient visits, death and disability. T2DM represents a large part of the disease and cost burden of healthcare in North West London (NWL) to the value of £600m annually. Patients with T2DM constitute over 40% of all NWL admissions, with complications of type 2 diabetes representing a significant factor in the morbidity and cost associated with this chronic disease. To this end, there is an urgent need for healthcare professionals to provide the same or better care without increasing healthcare expenditure. Digital interventions/ healthcare solutions may provide an opportunity to achieve these goals.

The Type 2 Diabetes Exemplar Programme has designed the Fresh Start service for use in primary care to demonstrate how real-world data and technology can improve health outcomes for T2DM patients. Fresh Start has been designed by the Discover-NOW Health Data Research Hub in a cross-industry collaboration between North-West London CCGs, NHSX, AstraZeneca, Imperial College Health Partners and Huma. Fresh Start is offered to patients at high risk of developing complications from T2DM and combines video group consultations, a remote monitoring solution, and educational content.

Fresh Start seeks to support population stratification and strengthen population health management by providing better-tailored services and proactive interventions, particularly among population groups more at risk of the adverse impacts of COVID-19. Mortality risk from COVID-19 is approximately 25% higher in patients with T2DM and shielding has resulted in reduced primary care appointments for patients with T2DM. This has created an immediate need for primary care to adapt and provide remote care pathways to patients. Digital-first remote pathways could make care more accessible while finding time and cost efficiencies. By combining remote monitoring and video group consultations, we can inform the patient-clinician conversation making remote care in group settings safer, efficient and more personalised.

It is our opinion that generating credible evidence for digital health solutions remains an industry-wide challenge, hindering widespread adoption, and that traditional approaches present limitations for researchers to create evidence. Evaluation of digital health solutions has also been identified as requiring improvement and has been cited as a major obstacle for wider adoption. This study will use pragmatic methods to evaluate Fresh Start, with a view to support successful adoption of Fresh Start in primary care practices in the UK.

4. Study Objectives

4.1. Primary objectives

1) To assess the feasibility of uptake amongst people with ‘high risk’ or ‘very high risk’ type 2 diabetes.
2) To assess the usability of Fresh Start amongst people with ‘high risk’ or ‘very high risk’ type 2 diabetes.
3) To assess the acceptability of Fresh Start amongst people with ‘high risk’ or ‘very high risk’ type 2 diabetes.
4) To assess the acceptability of Fresh Start amongst HCPs.
5) To assess the cost-effectiveness of delivering Fresh Start.

4.2. Secondary objectives (Exploratory)

1) To assess the safety of Fresh Start.
2) To assess the impact of Fresh Start on clinical outcomes.

5. Design

5.1. Study Design

An experimental feasibility study with an additional exploratory pre-test/post-test design using a matched control implemented via propensity score matching.

5.2. Treatment Groups

5.2.1. The *Fresh-Start* Service

This 12-week service has been designed to optimise patient care based on pro-active identification and prioritisation of clinical risk based on health, socioeconomic and demographic factors.

Fresh Start seeks to assess whether alternative methods of healthcare delivery for people with high-risk or very high risk T2DM are safe, scalable, and cost-effective. Fresh Start has been co-designed with people with type 2 diabetes, healthcare professionals (GPs, specialists, nurses, podiatrists, dietitians) and commissioners from Collaboration Of North-West London Clinical Commissioning Groups (NWL CCGs).

The 12-week service comprises the following elements:

Proactive risk stratification. An electronic patient record (EPR) based risk stratification search is run at primary care practice level to identify T2DM patients at high risk of cardiovascular complications who may benefit from and be eligible for Fresh Start.

Video Group Consultations (VGC). Each patient is invited to attend a total of three VGCs during the 12-weeks lasting approximately one hour and 15 minutes each. Each session is facilitated by a Practice Nurse (PN) and consists of 6-10 people with T2DM. The self-reported Huma app (see below) and patient EPR data are used to populate a "Discussion Dashboard" which is used in each VGC to facilitate discussion. During the first VGC session, patient goals are discussed and adjusted in a group setting with topics relevant to their condition covered by the PN. Between each VGC session, patients spend time working on their goals and continuing to enter self-reported metrics into the Huma app. During the second and third VGC sessions, each patient is discussed, along with their performance against agreed goals. The PN also uses pre-prepared content to discuss topics relevant to managing type 2 diabetes (e.g., staying motivated, low carb diets).

