Prevent from Home: Young person and buddies' cardiovascuLar health Improvement feasibility Study

Protocol Short Title/Acronym: *PHYLLIS*

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Trial Identifiers

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1. Study Synopsis

Title of clinical trial	**P**revent from **H**ome: **Y**oung person and buddies' cardiovascu**L**ar hea**L**th **I**mprovement feasibility **S**tudy
Protocol Short Title/Acronym	PHYLLIS
Trial Phase	Phase II
(Co-)-Sponsor(s) name	King's College Hospital NHS Trust and King's College London
Chief Investigator	Dr Kate Bramham
IRAS number	1008673
Medical condition or disease under investigation	Hypertension in pregnancy and gestational diabetes
Purpose of clinical trial	To assess the feasibility of randomising postpartum individuals (with enhanced recruitment from under-served communities) with risk factors for cardiovascular disease to Sodium glucose transport protein-2 inhibitors (SGLT2i), Glucagon-like peptide 1 (GLP-1) and standard care. To optimise methodologies and collect data to inform future community-based point-of-care, digital and peer-supported / co-recruitment trials, with enhanced recruitment of participants from under-served communities.
Primary objective	• Part A: To standardise baseline treatment to enalapril or other breastfeeding-compatible antihypertensive medication, prior to Part B • Part B: To assess the feasibility of undertaking a randomised controlled trial comparing SGLT2i, GLP-1 and standard care in postpartum individuals with CVD risk factors, with peer support, optional co-recruitment (study-buddy) and remote monitoring.
Secondary objective (s)	<u>Secondary process objectives:</u> • To determine adaptations to meet the needs of different under-served communities. • To explore the feasibility and acceptability of: • recruiting peer-educator postpartum health champions • co-recruitment of study-buddies • novel community/home-based assessments of early endothelial dysfunction <u>Secondary clinical objectives:</u>

	• To compare longitudinal changes in clinical parameters (including blood pressure, weight, cardiometabolic profile, anthropometric measures including waist, hip and upper arm circumference and assessments of endothelial dysfunction) for participants (and study-buddies) between study arms
Trial design	Prospective, phase II, parallel group, open-label, multicentre, three-arm feasibility randomised controlled trial. <u>Part A:</u> 1:1 participants will be randomised to enalapril or other antihypertensive. <u>Part B:</u> 1:1:1 participants (and study buddies) will be randomised to SGLT2i, GLP-1 or standard care.
Primary Endpoint	1. Overall recruitment rate of postpartum participants with hypertension in pregnancy and/or gestational diabetes (number of participants per site per month).
Secondary Endpoints	<u>Secondary process endpoints:</u> 1. Overall uptake and recruitment rate of study-buddies assessed at the end of the study. 2. Longitudinal assessment of retention of postpartum participants and study-buddies across both arms (assessed at end of study) 3. Number of blood pressures, weights, pregnancy test results, urine-dip results (at 26 weeks for each participant, total number assessed at end of study) 4. Number of returned blood and urine tests at 26 weeks 5. Evaluation of acceptability and experience of all study activities (For Part A: End of study survey and focus group at 16 weeks and for Part B: End of study survey with postpartum participants and study buddies at 52 weeks and completion of focus group with postpartum participants, study buddies and health champions at 26 and 52 weeks) 6. Study resource use (at 26 weeks and 52 weeks) <u>Secondary clinical endpoints:</u>

	7. Adherence to daily SGLT2i (intervention arm i) by pill-counting at 26 weeks or 4-weekly photographs of blister packs. Adherence to weekly GLP-1 injections (intervention arm ii) through patient diaries. Adherence will also be assessed at 16 weeks in Part A and at 26 weeks in Part B using the Medication Adherence Report Scale-5 (MARS-5). 8. Pregnancy rate during the study period (Part B) and pregnancy outcomes (pregnancy tests performed 4 weekly, overall pregnancy rates assessed at end of study) 9. Longitudinal changes in BP and weight at 4 weekly intervals, and 26 and 52 weeks 10. Longitudinal changes in creatinine, HbA1C, albumin creatinine ratio (ACR), lipid profile and liver function tests at 2, 14, and 38-weeks from home testing. 11. Longitudinal changes in anthropometric measures (waist, hip and upper arm circumference), creatinine, cystatin, HbA1C, cholesterol and ACR at baseline, 26 and 52 weeks from onsite testing 12. Longitudinal changes in retinal measurements (as measured by ophthalmic assessment), cardiac structure and function (as measured by echocardiography and electrocardiogram), pulse wave velocity and metabolomic profiles.
Sample size	324 (At least 162 postpartum participants and up to 162 study-buddies)
Summary of eligibility criteria	**Inclusion Criteria Part A:** • Person with current pregnancy, or within six weeks of pregnancy, complicated by hypertension • Able to provide written informed consent • Age ≥ 18 years • Body mass index >23kg/m^2. **Exclusion Criteria Part A** Pregnant or postpartum person *(including people not identifying as female)* with*:* • Diabetes (Type-1 or 2) • Chronic Kidney Disease or Heart failure and recommended routine SGLT2i • Severe hepatic impairment • Allergy to dapagliflozin (SGLT2i), tirzepatide (GLP-1) or its excipients • Hereditary galactose intolerance, total lactase deficiency or glucose-galactose malabsorption • Contraindication to postpartum enalapril, amlodipine, nifedipine, or labetalol - including allergy

	• Moving away from study site within 12 months • Planning pregnancy ≤6-months **Inclusion Criteria Part B:** Postpartum person *(including people not identifying as female)* with*:* • Previous pregnancy complicated by hypertension in pregnancy and/or gestational diabetes (defined by National Institute for Health and Care Excellence) ≤12-months • Able to provide written informed consent • Age ≥ 18 years • Completed breastfeeding • Body mass index ≥27kg/m^2 Study buddy *(co-recruitment as selected by the postpartum person):* • Age 18 years – 60 years • Body mass index ≥27kg/m^2 • Able to provide written informed consent • Person with ≥1 of the following pre-cardiovascular disease risk factor (NICE 2024): i) Pre-hypertension (systolic blood pressure 120-139 and/or diastolic blood pressure 80-89 mmHg) ii) Parent or sibling with diabetes or body mass index >30kg/m2 AND age > 25 years if African Caribbean, Black African, or South Asian or age > 40 years if any other ethnicity AND Haemoglobin A1c of 42-47 mmol/mol (6-6.4%) iii) Postpartum person with previous pregnancy complicated by hypertension in pregnancy and/or gestational diabetes >12-months **Exclusion criteria Part B:** Postpartum person and study-buddies with: • Diabetes (Type-1 or 2), or history of diabetic ketoacidosis or hyperosmolar state or diabetic coma • Chronic Kidney Disease or Heart failure and recommended routine SGLT2i • Liver disease (AST or ALT > 2x upper limit of normal) • History of acute or chronic pancreatitis • Severe gastrointestinal disease • Oral medications with a narrow therapeutic window (e.g. warfarin, digoxin) • Any drug associated with hypoglycaemia (e.g. antimalarial agents, lithium) • Allergy to dapagliflozin (SGLT2i), tirzepatide (GLP-1), or its excipients • Pregnant*, planning pregnancy within 6 months or breastfeeding **(**females of

	childbearing potential* with a positive pregnancy test at screening) • Moving away from study site within 12 months • Severe hepatic impairment • Hereditary galactose intolerance, total lactase deficiency or glucose-galactose malabsorption • Use of GLP-1 receptor agonists within the past 3 months • History of organ transplantation * A pregnancy test (urine) will be performed for all persons of childbearing potential at all onsite visits and monthly at home tests performed. Study drugs will not be dispensed without a negative pregnancy test. Women randomised to tirzepatide on oral contraception will be counselled on the potential for reduced efficacy and advised to use a barrier method or switch to non-oral contraception methods.
IMP, dosage and route of administration	Part B: Intervention: (i) SGLT2i, oral dapagliflozin 10 mg once a day for 26 weeks; (ii) GLP-1, tirzepatide, weekly subcutaneous injections for 26 weeks. Starting dose will be 2.5mg for at least 4 weeks, with subsequent increases of 2.5 mg every 4 weeks based on symptom tolerance and weight loss response, up to a maximum dose of 15 mg.
Active comparator product(s)	Part B: Standard care
Maximum duration of treatment of a participant	Part A: up to 16 weeks or until completion of breastfeeding Part B: (i) 52 weeks study duration with maximum duration on SGLT2i of 26 weeks; (ii) 52 weeks study duration with maximum duration on GLP-1 of 26 weeks

2. Protocol Version History

Version Number	Date	Reasons for Update
0.9	25.09.24	Initial release
1.0	02.11.24	Additional description of MACRO database added
1.1	04.01.25	Addition of recommendations made by REC and MHRA
2.0	06.03.25	Changes to ensure consistent with EDC database: - PHQ-9 at baseline and end of Part A and B - Cystatin C at each visit for Part A - Full blood count and liver function tests added to onsite visits for Part B - MARS-5 tool added to Part A at 16 weeks and Part B at 26 weeks to assess adherence - Additional clarification around ethnicity for study buddy selection. Clarification added re: end of study survey and focus group at 16 weeks in Secondary outcomes. Clarification added re: blood test timing to 8.2. The timing of tests for Part A had been previously omitted – this has been amended. Section 10.3 has been amended to state that all AEs will be reported for participants from part A and part B, from the time the consent form is signed.
2.1	06.05.25	Correction of an error in trial flowchart (section 5.5, Part A). Clarification of IMP dispensing timings (sections 5.6 & 6, Part B).
5.0 (version 3.0 submitted as part of original amendment 10/25, Version 4.0 with changes from REC Version 5.0 with changes from MHRA)	25.02.2026	Third arm of GLP-1 added to Part B. Inclusion (Body mass index threshold adjusted to ≥27kg/m^2) and exclusion criteria for Part B adjusted to account for the third arm. Additional investigations added (where available): - For Part A at baseline and 16 weeks: Ophthalmic assessment, echocardiogram, electrocardiogram - For Part B at baseline, 26 weeks and 52 weeks: Ophthalmic assessment, echocardiogram, electrocardiogram, pulse wave velocity measurement. - For Part B at baseline and 26 weeks: metabolomic assessment At each onsite visit for Part B, additional blood and urine samples taken for freezing.