Fresh Start educational email campaigns. Each patient is signed up to a series of educational email campaigns to complement the VGC sessions and provide broader education around type 2 diabetes management. Patients receive two emails per week during the 12-week service on a variety of topics.

Clinical protocols. A series of best-practice CRG approved clinical protocols are in place to be triggered based on thresholds and values captured via the Huma app and as part of the VGC sessions. Protocol examples include medications review, foot care, renal, and mental health.

Digital remote patient monitoring using blood pressure and blood sugar devices in combination with a smartphone application ('the Huma app'). Participants are provided with home monitoring devices and download the Huma app. Participants are shown how to use the devices, how to input measurements into a smart phone and how to set personal goals. Data recorded via the Huma app is self-reported and includes activity data, diet information, blood glucose measurements, blood pressure measurements, weight, and the Diabetes Distress Scale (a self-reported questionnaire used to measure distress related to living with diabetes). A Health Care Assistant (HCA) observes these data via a Huma clinician dashboard that complements the Huma app. The HCA presents these data in combination with relevant EPR data to the PN for review ahead of each VGC appointment.

One-to-one routine patient review. At the end of the 12-weeks participants are invited to a one-to-one review session with their primary care practice. The patient's progress over the 12-week service is reviewed and a decision is made whether to discharge patient, repeat them for another 12 weeks on Fresh Start, or escalate them to MDT.

5.2.2. Matched Control Group

Several of the study's objectives and associated outcome measures will require a control group for comparison. This includes the primary objective investigating cost-effectiveness and secondary objectives investigating safety and efficacy of Fresh Start on clinical outcomes.

To achieve this, the study will establish a matched control group using propensity score matching (PSM). PSM uses statistical techniques to construct an artificial control group by matching each study participant with a non-treated participant of similar characteristics. This is achieved by estimating the probability that a person would enrol in a program given a set of pre-defined characteristics, with the resulting probability providing a 'propensity score'.

Data for the matched control group will be identified using NWL's Whole of Systems Integrated Care (WSIC) database. WSIC links provider data from four acute, two mental health and two community Trusts across eight CCGs, social care data from eight boroughs and 380 GP practices to generate an integrated care record.

5.3. Study Population

The study population includes people with 'high risk' and 'very high risk' type 2 diabetes as defined by guidance for primary care from NHS England and NHS Improvement (London). All additional inclusion and exclusion criteria are defined within section 5.4 below:

5.4. Eligibility

5.4.1. Inclusion Criteria

- Patients over the age of 18 with the capacity to give consent
- Patients with 'high risk' OR 'very high risk' T2DM as defined by:
    - **Very high risk** - **T2DM with existing ASCVD** OR T2DM without ASCVD but with any **3 of the following**:
        - HbA1c >58 mmol/mol
        - SBP >140 mm Hg
        - Non-HDL >3.35 mmol/L or LDL-C >2.5 mmol/L
        - Nephropathy (eGFR <45 ml/min, or Urine ACR >3 mg/mol)
        - Retinopathy
        - Neuropathy (including moderate/high risk feet, previous foot ulceration and erectile dysfunction)
        - Currently smoking
    - **High risk** - T2DM without ASCVD but with any **2 of the following**:
        - HbA1c > 58 mmol/mol
        - SBP >140 mm Hg
        - Non-HDL >3.35 mmol/L or LDL-C >2.5 mmol/L
        - Nephropathy: eGFR <45 ml/min or Urine ACR >3 mg/mol
        - Retinopathy

5.4.2. Exclusion Criteria

- Participants too ill to participate in the study (i.e., presence of a life-threatening condition, expected survival less than 3 months, clinically unstable)
- Participants who have previously participated in efforts that have informed the design of this research.
- Participant without access to a smartphone.
- Non-English language (the remote monitoring technology currently does not support additional languages).
- Visual disability (the remote monitoring technology currently does not natively support visual assistance).
- Active severe mental illness (SMI).
- Alcohol / drug abuse.

- Severe frailty (identified via the Electronic Frailty Index – eFI).
- Housebound / living in nursing home.
- Currently on the REWIND Programme (a NWL total diet replacement programme for patients with type 2 diabetes).

5.5. Sample Size

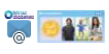
The study will seek to collect and analyse data from a minimum of 300 participants to Fresh Start. With an estimated enrolment rate of 20%, 1,500 eligible patients will need to be identified and we will be able to estimate this rate within a 95% confidence interval of +/-3%, accounting for variance inflation due to clustering with the assumption of 10 GP practices and Intraclass Correlation Coefficient (ICC) of 0.05.

The study's secondary objectives are exploratory only and will not be demonstrated to a level of statistical significance in this study.

5.6. Randomisation

No randomisation will take place during this feasibility study. Patients in the 'control' arm will be selected based on the Propensity Score Matching procedure described within section 7.1.2 .

5.7. Schedule of Study Procedures

									
Step	**Patient search**	**Outreach, Qualification & Booking**	**Onboard**	**Know Diabetes Emails**	**Huma App and Devices**	**Virtual Group Consultations (VGC)**			**12wk Review Discharge, Repeat or MDT**
						Before	During	After	
Staff actions at primary care practice	Run EPR search report to find list of patients.	Contact patients by phone, invite them to the service and ensure they can participate. Book them onto a formal onboarding appointment and book bloods if missing. Book to collect devices.	Run virtual appointment or phone call to onboard patient onto the service. Provide Huma app, book 3 x VGC sessions, sign up for Know Diabetes emails, answer questions Patient collects devices from practice.	Sign the patient up by email and make sure they are receiving emails OK.	Check Huma clinician dashboard daily for safety (red flags) and to see whether patients are using app. Escalate care if red flag spotted. Patients set their own goals.	Look at Huma dashboard, move some key data into EPR. Fill out VGC "discussion board" slide and agree talking points for VGC session. Discuss possible clinical and care plan decisions.	Run VGC session with 6-10 patients. Review and discuss patient goals and clinical metrics. Identify and note clinical treatment or care plan changes and referrals required.	Internally discuss notes and actions from VGC after session. Refer to clinical protocols; agree and action any required care plan and treatment changes or referrals.	Decide whether to discharge patient, repeat service for 12-weeks or escalate them to an MDT for further support.
How long it should take?	**5m total**	**10m per patient**	**30m-45m per patient**	**1m per patient**	**1-2m per patient**	**1hr total**	**1hr15m total**	**1hr total**	**1hr total**
How often it should be done?	Once, at beginning of 12 weeks	Once, at beginning of 12 weeks	Once, at beginning of 12 weeks	Twice, at beginning and at first VGC session	Daily	Before each VGC	During each VGC	After each VGC	Once, at end of 12 weeks

6. Variables of Analysis

6.1. Summary of Analysis Variables

Primary Objective	Outcome	Source	Freq.	Comp. w/ control?
1) To assess the **feasibility of uptake** amongst people with 'high risk' or 'very high risk' **type 2 diabetes**.	Patients offered Fresh Start vs. **enrolled**	EPR	Once	No
	Patients enrolled vs. downloading **Huma app**	Huma	Once	No
2) To assess the **usability** of Fresh Start amongst **people** with 'high risk' or 'very high risk' **type 2 diabetes**.	Number of **VGCs** attended	EPR	Every 4 weeks	No
	Number of **Fresh Start emails** opened	KD	Twice weekly	No
	Number of **blood glucose** measurements recorded	Huma	Daily	No
	Number of **blood pressure** measurements recorded	Huma	Daily	No
	Number of **weight*** measurements recorded	Huma	Daily	No
	Number of **Diabetes Distress Scale** measurements recorded	Huma	Monthly	No
3) To assess the **acceptability** of Fresh Start amongst **people** with 'high risk' or 'very high risk' **type 2 diabetes**.	**Interviews** with patients (x10)	Interview	At 12 weeks	No
4) To assess the **acceptability** of Fresh Start amongst **HCPs.**	**Interviews** with healthcare professionals (HCPs, x10)	Interview	After intervention	No
5) To assess the cost-effectiveness of delivering Fresh Start.	**Number of primary care appointments per patient**	EPR	Data extracted from EPR	**Yes**
	Cost per appointment per patient	EPR	Data extracted from EPR	**Yes**
	Cost of equipment per patient	Huma	N/A	No

* In the event where BMI data is more routinely collected the endpoint may be adjusted to BMI