		PHQ-9 in Part A removed from baseline and added to all site visits. PHQ-9 in Part B included in all on site visits. Exclusion criteria for Part A adjusted to ensure women with severe preeclampsia are not excluded. Exclusion criteria for Part B amended in line with the addition of the third arm and MHRA feedback. Additional safety monitoring of amylase and lipase included.

3. Glossary of Terms

ACR	Albumin creatinine ratio
AE	Adverse event
AR	Adverse reaction
BMI	Body Mass Index
BP	Blood pressure
CVD	Cardiovascular disease
DSUR	Development Safety Update Report
ECG	Electrocardiogram
eCRF	Electronic case report form
GDM	Gestational diabetes
GLP-1	Glucagon-Like Peptide- 1
HbA1c	Haemoglobin A1c
HDP	Hypertensive disorders of pregnancy
HRA	Health Research Authority
KHP-CTO	King's Health Partners Clinical Trials Office
MHRA	Medicines and Healthcare products Regulatory Agency
NICE	National Institute of Health and Care Excellence
PHQ-9	Patient Health Questionnaire
PIL	Participant Information Leaflet
PPI	Patient and Public Involvement
REC	Research Ethics Committee
SAE	Serious adverse event
SAR	Serious Adverse Reaction
SGLT2i	Sodium glucose transport protein-2 inhibitors
SmPC	Summary of Investigational Medicinal Product
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
TTE	Transthoracic echocardiogram
UAR	Unexpected Adverse Reaction
UK	United Kingdom

CONTENTS

4. Background & Rationale

Cardiovascular disease (CVD) causes the greatest number of preventable deaths in the United Kingdom (UK), with high rates in ethnic minority groups and the most deprived socioeconomic groups. Pre-cardiovascular disease risk factors are considered either modifiable, such as elevated body mass index, elevated cholesterol levels and the presence of certain comorbidities such as hypertension, diabetes (and pre-diabetes) and non-modifiable which include a family history of CVD and certain ethnic backgrounds such as people of South Asian or sub-Saharan African origin (NICE 2024).

In the UK CVD is also the leading overall cause of death in women, with higher mortality and worse outcomes than men (DeFilippis, Collins et al. 2020). Despite this, ethnic minorities, deprived socioeconomic groups and women are disproportionality under-represented in research (Treweek, Banister et al. 2021). Addressing these inequalities using novel approaches to identify early disease, engage under-served communities and provide culturally acceptable, scalable and cost-effective interventions are urgently needed (Treweek, Banister et al. 2021).

Pregnancy is a 'physiological stress test' revealing pre-dispositions to future cardiovascular and metabolic complications. Hypertensive disorders of pregnancy (HDP) and gestational diabetes (GDM) affect at least 10% of UK pregnancies with the highest rates in ethnic minority groups. National Institute of Health and Care Excellence (NICE) guidelines for both HDP and GDM recommend research into postpartum interventions which prevent future onset of CVD risk factors and recurrent pregnancy complications (National Institute for Health and Care Excellence 2015, National Institute for Health and Care Excellence 2019); however, the challenges of engaging high-risk postpartum women and the development of novel interventions pre-conception and during breastfeeding remain prominent.

Assessment of interventions to reduce postpartum CVD risk is expensive due to the length of time needed for follow-up. Endothelial dysfunction, a ubiquitous and early feature of CVD, is evident in women with HDP and GDM and could provide an important short-term surrogate for assessing CVD risk modification. Current methods (e.g. flow-mediated dilatation) to quantify endothelial dysfunction are labour-intensive and costly. Less technically demanding investigations of endothelial dysfunction include cardiac assessments (electrocardiogram (ECG) assessing electrical activity of the heart, transthoracic echocardiogram (TTE) assessing the structure and function of the heart, pulse wave velocity (PWV) assessing arterial stiffness), ophthalmic assessments (including retinal photograph, optical coherence tomography (OCT) and optical coherence tomography-angiography (OCT-A) and metabolomic profiles analysed from a blood sample and/ or urine sample can reveal individualised information about inflammation, lipid metabolism and oxidative stress. Prior to a large-scale study of simpler endothelial assessments as novel endpoints in CVD trials, feasibility and acceptability need to be tested.

Postpartum studies have demonstrated cardiovascular risk improvement with prolonged effects from early interventions targeting BP, endothelial and diastolic dysfunction (Ormesher, Higson et al. 2020, Kitt, Fox et al. 2021). The recent PICk-UP (Postnatal Enalapril to Improve Cardiovascular Function Following Preterm Preeclampsia) study, although powered to identify a reduction in total vascular resistance, showed significantly improved diastolic dysfunction with enalapril (Ormesher et al. 2020). This suggests that the immediate postpartum period is an important time to reset future risk trajectories. Women with complicated pregnancies are highly motivated to improve their future health (Smith, Louis et al. 2019) but only 70% return for follow-up visits (Kountouris, Clark et al. 2021) with lower attendance in ethnic minority groups despite higher CVD risk (Smith, Louis et al. 2019). Furthermore, early interventions to prevent the onset of diabetes and hypertension are proposed to be more effective than

secondary prevention and are considered urgently needed more widely within ethnic minority and deprived socioeconomic groups by Patient and Public Involvement (PPI) whereby pregnancy is often the only contact with health care for individuals from underserved communities and provides a unique opportunity for engagement with other community members.

Different interventions to optimise modifiable CVD risk factors were discussed with PPI groups and Sodium glucose transport protein-2 inhibitors (SGLT2i) were selected due to likelihood of success, safety profile and potential for weight loss. SGLT2i (gliflozins) are likely to transform CVD outcomes due to unequivocal evidence supporting use for CVD prevention with evidence of reversal of vascular pathology within 3-6 months (Verma, Mazer et al. 2019). SGLT2i block proximal tubule reuptake of glucose and sodium, which leads to daily urinary glucose loss (200–300 kcal), reduced Haemoglobin A1c (HbA1c) (~0.5%–0.8%), systolic-BP (3-6 mmHg), albuminuria and visceral adiposity weight loss (1-3 kg) and fasting lipids and improvements in endothelial health with minimal side effects (Batzias, Antonopoulos et al. 2018).

SGLT2i have been demonstrated to prevent the onset of diabetic retinopathy (Sabaner, Duman et al. 2021) and trials are underway to explore the effects of SGLT2i in people with pre-diabetes and polycystic ovary disease (https://clinicaltrials.gov/ct2/show/NCT04401904).

There is a myriad of evidence demonstrating not only safety but also the benefit of dapagliflozin to address cardiovascular risk by slowing, even preventing, the progression of pre-diabetes to overt Type II diabetes and pre-hypertension to chronic hypertension. A systematic review and metanalysis of four randomised controlled trials with 5655 participants revealed that the use of dapagliflozin (and empagliflozin, another SGLT2i) was associated with a decreased risk of new-onset diabetes in adults with prediabetes and heart failure or chronic kidney disease (relative risk ratio, 0.79; 95% CI, 0.68-0.93) (Mori et al. 2022).

A pooled analysis of the DAPA-Chronic Kidney Disease and DAPA- Heart Failure trials with over 4000 participants revealed a lower prevalence of T2DM in the dapagliflozin group compared to the placebo group over a median of 21.2 months (hazard ratio, 0.67; 95% CI, 0.51-0.88) (Rossing et al. 2022). A double- blind, randomised, placebo-controlled trial of 30 individuals with pre-diabetes and pre-hypertension demonstrated that dapagliflozin, at the dose of 10mg (as proposed in PHYLLIS) for three months, significantly reduced the incidence of both pre-diabetes and pre-hypertension by 27% and improvements were also recorded for body weight, body mass index, and blood pressure (Díaz-Cruz et al. 2020). Further randomised controlled trials are crucial to provide more robust evidence for the use of dapagliflozin in this setting. Dapagliflozin (SGLT2i) is associated with renal abnormalities *in utero* and with lactation exposure, therefore, use in pregnancy and breastfeeding is not recommended thus regular testing for pregnancy is needed.