Secondary Objective	**Outcome**	**Source**	**Freq.**	**Compare with control?**
1) To assess the **safety** of Fresh Start.	Number of **deaths**	EPR	Data extracted from EPR	**Yes**
	Number of **emergency department** admissions	WSIC	Data extracted from WSIC	**Yes**
	Number of **hospital** admissions	WSIC	Data extracted from WSIC	**Yes**
2) To assess the impact of Fresh Start on **clinical outcomes**.	HbA1c	EPR	Baseline, 12 weeks, 6 months	**Yes**
	Lipids, incl. LDL and non-HDL cholesterol	EPR	Baseline, 12 weeks, 6 months	**Yes**
	Weight *	EPR	Baseline, 12 weeks, 6 months	**Yes**
	Diabetes Distress Scale score (DDS[iii])	Huma	Monthly during service (and at 6 month follow-up appt.)	No
	Blood glucose time-in-range	Huma	Daily	**Yes**
	Systolic blood pressure (**SBP**)	Huma	Daily	**Yes**

* Note, if patient Height is also recorded BMI may be presented as an alternative

6.2. Primary Analysis Variables

6.2.1. Feasibility of uptake amongst people with 'high risk' or 'very high risk' type 2 diabetes

Feasibility of uptake is to be determined by the following measures:

- Patients enrolled with Fresh Start in comparison to those offered the Fresh Start service. Enrolment is defined as all patients entered within the study dataset. Offered is defined as those contacted about Fresh Start by their PCN by phone call or SMS and recorded in the Screening Log for that PCN.
- Patients collecting Fresh Start data in comparison to those enrolled. Patients collecting data is defined as a patient that records just one entry in any of the HUMA collected variables.

6.2.2. Usability of Fresh Start amongst people with 'high risk' or 'very high risk' type 2 diabetes.

Usability is to be determined by the following measures recorded over the 12-week assessment period:

- Number of **Video Group Consultations (VGC)** attended per patient
- Number of **Fresh Start** emails opened per patient
- Number of **Blood Glucose** measurements recorded per patient within HUMA
- Number of **Blood Pressure** measurements recorded per patient within HUMA
- Number of **Weight** measurements recorded per patient within HUMA
- Number of **Diabetes Distress Score (DDS)** measurements recorded per patient within HUMA

6.2.3. Acceptability of Fresh Start amongst people with 'high risk' or 'very high risk' type 2 diabetes.

Acceptability is to be determined by qualitative patient interviews completed by the ICHP team after the 12-week assessment period.

6.2.4. Acceptability of Fresh Start amongst HCPs

Acceptability is to be determined by qualitative interviews with HCPs completed by the ICHP team after the Fresh Start intervention has been delivered to enrolled patients

6.2.5. Cost-effectiveness of delivering Fresh Start

Cost-effectiveness is to be determined by the following measures:

- Number of primary care appointments per patient - as entered in study dataset over the 12-week assessment period
- Cost per appointment per patient - as entered in study dataset
- Cost of equipment per patient – defined below:

6.2.6. Cost of equipment per patient

Equipment	Unit Cost
Omron M4 BP Monitor	37.93
Omron HEM-9210 BP Monitor	130.00
Glucomen Areo Glucometer	2.00
Glucomen Areo Glucometer Strips	5.95
Glucomen Areo Glucometer Lancets	3.77
Sharps Bin	3.00
Belter CF-989 Weigh Scale	20.00

6.3. Secondary Analysis Variables

6.3.1. Safety of Fresh Start

Safety is to be determined by the following as entered in study dataset over the 12-week assessment period:

- Number of deaths
- Number of emergency department admissions
- Number of hospital admissions

6.3.2. Impact of Fresh Start on clinical outcomes.

To evaluate the impact of Fresh Start on clinical outcomes the following outcomes will be assessed:

- HbA1c, recorded via patient records at baseline, upon completion of 12-week assessment period and at 6 months
- Lipids, incl. LDL and non-HDL cholesterol, recorded via patient records at baseline, upon completion of 12-week assessment period and at 6 months
- Weight, recorded via patient records at baseline, upon completion of 12-week assessment period and at 6 months
- Diabetes Distress Scale score (DDS), as recorded within HUMA once monthly across the 12-week assessment period and also at 6 months
- Blood glucose time-in-range, as recorded within HUMA over the 12-week assessment period

  Time-in-range is to be defined as the percentage of time that a participant spends with their blood glucose levels between 70 to 180 mg/dl.
- Systolic blood pressure (SBP), as recorded within HUMA, as recorded within HUMA over the 12-week assessment period

7. Statistical Methodology

7.1. General Methodology

7.1.1. Descriptive Output for Feasibility Outcomes

To investigate feasibility of Fresh-Start, analysis of primary endpoints will be descriptive in nature to establish how many patients engaged with the Fresh Start program, and if so, to what extent.

Continuous variables will be presented as means and standard deviations if normally distributed, and as medians and inter-quartile ranges for skewed data. Categorical variables will be presented as frequencies and percentages.