Recent evidence also supports the use of GLP-1 receptor agonists in reducing cardiovascular disease risk, notably through substantial weight loss, improvement in glycaemic control, blood pressure reduction, and positive effects on endothelial function. GLP-1 receptor agonists, such as semaglutide and liraglutide, or dual-acting GLP-1/GIP agonists like tirzepatide, stimulate insulin secretion, inhibit glucagon release, and slow gastric emptying, thereby enhancing satiety and promoting significant weight reduction (Gul et al. 2024). Clinical trials have demonstrated marked cardiovascular risk reduction associated with GLP-1 receptor agonists, particularly in populations with pre-diabetes, type 2 diabetes, obesity, and hypertension (Kristensen et al. 2019, Diallo et al. 2023, Yin et al. 2025),aligning closely with the postpartum population targeted in this study. GLP-1 receptor agonists are also associated with beneficial cardiovascular outcomes and demonstrate favourable safety profiles. There have been an overwhelming number of requests from postpartum women for GLP-1 agonists, but there is an urgent need to provide robust evidence of efficacy in this setting with prior assessment of feasibility. As such, incorporating a GLP-1 receptor agonist intervention alongside SGLT2i and

standard care enables direct comparison of two promising therapies to address modifiable postpartum cardiovascular risk factors, providing comprehensive evidence to inform future clinical guidelines and patient care strategies. Inclusion of GLP-1 have been strongly supported by our PPIE group.

We anticipate that dapagliflozin (SGLT2i) or tirzepatide (GLP-1) will lead to macro and microvascular remodelling; however other antihypertensive medications may also contribute to remodelling and affect secondary clinical trial outcomes, especially angiotensin-converting enzyme (ACE) inhibitors, such as enalapril (Lytvyn et al. 2022). We would like to ensure that participants randomised are comparable at baseline and want to avoid imbalance of those taking the ACE inhibitors in either arm.

Only a limited number of antihypertensive medications are safe while breastfeeding (enalapril, nifedipine, amlodipine, labetalol) and are currently offered within standard NHS postnatal care. There is no clear evidence which antihypertensive is superior in the postnatal period and as a result, prescribing practices vary across the UK. There is likely to be clinician preference for the choice of postpartum antihypertensives (e.g. according to ethnicity, age, and presence of chronic hypertension); therefore, to make the two arms balanced we plan to randomise women who require antihypertensive treatment for clinical care to take enalapril or other breastfeeding compatible antihypertensive medication (Part A). This Part A randomisation will standardise baseline conditions. After women have completed breastfeeding, they can then proceed to Part B (dapagliflozin, tirzepatide or standard care), and the arms will be minimised according to ACEi use. This approach will reduce the potential for confounding on secondary clinical outcomes (e.g. blood pressure, albuminuria, kidney function i.e. macro and microvascular remodelling) due to concomitant ACEi use, as there will be equal numbers of those treated with this agent in each arm.

If a participant is randomised to take enalapril after delivery, clinicians will be recommended to prescribe enalapril or other antihypertensives as part of clinical care to treat hypertension if required. If women do not tolerate or respond to the randomised choice of antihypertensive the clinician will change/titrate according to routine practice. All medication taken postpartum will be recorded and used to inform randomisation for Part B trial participation (enalapril taken or not). Only when women stop breastfeeding, they will enter Part B of the study (up to 52 weeks after delivery). Ongoing antihypertensives, if needed, will be continued, or adjusted according to clinical need, and recorded as concomitant medications.

In summary, the aim of Part A (randomisation to enalapril or other breastfeeding-compatible antihypertensive medication) is to standardise baseline conditions for Part B of the study; it is essential to balance baseline treatment across study arms to reduce the potential for confounding on clinical outcomes of Part B. The aim of Part B (randomisation to dapagliflozin, tirzepatide or standard care) is to investigate the feasibility of recruiting to a trial of randomisation to dapagliflozin and tirzepatide and evaluate effect of dapagliflozin and tirzepatide on clinical outcomes. The investigational medicinal products (IMP) in the study are dapagliflozin and tirzepatide, not enalapril; enalapril and other breastfeeding-compatible antihypertensive medication (nifedipine, amlodipine, labetalol) are all part of standard care for postnatal hypertension.

Extensive PPI work to inform this study design in order to facilitate recruitment of postpartum women, improve intervention fidelity, address health inequalities and engage under-served communities has informed the inclusion of:

- home-testing, sample collection and digital data collection. Public Health England and the NHS Long-Term-Plan highlight the need for enhanced access, point-of-care and use of digital support.
- study materials will be provided for women's partners and community leaders
- Inclusion of women planning further pregnancies

- Inclusion of ‘study-buddies’ (friend or family members) with pre-CVD risk factors. Study buddies will not receive any formal training so that their inclusion will provide an insight into whether this method of peer support will help people to participate in research in the postpartum period. Study- buddies will be treated as participants in their own right and will be randomised with the main participant, to receive the IMP or standard care, and to undergo the same follow-up.
- culturally congruous peer-educator ‘postpartum health champions’, as recommended in NIHR BAME-toolkit (https://arc-nenc.nihr.ac.uk/resources/toolkit-for-increasing-participation-of-bame-groups-in-health-and-social-careresearch). These will be individuals, who are healthcare workers within the NHS who will provide culturally congruent support to participants. These individuals will be recruited through the Race Ethnicity and Cultural Heritage (REACH) Network. The participants will consent to their contact details being provided to health champions to facilitate support for participation. These contact details, only released with the participant’s consent, will be the only patient identifiable data accessed by the health champion. The health champion will be trained by the research team to check-in with participants (telephone or text), encourage uploading of home measurements and return of samples and will communicate any obstacles to participation to the research team. It will be made clear to the participant in the PIS that the role of the health champion is not to provide any healthcare advice and to contact the research team instead.

The proposed feasibility study will allow the design of a definitive multicentre trial of SGLT2i, GLP-1 and standard care in postpartum individuals (including those who do not identify as women) with CVD risk factors. Further it will optimise methodologies and collect data to inform future community-based point-of-care, digital and peer-supported / co-recruitment trials, with enhanced recruitment of participants from under-served communities.

5. Trial Objectives and Design

5.1. Trial Objectives

Primary objective

- Part A: To standardise baseline treatment to enalapril or other breastfeeding-compatible antihypertensive medication
- Part B: To assess the feasibility of undertaking a randomised controlled trial comparing SGLT2i, GLP-1 and standard care in postpartum individuals with CVD risk factors, with peer support, optional co-recruitment (study-buddy) and remote monitoring.

Secondary process objectives

- To determine adaptations to meet the needs of different under-served communities
- To explore the feasibility and acceptability of:
    - recruiting peer-educator postpartum health champions
    - co-recruitment of study-buddies
    - novel community/home-based assessments of early endothelial dysfunction

Secondary clinical objectives:

- To compare longitudinal changes in clinical parameters (including blood pressure, weight, cardiometabolic profile, anthropometric measures (waist, hip and upper arm circumference) and assessments of endothelial dysfunction) for participants (and study-buddies) between the three study arms

5.2. Primary Endpoint

Overall recruitment rate of postpartum participants with hypertension in pregnancy and/or gestational diabetes (number of participants per site per month, assessed at end of study). Determined from screening logs with eligibility criteria met and reasons for exclusion reported.

This primary endpoint and secondary endpoints 1, 2 &3 will be assessed at “end of study”. The ‘end of study’ will be defined as a database lock.

5.2. Secondary Endpoint

Process Endpoints:

1. Overall uptake and recruitment rate of study-buddies assessed at the end of the study. Determined from screening logs with eligibility criteria met and reasons for exclusion reported.
2. Longitudinal assessment of retention of postpartum participants and study-buddies across both arms (assessed at end of study)
3. Number of blood pressures, weights, pregnancy test results, urine-dip results (up to and including 26 weeks for each participant, total number assessed up to and including 52 weeks) from home results sent in by participants on the clinical portal (MyChart, or local patient electronic portal).
4. Number of returned blood and urine tests up to and including 26 weeks.
5. Evaluation of acceptability and experience of all study activities (For Part A: End of study survey and focus group at 16 weeks and for Part B: End of study survey with postpartum participants and study buddies at 52 weeks; focus group with postpartum participants, study buddies and health champions at 26 and 52 weeks*)
6. Study resource use: Contacts with health champions, time for health champion training, expenditure on printing (£), time (hours) on recruitment and data extraction, home testing kit use (up to and including 26 weeks and 52 weeks)

Clinical Endpoints:

7. Adherence to (i) daily SGLT2i (intervention arm 1) and weekly injections of GLP-1 (intervention arm 2) assessed either at 26 weeks by a member of the research team pill-counting, by reviewing 4 weekly photographs of drug blister packs, or patient’s diaries. Adherence will also be assessed at 16 weeks in Part A and at 26 weeks in Part B using the Medication Adherence Report Scale-5 (MARS-5).
8. Pregnancy rate during the study period (Part B) and pregnancy outcomes (pregnancy tests performed 4 weekly, overall pregnancy rates assessed at end of study) recorded in Macro database
9. Longitudinal changes in BP and weight at 4 weekly intervals, and 26 and 52 weeks sent in by participants on the clinical portal (MyChart or local patient electronic portal) and recorded in the Macro database
10. Longitudinal changes in creatinine, HbA1C, lipid profile and liver function tests (Thriva) and albumin creatinine ratio (ACR) (Synnovis) at 2, 14, and 38-weeks from home testing recorded in Macro database.
11. Longitudinal changes in anthropometric measures (waist, hip and upper arm circumference), creatinine, cystatin, HbA1C, cholesterol and ACR at baseline, 26 and 52 weeks from onsite testing (Synnovis) recorded in Macro database.
12. Longitudinal changes in retinal measurements (as measured by ophthalmic assessment), cardiac structure and function (as measured by echocardiography and electrocardiogram), pulse wave velocity and metabolomic profiles.

* **Mixed methods evaluation (process endpoints 5&6):**

- Acceptability and experience of study activities assessed:
    - i) Quantitatively by the end of the study survey at 16 weeks for Part A and at 52 weeks for Part B.