Details of the output provided will be included within sections 7.5.1 – 7.5.5. Dummy shells for tables, figures and listings will be provided within appendix 2.

7.1.2. Propensity Score Matching

For the primary cost-benefit comparison and secondary safety and efficacy comparisons, study data will be compared against a matched-control group established via propensity score matching. This is achieved by deriving a propensity score for each enrolled patient based on the following characteristics:

- Age
- Gender
- Geographical proximity
- Social deprivation index (by practice)

- Ethnicity

Using the above categories, taking 'arm' as the dependent variable, logistic regression using a generalised logit model will be used to generate the estimated propensity scores. Scores are also applied to a control 'arm' taken from the WSIC database as section 5.2.2 with everyone in the matched control identified within one month of the index case. The scores are then used to 'pair-up' patients within both groups, patients will be matched on a 1:1 basis without replacement.

Scores are to be calculated using PSCORE in STATA. Matching is to be carried out using PSMATCH2 (or a suitable alternative). Balancing on matching variables is to be checked once matching is completed using PSTEST. If any variable is found to be unbalanced the matching is repeated, either adjusting the matching method or caliper used.

7.2. Summary of Analysis Methods

Primary Objective	**Outcome**	**Comp. w/ control?**	**Analysis Methods**
1) To assess the **feasibility of uptake** amongst people with 'high risk' or 'very high risk' **type 2 diabetes**.	offered Fresh Start vs. **enrolled**	No	Frequency and percentage enrolled presented
	enrolled vs. downloading **app**	No	Frequency and percentage downloading presented
2) To assess the **usability** of Fresh Start amongst **people** with 'high risk' or 'very high risk' **type 2 diabetes**.	**VGCs** attended	No	Summary stats of VGCs attended overall and per unit time
	emails metrics as section 7.5.2	No	Frequency and percentages presented
	blood glucose measurements recorded	No	Summary stats of meas. recorded by patient overall and per unit time
	blood pressure measurements recorded	No	Summary stats of meas. recorded by patient overall and per unit time
	weight* measurements recorded	No	Summary stats of meas. recorded by patient overall and per unit time
	Diabetes Distress Scale measurements recorded	No	Summary stats of meas. recorded by patient overall and per unit time
4) To assess the **acceptability** of Fresh Start amongst **people** with 'high risk' or 'very high risk' **type 2 diabetes**.	**Interviews** with patients (x10)	No	*As per ICHP team*
5) To assess the **acceptability** of Fresh Start amongst **HCPs.**	**Interviews** with healthcare professionals (HCPs, x10)	No	*As per ICHP team*
6) To assess the cost-effectiveness of delivering Fresh Start.	**primary care appointments per patient (as recorded)**	**Yes**	Summary stats of no appts. attended.per patient up to 6 months post enrollment

Primary Objective	**Outcome**	**Comp. w/ control?**	**Analysis Methods**
			Comparison between groups via poisson mixed model
	Cost per appointment per patient	**Yes**	Summary stats of appt. cost per patient. **Comparison between groups via mixed model**
	Cost of equipment per patient	No	Summary stats of overall cost per patient.

Secondary Objective	**Outcome**	**Comp. w/ control?**	**Analysis Methods**
1) To assess the **safety** of Fresh Start.	Number of **deaths**	**Yes**	Frequency and percentages presented up to 6 months post enrollment
	Number of **emergency department** admissions	**Yes**	Frequency and percentages presented up to 6 months post enrollment
	Number of **hospital** admissions	**Yes**	Frequency and percentages presented up to 6 months post enrollment. Difference presented with 95% CI
2) To assess the impact of Fresh Start on **clinical outcomes**.	HbA1c	**Yes**	Summary stats of HbA1c by visit (BL, W12, M6) **Comparison within & between groups via mixed model**
	Lipids, incl. LDL and non-HDL cholesterol	**Yes**	Summary stats of Lipids by visit (BL, W12, M6) **Comparison within & between groups via mixed model (if available)**
	Weight (or BMI as appropriate)	**Yes**	Summary stats of Weight by visit (BL, W12, M6) **Comparison within & between groups via mixed model**
	Diabetes Distress Scale score (DDS[iii])	No	Summary stats of DDS at per visit (M0, M1, M2, M3). **Comparison within groups via mixed model (if available)**
	Blood glucose time-in-range	**Yes**	Summary stats of days in range up to 6 months post enrollment

Secondary Objective	**Outcome**	**Comp. w/ control?**	**Analysis Methods**
			Comparison against control via mixed model (if available)
	Systolic blood pressure (**SBP**)	**Yes**	Summary stats of SBP **Comparison between groups via mixed model (if available)**

7.3. Patient Flow (CONSORT)

A CONSORT diagram covering patient flow into the study will be produced.