This will capture all aspects of an individual's experience of participation including engagement materials, postpartum health champions and study-buddy support, home-lab testing and digital data collection.

ii) Qualitatively by focus groups.
Group 1: 10-participants and up to 10- study-buddy from each site (representative of different sub-groups) will be invited to a semi-structured interview. A maximum variation purposive sampling strategy will be used (Coyne 1997). Focus groups (6-8 participants) will be undertaken at 26 weeks and at 52 weeks.

Focus groups for participants and study-buddies will be held at each site to explore recommendations for raising future engagement and health awareness. Separate focus groups will be held for participants with a study- buddy and participants without a study- buddy.

Group 2: Postpartum health champion. Focus groups at each site.

Focus group discussions for groups 2 will include material development, champion recruitment methods, barriers and facilitators for study engagement and optimal use of peer-educator support (e.g. prior to, during or after testing) in under-served communities.

5.3. Trial Design

Feasibility study for a randomised controlled trial with a mixed-methods evaluation. A prospective, phase 2, parallel groups, open-label, multicentre, three-arm randomised controlled trial. 1:1:1 participants (and study buddies) will be randomised to either; 26-weeks SGLT2i (dapagliflozin), GLP-1 (tirzepatide) or standard care.

Study Design: Feasibility study for a randomised controlled trial with mixed-methods evaluation.

Study Duration per participant: Part A: up to 16 weeks or until completion of breastfeeding; Part B: 52 weeks; Part A and B: up to 68 weeks

Total Study Duration: 36-months

Most individuals will participate in this study on the completion of breastfeeding. This pathway is referred to as PHYLLIS Part B. Participants who chose not to breastfeed and are normotensive will proceed directly to the Part B pathway.

Potential participants with hypertensive disorders of pregnancy will be offered to participate in PHYLLIS Part A to reduce the imbalance of use of antihypertensive medications between arms which may affect overall secondary clinical endpoints (See Page 12).

Part A: Participants taking antihypertensives for hypertensive disorders of pregnancy who meet inclusion criteria (Part A) and who are currently pregnant or before 6 weeks postpartum will be invited to participate and provided with Part A PIS and asked to provide informed consent after 24 hours, or before according to participant preference.

Data will be collected at recruitment and when they commence medication if needed after delivery. Participants will be randomised to be recommended to take enalapril or an alternative agent (nifedipine, amlodipine or labetalol) if they still require an antihypertensive agent to maintain a blood pressure of <140/ <90mmHg after delivery or at any point in the first six weeks following delivery.

The recommendations will be clearly written in their clinical notes to inform their clinicians and communicated to the clinical teams. The research team will identify participants on admission for delivery and in postpartum clinics and prompt local clinicians to prescribe according to the randomisation arm. Medication will be commenced prior to discharge from the hospital following delivery where possible. Prior to discharge from hospital following delivery, all participants will be invited to undergo a transthoracic echocardiogram (TTE), electrocardiogram (ECG) and ophthalmic assessment (at sites where these investigations are available). In the event an individual does not require an antihypertensive agent prior to discharge but does need an antihypertensive agent in the first six weeks their clinical team will be encouraged to prescribe the medication originally assigned during the randomisation.

Routine clinical kidney profile at 2 weeks and blood pressure and urinary albumin creatinine ratio check at 16 weeks (or as clinically indicated) after commencing medication will be taken for all participants and recorded in Macro database. Ongoing medication decisions will be made according to clinical needs by the clinical team and recorded. At 16 weeks, the ophthalmic assessment, TTE and ECG will be repeated if the participant has been recruited at a site where these investigations are available.

If antihypertensive therapy is no longer required to maintain a blood pressure of <140/<90 mmHg, the agent shall be discontinued as per standard practice. If participants do not need any antihypertensives after delivery after recruitment to Part A, this will be recorded, and they will proceed to Part B below.

Individuals recruited to Part A who choose not to breastfeed will be invited to participate in Part B after they have been randomised to enalapril or other antihypertensive medication, as part of the Part A randomisation. Individuals recruited to Part A who choose to breastfeed, will be invited to participate in Part B once they have completed breastfeeding, up to 52 weeks.

Participants recruited to Part A who continue to breastfeed after 52 weeks/12 months (due to time period of funding being prohibitive); or do not meet all inclusion and exclusion criteria for Part B will not be able to participate (but individuals will NOT be discouraged from breastfeeding). No additional data will be recorded other than which criterion(a) were not met.

Postpartum health champions will contact participants taking part in Part A every 4-6 weeks to build trust, ensure retention and check ongoing eligibility for Part B.

Healthcare champions will be individuals, who are healthcare workers within the NHS who will provide culturally congruent support to participants. These individuals will be recruited through the Race Ethnicity and Cultural Heritage (REACH) Network. The participants will consent to their contact details being provided to health champions to facilitate support for participation. These contact details, only released with the participant's consent, will be the only patient identifiable data accessed by the health champion. The health champion will be trained by the research team to check-in with participants (telephone or text), encourage uploading of home measurements and return of samples and will communicate any obstacles to participation to the research team. It will be made clear to the participant in the PIS that the role of the health champion is not to provide any healthcare advice and to contact the research team instead.

No changes will be made to the trial schedule for participants in Part B following participation in Part A. The Patient Health Questionnaire-9 (PHQ-9) is a validated screening tool for postpartum depression and will be administered at 2 weeks and again within the end of study survey.

Part B: Individuals who meet inclusion and exclusion criteria for Part B (including those recruited to Part A, after they have completed breastfeeding) will be identified by the clinical

teams, and research teams (Part A) and provided with Part B PIS and will be asked for informed consent to Part B (including those who have already consented to Part A). Participants will be also offered to invite a study-buddy (friend or family member) to be assessed for eligibility. The study buddy will be provided with a PIS by the participant and offered an opportunity to discuss the study with the research team. They will be invited to attend a screening visit.

If a potential study buddy participants fails to meet the eligibility criteria, up to three study buddies can be screened. This approach aims to increase the chances of finding eligible candidates while saving time and resources. By limiting the number of additional screenings to three, we ensure a thorough selection process while adhering to the practical constraints of our trial's resources. Participants can decline to have a study-buddy at recruitment but will not be able to invite someone later to take part as they will not be able to take dapagliflozin for the study period. Study-buddies will not receive any formal training which will allow us to explore whether this is a useful option for supporting individuals, from underserved communities, to participate in research. Study- buddies will be treated as participants in their own right and will be randomised with the main participant, to receive the IMP or standard care, and to undergo the same follow-up

Participants/ study buddy pair will be randomised to either: 26-weeks SGLT2i (54 participants/pairs), 26-weeks GLP-1 (54 participants/pairs) or standard care (54 participants/pairs).

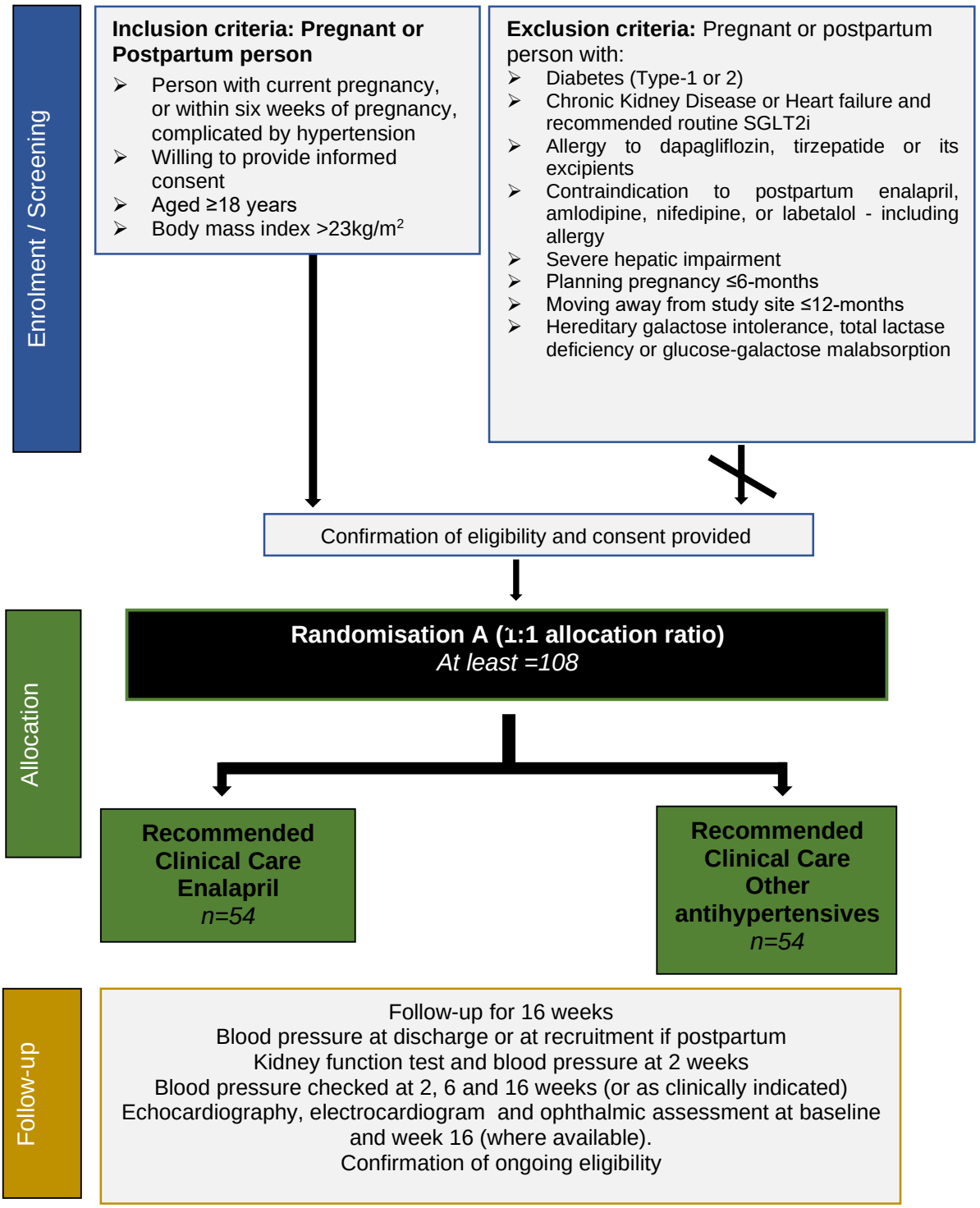
Healthcare champions will check in (Phone / Message / WhatsApp) with participants every 4-6 weeks to offer support and identify any issues from the participants' perspective, related to the study, which the healthcare champion can then communicate to the study team.