7.4. Patient Demographics & Baseline Readings

Tables summarising demographics are to be produced for both the FreshStart and propensity-matched groups. Additional output will be produced dichotomising the FreshStart group into 2 subgroups; those that used the HUMA device, and those that did not.

Demographics will cover Age, Gender, Ethnicity, Deprivation Score & Location

7.5. Primary Analysis Methodology

7.5.1. Feasibility of uptake amongst people with 'high risk' or 'very high risk' type 2 diabetes

For both definitions of comparative measures as defined in 6.2.1, frequencies of each category will be presented with proportions established as percentages presented to 1 decimal place (dp)

- Patients enrolled vs patients initially offered device
- Patients collecting Fresh Start data vs patients enrolled.

7.5.2. Usability of Fresh Start amongst people with 'high risk' or 'very high risk' type 2 diabetes.

Summary statistics denoting mean, sd, median, 1st/3rd quartiles, and minimum/maximum events per patient and per patient per unit time (day/week as appropriate) will be derived. Results will be presented as mean (SD) for normally distributed data and median [Q1-Q3] for skewed:

- Number of **Video Group Consultations (VGC)** attended per patient
- Number of **Blood Glucose measurements** recorded per patient within HUMA
- Number of **Blood Pressure measurements** recorded per patient within HUMA
- Number of **Weight measurements** recorded per patient within HUMA
- Number of **Diabetes Distress Score (DDS)** measurements recorded per patient within HUMA

For Fresh Start emails, the following frequencies will be presented, any additional information may also be presented:

- Number of patients that interacted with all emails

- Number of patients that interacted with no emails
- Interactions per email (click rates)

7.5.3. Acceptability of Fresh Start amongst people with 'high risk' or 'very high risk' type 2 diabetes.

Interviews are to be carried out by members of the research team from the Institute of Global Health Innovation (IGHI) at Imperial College London and will form part of a qualitative analysis. Interviews conducted with participants will be analysed using NVivo, where responses will undergo thematic analysis using an inductive approach to derive key themes.

7.5.4. Acceptability of Fresh Start amongst HCPs

Interviews are to be carried out by members of the research team from the Institute of Global Health Innovation (IGHI) at Imperial College London and will form part of a qualitative analysis. Interviews conducted with HCPs will be analysed using NVivo, where responses will undergo thematic analysis using an inductive approach to derive key themes.

7.5.5. Cost-effectiveness of delivering Fresh Start

From the three sets of data established in 6.2.6, cost-effectiveness of Fresh Start is to be assessed via the following:

- Number of primary care appointments per patient - as entered in study dataset over the 12-week assessment period

  Summary statistics will be derived for mean, sd, median, 1st/3rd quartiles, and minimum/maximum. Results will be presented as mean (SD) for normally distributed data and median [Q1-Q3] for skewed.

  To assess for differences in frequency of appointments per patient between Fresh Start and the matched control group, a Poisson-based mixed effects model with covariates for sex, age, social deprivation index will be used allowing for clustering by GP practice.

- Cost per appointment per patient - as entered in study dataset

  Summary statistics will be derived for mean, sd, median, 1st/3rd quartiles, and minimum/maximum. Results will be presented as mean (SD) for normally distributed data and median [Q1-Q3] for skewed.

  To assess for differences in cost of appointments per patient between Fresh Start and the matched control group, a mixed-model approach with covariates for sex, age, social deprivation index will be used allowing for clustering by GP practice.

- Cost of equipment per patient

Costs per patient will be estimated using the figures provided in section 6.2.6.1. Once established, summary statistics will be derived for mean, sd, median, 1st/3rd quartiles, and minimum/maximum. Results will be presented as mean (SD) for normally distributed data and median [Q1-Q3] for skewed

7.6. Secondary Analysis Methodology

7.6.1. Safety of Fresh Start

From the safety parameters established in 6.3.1, safety of Fresh Start is to be assessed via the following over 6 months:

- Number of deaths

  Number of deaths is to be presented by frequency per group.