Assessments will be performed at baseline, 2 weeks and approximately 4 weekly thereafter to allow for variations in menstruation (urine dipstick, pregnancy test, weight and BP) with home-lab tests at weeks 2, 14 and 38 (capillary blood and urine samples). At baseline and all onsite visits participants will be asked to complete the PHQ-9 . All participants will have three on-site visits, at baseline, at 26 weeks and at 52 weeks/final assessment. These onsite visits will include a physical examination, blood test, urine test, urine pregnancy test, TTE, ECG, pulse wave velocity measurement and ophthalmic assessment (at sites where these investigations are available).

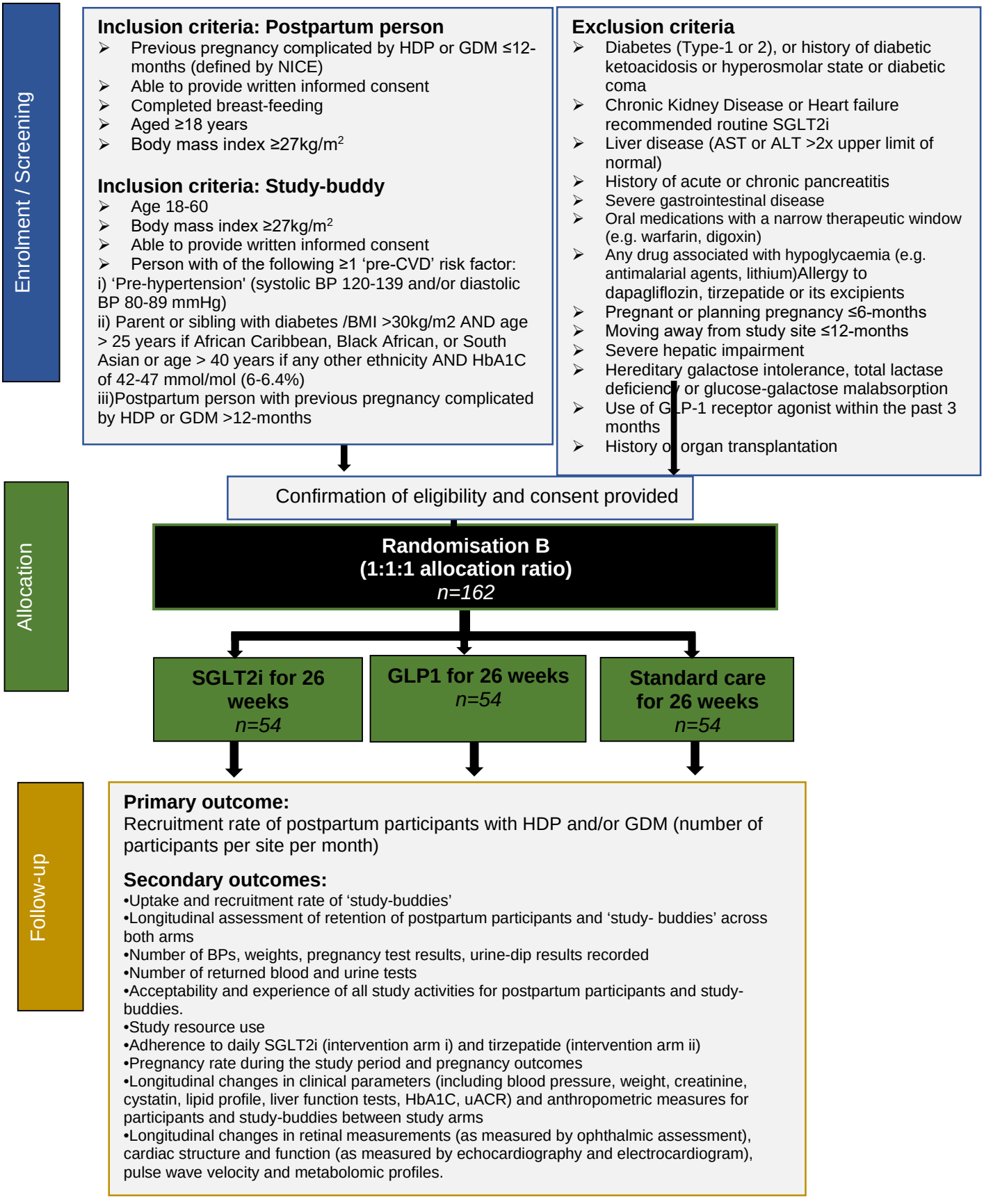
Postpartum participants and study buddy participants will be invited to complete end of study questionnaire (at the final assessment) including PHQ-9 and a sample (purposively selected to represent those who did and did not engage) invited to focus groups at exit from the trial to explore the acceptability of the trial and their experience of participation. Separate focus groups will be held for participants with a study- buddy and participants without a study- buddy. PHQ-9 is an open-access tool to screen for mood disorders and is validated the time point at which individuals would complete Part B.

5.5 Trial Flowchart

Part A:



Part B:


Enrolment / Screening
Inclusion criteria: Postpartum person
Previous pregnancy complicated by HDP or GDM ≤12-months (defined by NICE)
Able to provide written informed consent
Completed breast-feeding
Aged ≥18 years
Body mass index ≥27kg/m2
Inclusion criteria: Study-buddy
Age 18-60
Body mass index ≥27kg/m2
Able to provide written informed consent
Person with of the following ≥1 'pre-CVD' risk factor:
i) 'Pre-hypertension' (systolic BP 120-139 and/or diastolic BP 80-89 mmHg)
ii) Parent or sibling with diabetes /BMI >30kg/m2 AND age > 25 years if African Caribbean, Black African, or South Asian or age > 40 years if any other ethnicity AND HbA1C of 42-47 mmol/mol (6-6.4%)
iii)Postpartum person with previous pregnancy complicated by HDP or GDM >12-months
Exclusion criteria
Diabetes (Type-1 or 2), or history of diabetic ketoacidosis or hyperosmolar state or diabetic coma
Chronic Kidney Disease or Heart failure recommended routine SGLT2i
Liver disease (AST or ALT >2x upper limit of normal)
History of acute or chronic pancreatitis
Severe gastrointestinal disease
Oral medications with a narrow therapeutic window (e.g. warfarin, digoxin)
Any drug associated with hypoglycaemia (e.g. antimalarial agents, lithium)Allergy to dapagliflozin, tirzepatide or its excipients
Pregnant or planning pregnancy ≤6-months
Moving away from study site ≤12-months
Severe hepatic impairment
Hereditary galactose intolerance, total lactase deficiency or glucose-galactose malabsorption
Use of GLP-1 receptor agonist within the past 3 months
History of organ transplantation
Confirmation of eligibility and consent provided
Allocation
Randomisation B
(1:1:1 allocation ratio)
n=162
SGLT2i for 26 weeks
n=54
GLP1 for 26 weeks
n=54
Standard care for 26 weeks
n=54
Follow-up
Primary outcome:
Recruitment rate of postpartum participants with HDP and/or GDM (number of participants per site per month)
Secondary outcomes:
•Uptake and recruitment rate of 'study-buddies'
•Longitudinal assessment of retention of postpartum participants and 'study- buddies' across both arms
•Number of BPs, weights, pregnancy test results, urine-dip results recorded
•Number of returned blood and urine tests
•Acceptability and experience of all study activities for postpartum participants and study-buddies.
•Study resource use
•Adherence to daily SGLT2i (intervention arm i) and tirzepatide (intervention arm ii)
•Pregnancy rate during the study period and pregnancy outcomes
•Longitudinal changes in clinical parameters (including blood pressure, weight, creatinine, cystatin, lipid profile, liver function tests, HbA1C, uACR) and anthropometric measures for participants and study-buddies between study arms
•Longitudinal changes in retinal measurements (as measured by ophthalmic assessment), cardiac structure and function (as measured by echocardiography and electrocardiogram), pulse wave velocity and metabolomic profiles.

5.6. Schedule of Events: Table 1: Part A:

	Screening	Baseline	Visit 2	Visit 3 – Virtual	Visit 4 – Final
Weeks (Flexibility window of +/- 1 wk applies to each)	**36 wks gestation**	**0 wks (Following delivery prior to discharge or within 6 weeks of delivery)**	**2 wks**	**6 wks**	**16 wks**
Written informed consent	X				
Eligibility assessment	X				
Randomisation to enalapril or other antihypertensive		X			
• **Baseline demographics** • **Medication** • **Medical, family and obstetric history**		X			
Onsite visit: • **Physical examination (weight, height, BP, waist, hip and upper arm circumference)** • **Concomitant medication**		X	X		X
PHQ-9			X		X
Kidney function blood test*		X	X		X
Urinary pregnancy test (<u>only</u> If >one week following delivery)		X	X		
• **Urine albumin creatinine ratio (uACR)** •					X
ECG, TTE, ophthalmic assessment (where available)		X			X
Home blood pressure reading				X	
Adverse events review**	X	X	X	X	X
Assess Adherence (using MARS-5)					X
Focus group					X

End of Study Survey					X

*At baseline visit, visit 2 and visit 4, Cystatin C and serum standard renal profile blood test will be sent.
**Healthcare champions will contact participants at least monthly and will ask about adverse events during this contact.

Schedule of Events: Table 2: Part B:

	Screening															Final
Weeks (Flexibility window of +/- 1 wk applies to each)	**4 wks prior to baseline (antenatal/postnatal)**	**Baseline**	**IMP start† (0 wks)**	**2 wks**	**6 wks**	**10 wks**	**14 wks**	**18 wks**	**22 wks**	**26 wks**	**30 wks**	**34 wks**	**38 wks**	**42 wks**	**48 wks**	**52 wks.**
Written informed consent	X															
Eligibility assessment	X															
Randomisation		X														
• Baseline demographics • Medication • Medical, family and obstetric history		X														
Onsite visit: • Physical examination (weight, height, BP, waist, hip and upper arm circumference) • Concomitant medication • PHQ-9 • Assess adherence at week 26 only (MARS-5) • ECG, TTE, ophthalmic assessment, pulse wave velocity (where available)		X								X						X
Onsite visit blood tests: (FBC, LFTs, creatinine, cystatin, HbA1C, cholesterol)		X								X						X
Onsite visit blood tests: Serum amylase and serum lipase		X								X						
Onsite metabolomic profile (blood and urine samples)		X								X						
Onsite visit urine tests:																

(Urinary dipstick (protein/ glucose/leucocytes), urinary pregnancy test uACR		X								X						X
Samples to be frozen: -Plasma and serum -Urine		X								X						X
IMP dispense			X		X (8 weeks)		X (16 weeks)		X (24 weeks)							
Home assessments: • Weight • Urinary pregnancy test • Urine dipstick				X	X	X	X	X	X	X	X	X	X	X	X	X
Home-lab capillary blood tests*: (Creatinine, HbA1C, lipid profile, liver function tests)				X			X						X			
Home-lab urine tests: (Urinary dipstick (protein/ glucose/leucocytes), urinary pregnancy test uACR, urinary amylase)				X			X						X			
Pill photograph upload (via MyChart)				X	X	X	X	X	X	X						
IMP returns (unused IMP or used blister packs)																X
Study resource use**																X
Adverse events review***	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Focus group										X						X
End of study survey																X
Subsequent pregnancy outcome data				X	X	X	X	X	X	X	X	X	X	X	X	X

Within 2 weeks of baseline visit depending on menstrual cycle and negative pregnancy test.
*For home- lab blood tests: Lipid profile (LDL, Non- HDL, HDL, total cholesterol, triglycerides) and liver function test (total protein, albumin, globulin, alanine aminotransferase, GGT, alkaline phosphatase)
**Study resource use assessment refers to contacts with health champions, time for health champion training, expenditure on printing (£), time (hours) on participant recruitment and data extraction, home testing kit use (at 26 weeks and 52 weeks) and this will be recorded in study logs in local site files.
***Healthcare champions will contact participants at least monthly and will ask about adverse events during this contact

6. Trial Medication

6.1. Investigational Medicinal Product

This trial is comparing dapagliflozin and tirzepatide to standard of care. Dispensed dapagliflozin and tirzepatide will be collected from the site pharmacy by the site research team, who will arrange distribution of the medicine to the participant using tracked delivery.

(i)

Drug name:	Dapagliflozin propanediol monohydrate, equiv. to 10mg dapagliflozin.
Brand name:	Forxiga®
MAH:	AstraZeneca UK Limited
Dosage form:	Film-coated tablet
Dose:	10 mg once daily, taken orally.
Packaging:	Commercial/licenced packaging
Source of product:	Hospital stock. Each site pharmacy team to procure the supplies. No reimbursement from the Sponsor.
Labelling:	Trial-specific labelling (Annex13 compliant). Working under conditions outlined in Regulation 37 of The Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended), the labelling of the IMP must be carried out in the hospital undertaking this trial by a pharmacist or a person acting under the supervision of a pharmacist.
Prescription:	Trial-specific prescription.

Dapagliflozin is a SGLT2i, whereby SGLT2 protein is blocked in the kidneys reducing glucose reabsorption and increasing urinary glucose excretion.

(ii)

Drug name:	Tirzepatide
Brand name:	Mounjaro®
MAH:	Eli Lilly and Company Limited
Dosage form:	Solution for subcutaneous injection
Dose:	Initiate at 2.5 mg once weekly subcutaneously for at least 4 weeks, increasing by 2.5 mg increments every 4 weeks based on symptom tolerance and weight loss, to a maximum dose of 15 mg weekly
Packaging:	Commercial/licenced packaging
Source of product:	Hospital stock. Each site pharmacy team to procure the supplies. No reimbursement from the Sponsor.
Labelling:	Trial-specific labelling (Annex 13 compliant). Working under conditions outlined in Regulation 37 of The Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended), the labelling of the IMP must be carried out in the hospital undertaking this trial by a pharmacist or a person acting under the supervision of a pharmacist
Prescription:	Trial-specific prescription.

Tirzepatide (Mounjaro®) is a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, enhancing glucose-dependent insulin secretion, suppressing glucagon release, and delaying gastric emptying, promoting satiety and weight loss

6.2. Dosing Regimen

(i) Patients will be prescribed 10mg Dapagliflozin to be taken once daily orally. Dapagliflozin is usually prescribed for patients with type 2 diabetes or heart failure or chronic kidney disease There are no specific dietary or lifestyle adjustments needed. Dapagliflozin will be commenced in the treatment group within 2 weeks of the baseline visit depending on menstrual cycle and following a negative pregnancy test (week 0) and then taken for 26 weeks.

(ii) Patients will start tirzepatide at 2.5 mg weekly via subcutaneous injection for a minimum of 4 weeks. Dosing increments of 2.5 mg will be considered every 4 weeks based on individual symptom tolerance and observed weight loss efficacy, up to a maximum of 15 mg weekly. Treatment will begin within 2 weeks of the baseline visit, contingent upon menstrual cycle timing and following a negative pregnancy test (week 0) and continue for 26 weeks. Tirzepatide will be stopped if body mass index falls to less than 20kg/m^2. The prescribing clinician or a delegated healthcare professional will provide verbal instruction and demonstration on self-administration, including dose frequency, timing, injection site rotation, preparation, storage, and safe disposal. This will be supported by the Patient Information Leaflets (PILs) supplied with the tirzepatide medication.

6.3. IMP Risks

(i) The common side effects of dapagliflozin are hypoglycaemia (when used in combination with insulin or sulfonylurea), genital infections, urinary tract infection, dizziness, rash, back pain, urinary disorders, dyslipidaemia, haematocrit increased and decreased creatinine renal clearance at treatment initiation. It is recommended dapagliflozin is held if an individual is unwell or fasting for a procedure. These side effects and recommendations are detailed in the summary of product characteristics and the patient information leaflet included in the pack with the medicine.

(ii) Common side effects associated with tirzepatide include gastrointestinal symptoms such as nausea, vomiting, diarrhoea, constipation, and abdominal pain. Rare but important risks include pancreatitis, cholelithiasis, acute kidney injury, and injection site reactions. Full details of these side effects, management advice, and contraindications are provided in the summary of product characteristics and the patient information leaflet included in the medicine packaging.

6.4. Drug Accountability

Dispensed dapagliflozin and tirzepatide will be collected from the local site pharmacy by the site research team, who will arrange distribution of the medicine to the participant using tracked delivery in 8 weekly intervals.

This information will be recorded on a drug accountability log. Drug accountability records will be verified by the trial Clinical Research Associate (CRA/ Monitor) at each site. When permission has been granted by the Sponsor, returned IMP will be retrieved and destroyed as per local pharmacy SOPs. Returns and destruction of the IMP at other research sites will follow their local protocol.

6.5. Storage of IMP

The IMP will be dispensed from local pharmacy in 8 week batches. In accordance with the manufacturer’s instructions, dapaglifozin does not require any special storage conditions. Temperature monitoring is not required. Tirzepatide must be refrigerated (2°C to 8°C) until use. Participants will be instructed clearly on appropriate home storage conditions.

Temperature monitoring will be conducted at the dispensing pharmacy; participants will be instructed on appropriate handling for home storage.

6.6. Participant Compliance

Adherence which will be assessed through 4-weekly pill-packet photograph and presence of glucose on urine dipsticks performed 4 weekly as outlined in trial schedule. The pill-packet photograph (for dapagliflozin) and urine dipstick result will be uploaded to MyChart (or local patient electronic portal) and reviewed by the research team. The Medication Adherence Report Scale-5 (MARS-5) is a validated, self- reported instrument which contains five questions to measure an individual's reports of their medication use.