- Number of emergency department admissions

  Number of patients with emergency admissions is to be presented by frequency per group

- Number of hospital admissions

  Frequency of events per patient is to be presented in a frequency table by treatment group with percentages to 1 dp.

  Number of patients with hospital admissions is to be presented by frequency per group

  Statistical comparison of safety will consist of a composite outcome, including all three events listed above. Number of patients with a safety event occurring is to be presented by frequency per group with difference in number of patients presented with a 95% CI.

7.6.2. Impact of Fresh Start on clinical outcomes.

From the clinical outcome parameters established in 6.3.2, potential efficacy of Fresh Start is to be assessed via the following

- **HbA1c, at baseline, 12-week and at 6 months**
- **Lipids, at baseline, 12-week and at 6 months**
- **Weight, at baseline, 12-week and at 6 months**

  Tables displaying summary statistics will be produced displaying mean, SD, median, minimum & maximum at timepoints BL, W12 & M6

  Within-group change from baseline at 12 weeks will be assessed via a mixed-effects model taking values at 12-weeks as the dependant variable and adjusting for covariates; baseline, sex, age, social deprivation index and allowing for clustering by GP Practice

  Between-group differences in change from baseline at 12 weeks will be analysed using a similar mixed-effects model including an additional parameter for treatment effect and again adjusting for covariates; baseline, sex, age, social deprivation index and allowing for clustering by GP Practice

  Further analysis will take place once long-term (6-month) follow-up is completed using an adjusted version of the above models containing additional terms for visit and visit*treatment interaction.

- **Diabetes Distress Scale score (DDS), as recorded within HUMA once monthly across the 12-week assessment period and also at 6 months**

  Summary statistics displaying mean, SD, median, minimum & maximum DDS will be produced at for first reading and last reading.

  Within-group change from first DDS score to last DDS score will be assessed via a mixed-effects model taking DDS Score as dependant variable and adjusting for covariates; study day (of reading), sex, age, social deprivation index and allowing for clustering by GP Practice

- **Blood glucose time-in-range, as recorded within HUMA over the 12-week assessment period**

  investigating difference between means of days in-range after 12-weeks will be analysed using mixed-effects model adjusting for covariates; sex, age, social deprivation index and allowing for clustering by GP Practice.

  The above analysis is dependent on a suitable number of data points being collected per patient to assess time-in-range. If this analysis is deemed not feasible. Change in blood glucose will be presented using the same method as for HbA1c, Lipids & Weight. First blood glucose reading will be taken as baseline per patient.

  Summary statistics displaying mean, SD, median, minimum & maximum blood glucose will be produced at for first reading and last reading.

- **Systolic blood pressure (SBP), as recorded within HUMA, as recorded within HUMA over the 12-week assessment period**

  Summary statistics displaying mean, SD, median, minimum & maximum blood glucose will be produced at for first reading and last reading.

  investigating difference between means of SBP after 12-weeks will be analysed using mixed-effects model adjusting for covariates; sex, age, social deprivation index and allowing for clustering by GP Practice

7.7. Exploratory / Sub-group Analysis

For outcome measures defined in section 6.2, analysis may be repeated, breaking down the results into two separate sub-groups.

One potential classification relates to those enrolled who were able to strictly adhere to the FreshStart treatment protocol (including remote monitoring) and will be compared against those that were unable to adhere but were still able to participate in some manner (i.e take part in VGCs).

Additional sub-groups may be determined during the course of analysis and treated as post-hoc analysis.

Additional exploratory analysis may also be carried out for collected data not assessed in the above primary & secondary outcomes.

8. Missing Data

As a feasibility study, part of the feasibility assessment is to establish the extent of missing data. In the event where data in the propensity-matched control arm is missing it may be appropriate that replacement patients may be considered on the basis that they are still within suitable parameters of the matching algorithm and balancing remains unaffected.

9. SAP Revisions

Version	Date	Details
0.1	13MAY2022	Final Draft prior to signing off
0.2	11JULY2022	Removing definition of benchmark for time-in-range comparison (to be added post-hoc once a suitable reference point is found).