6.7. Non- Investigational Medicinal Products:

Enalapril, nifedipine, amlodipine and labetalol will be used for the treatment of postpartum hypertension, reflecting standard of care. Within PHYLLIS, these medications are considered non-Investigational Medicinal Product (nIMP) as they are background treatment for hypertension, whereas the main objective of this study is to assess the feasibility of larger study assessing SGLT2i (dapagliflozin) and GLP-1 (tirzepatide) against the standard of care. These medications are all oral agents, have been shown to be safe while breastfeeding (NICE 2019) and will be used within their marketing authorisation in the UK.

As dictated by standard of care, participants will take this nIMP to maintain a blood pressure of <140/<90mmHg. The starting dose of enalapril is 2.5mg once daily and this can be up-titrated to 40mg a day. The common side effects of enalapril are persistent dry cough, rash, headaches and diarrhoea. The starting dose of nifedipine is 5mg three times daily, up to 20mg three times daily. The common side effects of nifedipine include headaches, lower limb oedema and constipation. The starting dose of amlodipine is 5mg once daily, up to 10mg once daily. The common side effects of amlodipine include headaches, lower limb oedema and palpitations. The starting dose of labetalol is 100mg twice daily and can be up-titrated to 2400mg daily. The common side effects of labetalol include diarrhoea, headaches and nausea. All implications of taking these medications will be fully explained to participants.

6.8. Concomitant Medication

All concomitant medications received during Part A and Part B will be recorded in the electronic Clinical Report Form (eCRF) at all onsite visits. For management of concomitant therapies, please refer to the SmPC. The exclusion criteria specify that participants with a diagnosis of type 1 or type 2 diabetes mellitus are excluded (therefore excluding individuals taking insulin or sulfonylureas, which can cause hypoglycaemia). In addition, medications with narrow therapeutic windows and any drugs associated with hypoglycaemia are also excluded.

7. Selection and Withdrawal of Participants

7.1. Inclusion Criteria Part A

- Person with current pregnancy, or within six weeks of pregnancy, complicated by hypertension
- Able to provide written informed consent
- Age ≥ 18 years
- Body mass index >23kg/m^2

7.2. Exclusion Criteria Part A

Pregnant or postpartum person *(including people not identifying as female)* with:

- Diabetes (Type-1 or 2)
- Chronic Kidney Disease or Heart failure and recommended routine SGLT2i
- Severe hepatic impairment
- Allergy to dapagliflozin, tirzepatide or its excipients
- Hereditary galactose intolerance, total lactase deficiency or glucose-galactose malabsorption
- Contraindication to postpartum enalapril, amlodipine, nifedipine, or labetalol - including allergy
- Moving away from study site within 12 months
- Planning pregnancy ≤6-months

7.3. Inclusion Criteria Part B

Postpartum person *(including people not identifying as female):*

- Previous pregnancy complicated by HDP and/or GDM (defined by NICE) ≤12-months
- Able to provide written informed consent
- Age ≥ 18 years
- Completed breastfeeding
- Body mass index ≥27kg/m^2

Study buddy:

- Age 18 – 60 years
- Body mass index ≥27kg/m^2
- Able to provide written informed consent
- Person with ≥1 pre-CVD risk factor:
  i) Pre-hypertension (systolic BP 120-139 and/or diastolic BP 80-89 mmHg)
  ii) Parent or sibling with diabetes or body mass index (BMI) >30 kg/m2 AND age > 25 years if African Caribbean, Black African, or South Asian or age > 40 if any other ethnicity AND HbA1C of 42-47 mmol/mol (6-6.4%)
  iii)Postpartum person with previous pregnancy complicated by HDP and/or GDM > 12 months

7.4. Exclusion Criteria Part B

Postpartum person *(including people not identifying as female)* and study-buddies with:

- Diabetes (Type-1 or 2), or history of diabetic ketoacidosis or hyperosmolar state or diabetic coma
- Chronic Kidney Disease or Heart failure and recommended routine SGLT2i
- Liver disease (AST or ALT > 2x upper limit of normal)
- History of acute or chronic pancreatitis
- Severe gastrointestinal disease
- Oral medications with a narrow therapeutic window (e.g. warfarin, digoxin)
- Any drug associated with hypoglycaemia (e.g. antimalarial agents, lithium)
- Allergy to dapagliflozin, tirzepatide or its excipients
- Pregnant*, planning pregnancy within 6 months or breastfeeding **(**females of childbearing potential* with a positive pregnancy test at screening)
- Moving away from study site within 12 months
- Severe hepatic impairment

- Hereditary galactose intolerance, total lactase deficiency or glucose-galactose malabsorption
- Use of GLP-1 receptor agonists within the past 3 months
- History of organ transplantation

* A pregnancy test (urine) will be performed for all persons of childbearing potential. An individual is considered of childbearing potential *i.e.*, fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. Pregnancy tests will be performed at all onsite visits and monthly by participants with tests provided within their at home kits. Study drugs will not be dispensed without a negative pregnancy test. Women randomised to tirzepatide on oral contraception will be counselled on the potential for reduced efficacy and advised to use a barrier method or switch to non-oral contraception methods.

Contraception/family-planning advice will be provided, and monthly pregnancy testing requested. The use of more than one contraceptive method will be encouraged and there will be an emphasis on efficacy in the advice provided. . Women on oral contraception will be counselled on the potential for reduced efficacy and advised to use a barrier method or switch to non-oral contraception methods. In line with MHRA guidance, highly effective methods of contraception, which are defined as those with a failure rate of <1% per year when employed consistently and correctly, which include combined hormonal contraception, intrauterine devices, and transdermal progestogen- only hormonal contraception, will be recommended to participants. In line with PPI guidance, this advice will be culturally appropriate and considerate of religious beliefs. Optimising safety will be prioritised whilst ensuring participants from underserved communities are not excluded.

The study drug will not be dispensed without a negative pregnancy test. If pregnancy occurs study activity will stop, and permission requested to collect pregnancy and baby outcomes.

7.5. Selection of Participants

Participants will be identified in either the antenatal or postnatal care settings and pre-screened for eligibility by their usual care team. Potential participants will have any questions they have about the study answered by local clinical teams and will be given at least 24 hours to decide to participate, or less than 24 hours if the participant prefers. Eligibility will be confirmed by a medically qualified individual (all inclusion criteria met and none of the exclusion criteria). A clinician (on the delegation log with consent as a delegated responsibility) from the research team will obtain informed consent for participation. Individuals from ethnic minorities will be prioritised but not targeted for recruitment. Individuals who decline to participate will be asked to answer a short questionnaire. Recruitment and retention will be facilitated by an approachable study team, through having study buddies co-participating, and through regular contact every 4-6 weeks by healthcare champions to offer support and link the participant with the study team if needed.

7.6. Consent

Consent will be obtained separately for Part A and Part B.

Part A:
People who are pregnant or who have delivered in the last 6 weeks will be identified in either antenatal or postnatal care settings. A member of the direct care team may approach potential participants with information about the trial. If a patient is interested, they will be given the Part

A information sheet to read and the opportunity to have a further discussion with their care team, maternity research team members and health champions.

The participants will be given an appropriate amount of time to consider their participation in the study (participants will be encouraged to take at least 24 hours to consider whether to take part) and the opportunity to ask questions. Before seeking participants' consent, details of the trial aim, trial arms/treatment, anticipated benefits, and risks to taking part in addition to the understanding that participation is voluntary (and they can withdraw at any time) will be explained. Eligibility for Part A and written informed consent will be taken by a clinician from the research team.

Part B:
People who have delivered in the last 12 months will be identified in the postnatal care setting. A member of the direct care team may approach potential participants with information about the trial. If a patient is interested, they will be given the Part B information sheet to read and the opportunity to have a further discussion with their care team, maternity research team members and health champions.

The participants will be given an appropriate amount of time to consider their participation in the study (participants will be encouraged to take at least 24 hours to consider whether to take part) and the opportunity to ask questions. Before seeking participants' consent, details of the trial aim, trial arms/treatment, anticipated benefits, and risks to taking part in addition to the understanding that participation is voluntary (and they can withdraw at any time) will be explained.

Study buddies will be approached by participants and offered the opportunity to discuss the study with the research team.

Trial eligibility for Part B and written informed consent for both participants and study buddies will be taken by a physician from the research team.

For participants who have participated in Part A, they will be eligible to participate in Part B immediately if they are choosing not to breastfeed, or if they are choosing to breastfeed, then they will be eligible to participate in Part B after they have completed breastfeeding.

The original completed consent form will be kept in the Investigator’s Site File, one copy will be provided to the participants and one copy saved in the participants' medical notes.

Where English is limited, provisions to translate study materials will be undertaken to ensure consent (if provided) is informed.

7.7. Randomisation Procedure / Code Break

A web-based randomisation system will be designed, using the bespoke KCTU randomisation system. The randomisation system will be created in collaboration with the trial analyst/s and the CI and maintained by the King’s Clinical Trials Unit for the duration of the project. It will be hosted on a dedicated server within KCL.

Part A: Following informed consent participants recruited during pregnancy will be randomised to receive recommended postpartum care of enalapril or other antihypertensives safe for breastfeeding if required (1:1 ratio) to minimise the impact on BP control and renal outcomes between groups. Minimisation (A) will be performed based on site, type of hypertension (chronic hypertension (defined as blood pressure systolic BP ≥ 140 and/or diastolic BP ≥ 90 mmHg measured in the office or clinic pre-pregnancy at or <20 weeks’

gestation)/gestational hypertension/no hypertension and severity (0/ 1-2/ ≥3 antihypertensive agents).