Appendix 1
Summary of Tables, Figures & Listings

Reference	Title	Template
1.1	CONSORT Diagram	N/A
2.1	Demographics – Treatment & Control	1
2.2	Demographics – HUMA Users vs Non-Users in Treatment Arm	1
3.1	Uptake - offered Fresh Start vs. enrolled	N/A
3.2	Uptake - enrolled vs. collecting devices	N/A
4.1	Usability - VGCs attended	2
4.2	Usability - blood glucose measurements recorded	2
4.3	Usability - blood pressure measurements recorded	2
4.4	Usability - weight measurements recorded	2
4.5	Usability - Diabetes Distress Scale measurements recorded	2
5.1.1-2	Costings - Primary care appointments per patient	2 & 5
5.2.1-2	Costings - Cost per appointment per patient	3 & 5
5.3	Costings - Cost of equipment per patient	3
6.1	Safety - Number of deaths	6
6.2	Safety - Number of emergency department admissions	6
6.3	Safety - Number of hospital admissions	6
7.1.1-2	Clinical – HbA1c Within Groups	3 & 5
7.1.3-2	Clinical – HbA1c Between Groups	4 & 5
7.2.1-2	Clinical – Lipids, incl. LDL and non-HDL cholesterol Within Groups	3 & 5
7.2.3-2	Clinical – Lipids, incl. LDL and non-HDL cholesterol Between Groups	4 & 5
7.3.1-2	Clinical – Weight (or BMI as appropriate) Within Groups	3 & 5
7.3.3-2	Clinical – Weight (or BMI as appropriate) Between Groups	4 & 5
7.4.1-2	Clinical – Diabetes Distress Scale score (DDS[iii]) Within Groups	3 & 5
7.4.3-2	Clinical – Diabetes Distress Scale score (DDS[iii]) Between Groups	4 & 5
7.5.1-2	Clinical – Blood glucose time-in-range Within Groups	3 & 5
7.5.3-2	Clinical – Blood glucose time-in-range Between Groups	4 & 5

Appendix 2
Shell/Dummy Tables, Figures & Listings

Template 1: Demographics

Variable		Unit	Group X	Group Y
Age	Years	Mean (SD)		
	Years	Median [Q1 – Q3]		
Sex	Male	n(%)		
Ethnicity	Asian (inc. Asian British)	n(%)		
	…	n(%)		
	…	n(%)		
DI Deciles	1	n(%)		
	…	n(%)		
	…	n(%)		

Template 2: Descriptive (Summary) Statistics – Frequency Output

	n	**Mean**	**SD**	**Median**	**Min**	**Max**
Average no. Readings	xx	xx.x	xx.x	xx.x	xx.x	xx.x
Ave. Readings/Day	xx	xx.x	xx.x	xx.x	xx.x	xx.x

Template 3: Descriptive (Summary) Statistics – Within Groups

	n	Mean	SD	Median	Min	Max
First Value/ Baseline	xx	xx.x	xx.x	xx.x	xx.x	xx.x
Final Value	xx	xx.x	xx.x	xx.x	xx.x	xx.x
Δ	xx	xx.x	xx.x	xx.x	xx.x	xx.x

Template 4: Descriptive (Summary) Statistics – Between Groups/Sub-groups

	n	Mean	SD	Median	Min	Max
Δ Group x	xx	xx.x	xx.x	xx.x	xx.x	xx.x
Δ Group y	xx	xx.x	xx.x	xx.x	xx.x	xx.x
Δ between groups	xx	xx.x	xx.x	xx.x	xx.x	xx.x

Template 5: STATA Mixed-Model Output (example)

```
Mixed-effects ML regression                     Number of obs     =        432
Group variable: id                              Number of groups  =         48
                                                Obs per group:
                                                              min =          9
                                                              avg =        9.0
                                                              max =          9
                                                Wald chi2(1)      =   25337.49
Log likelihood = -1014.9268                     Prob > chi2       =     0.0000

------------------------------------------------------------------------------
      weight | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
        week |   6.209896   .0390124   159.18   0.000     6.133433    6.286359
       _cons |   19.35561   .5974059    32.40   0.000     18.18472    20.52651
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters |   Estimate   Std. err.      [95% conf. interval]
----------------------------+-------------------------------------------------
id: Identity                |
                  var(_cons) |   14.81751   3.124226      9.801716    22.40002
----------------------------+-------------------------------------------------
               var(Residual) |   4.383264   .3163348      3.805112     5.04926
------------------------------------------------------------------------------
LR test vs. linear model: chibar2(01) = 472.65        Prob >= chibar2 = 0.0000
```

Template 6: Frequency of Events Table & Chi-Sq Test (Example)

Repair Record 1978	Car type		
	Domestic	Foreign	Total
1	2	0	2
2	8	0	8
3	27	3	30
4	9	9	18
5	2	9	11
Total	48	21	69

Pearson chi2(4) = 27.2640 Pr = 0.000