Part B: Once pregnancy and breastfeeding are completed participants will be re-screened and if they remain eligible, consent will be reconfirmed and participant and study-buddy pairs (if co-recruitment selected by the participant) will be randomised in a 1:1:1 ratio to either: 26-weeks SGLT2i, 26-weeks GLP-1 or standard care. Minimisation (B) will be performed based on site, last antihypertensive agent taken (current, or previous RAAS blockade agent (taken for at least two weeks postpartum)/ other antihypertensive agent/ no antihypertensive agent required postpartum) and presence of gestational diabetes in recent pregnancy (according to local guidelines).

Data entry:
Randomisation will be undertaken by study team onto the randomisation system by going to www.ctu.co.uk and clicking the link to access the randomisation system. A full audit trail of data entry will be automatically date and time stamped, alongside information about the user making the entry within the system.

Security:
The CI or delegate will request usernames and passwords from the KCTU. System access will be strictly restricted through user-specific passwords to the authorised research team members. It is a legal requirement that passwords to the randomisation system are not shared, and that only those authorised to access the system are allowed to do so. If new staff members join the study, a user-specific username and password must be requested via the CI or delegate (e.g., Trial Manager) from the KCTU team and a request for access to be revoked must be requested when staff members leave the project. Study site staff experiencing issues with system access or functionality should contact the CI or delegate (e.g., Trial Manager) in the first instance.

Participant initials and date of birth will be entered on the randomisation system. Whereas NHS number, email addresses, participant names and addresses and full postcodes will not be entered into the randomisation system. No data will be entered onto the randomisation system unless a participant has signed a consent form to participate in the trial.

Data Quality Processes:
The CI team will undertake appropriate reviews of the entered data for the purpose of data cleaning. No data can be amended in the system, however CI or delegate (e.g., Trial Manager) may request King's Clinical Trials Unit to add notes against individual subject entries to clarify data entry errors.

Database Lock:
Upon request, KCTU will provide a copy of the final exported dataset to the CI in .csv format and the CI will onward distribute as appropriate.

7.8. Emergency Code Break

As an open label study all participants (postpartum participants and study-buddies), healthcare providers, and outcome assessors will be unmasked to allocation. All data analysts will be masked to allocation unless required the Trial Steering Committee. Therefore, an emergency code break is not applicable.

7.9. Withdrawal of Participants

Participants have the right to withdraw from the study at any time for any reason. The investigator also has the right to withdraw patients from the study treatment in the event of intercurrent illness, Adverse Events, Serious Adverse Events, Suspected Unexpected Serious Adverse Reaction, protocol violations, administrative reasons or other reasons.

It is understood by all concerned that an excessive rate of withdrawals can render the study un-interpretable; therefore, unnecessary withdrawal of participants should be avoided. Should a participant decide to withdraw from the study, all efforts will be made to report the reason for withdrawal as thoroughly as possible. Should a participant withdraw, efforts will be made to continue to obtain follow-up data, with the permission of the participant.

Participants can withdraw from:

- the intervention only (study drug)
- home lab-tests and assessments (but will not be able to continue intervention)
- further contact with the study team (but will not be able to continue intervention)
- subsequent case note review (but will not be able to continue intervention)
- the entire study

Any form of withdrawal will be documented within eCRFs (date, reason, type of withdrawal and reason for the withdrawal).

Participants who become pregnant during the study period will not be withdrawn but will be asked to stop taking enalapril (Part A) or dapagliflozin (Part B) if in the intervention arm and the clinical data collection will continue. Other antihypertensive agents used in Part A do not need to be discontinued when pregnancy occurs. They will be invited to continue to participate in participate experience outcomes and be asked to provide their future pregnancy outcomes (only for Part B). Baby outcomes for participants from Part B that will be collected will include birthweight, gestation at birth, live birth and any health complications.

If a participant or study buddy decides to withdraw or is withdrawn from the study, their paired partner can continue to participate if they wish. Withdrawn participants and their study buddies may be replaced**.**

7.10. Expected Duration of Trial

Including set- up of 6 months, recruitment and follow up of 24 months and analysis, write up and dissemination of 6 months, the total expected duration of this trial will be 36 months. For Part A, the maximum duration will be 16 weeks. For Part B, the duration will be 52 weeks with a maximum duration on treatment of 26 weeks. The end of the study will be defined as the database lock.

8. Trial Procedures

8.1. By Visit

Part A: On-site visits and tests

Screening visit (36 weeks' gestation- window +/- 1 week)

At screening, participants will be asked to provide written informed consent as per Section 7.6. Only once this has taken place the doctor will screen and sign off the eligibility log. For currently pregnant participants (36 weeks' gestation - window 35-37 weeks)) no other study activities will occur until after delivery. (Identification and recruitment during pregnancy will help to maximise recruitment as antenatal care is more predictable (e.g. hypertension clinics)

and was considered acceptable by PPIE). The recording of adverse events will commence from the time the consent form is signed.

Baseline assessment

Details of participants' demographics (including gender identity) and their medication, medical and family and obstetric history (including birthweight, and gestation at delivery) will be recorded.

All tests are study-specific unless specified for routine clinical care.

Onsite baseline assessments will include:
- physical examination (weight, height, BP, anthropometric measures - waist, hip and upper arm circumference)
- urinary pregnancy test (if not still pregnant / or > 1 week postpartum)
- blood test (kidney function, including serum creatinine (routine clinical care) and cystatin)
- concomitant medication review

Randomisation

At baseline visit, individuals will be randomised to receive enalapril or amlodipine, nifedipine or labetalol (as per Section 7.7) and recommended antihypertensive if required written on their records and in the postpartum plan.

Participants will be contacted by health champions every 4-6 weeks to maintain contact, build trust and enhance research team awareness of the timing of delivery.

Pregnant individuals recruited prior to delivery who remain hypertensive after delivery, requiring treatment will be contacted by the research team to confirm they wish to continue to participate in Part A. Individuals who do not require medication will have ongoing contact with health champions and proceed to Part B when completed breastfeeding. Individuals who choose not to breastfeed can proceed to Part B immediately.

Individuals who are identified to have hypertension within six weeks after delivery will be approached by the clinical team and recruited by the research team from the postnatal ward, or postnatal clinics.

Visit 2: On-site tests (2 weeks following initiation of blood pressure treatment)

Onsite assessments will include: (all tests are for the study, unless specified for routine clinical care)
- physical examination (weight, height, BP, anthropometric measures - waist, hip and upper arm circumference)
- urinary pregnancy test (if not still pregnant / or > 1 week postpartum).
- blood test (kidney function, including serum creatinine and cystatin)
- concomitant medication
- adverse event check
- PHQ-9

- As per routine care individuals commenced on ACE inhibitors (such as enalapril), a repeat kidney profile blood test will be performed at 2 weeks onsite to ensure the medication has been safely tolerated. As per standard NHS practice, enalapril will be continued unless this blood test reveals that potassium is elevated above 5.5mmol/L, or serum creatinine has risen to greater than 30% of the baseline recorded following delivery.
- For completeness, all participants will be offered this blood test regardless of antihypertensive agent.

- All other care for Part A will follow local practice for the management of postnatal hypertension

Visit 3: Virtual visit (6 weeks: Window +/- 1 week)

-Participants will be asked to record blood pressure at home
-They will be phoned by a member of the research team who will ask for this reading and will ask about adverse events.

Visit 4: Onsite visit (16 weeks: Window +/- 1 week)

Onsite assessments will include:
- physical examination (weight, height, BP, anthropometric measures - waist, hip and upper arm circumference)
- blood tests: kidney function, including serum creatinine and cystatin
- Transthoracic echocardiogram (where available)
- Electrocardiogram (where available)
- ophthalmic assessment (where available)
- concomitant medication
- adverse event check
- urinary sample for urine albumin creatinine ratio
-Participants will also be invited to a focus group and will be asked to fill out an end of-study survey which incorporates the PHQ-9
- If participants become pregnant during Part A, they will not continue any additional data collection, and will not be able to participate in Part B
- Adherence will also be assessed using the MARS-5.

Part B: On-site visits and tests

Screening visit (4 weeks prior to baseline assessment: Window: +/- 1 week)

Potentially new eligible participants will be identified by the clinical care team and consent provided as per section 7.6. For individuals who have completed Part A, ongoing eligibility will be assessed by the research team. If participants recruited to Part A continue to breastfeed after 12 months, they will no longer be eligible for Part B. Breastfeeding will not be discouraged.

Sufficient time will be given for participants to consider consent for Part B (24 hours, or less than 24 hours if the participant prefers) and then informed written consent will be completed by the study clinician on the delegation log. Only once this has taken place the local clinical team will screen for eligibility.

Study buddy screening: Participants will be offered the opportunity to approach a study buddy to attend for screening as above. Up to three study buddies per participant can be screened in order to find one individual who meets eligibility.

Attendance of study buddies will be offered at the same time as their participant pair or separately if preferred.

The recording of adverse events will commence from the time the consent form is signed.

Baseline assessment & randomisation (week 0)

Details of participants and study buddies' demographics (including gender identity) and medication, obstetric (including birthweight, gestation at delivery), and medical and family history will be recorded.

Onsite baseline assessments will include:
- physical examination (weight, height, BP, anthropometric - waist, hip and upper arm circumference)
- blood test (full blood count, creatinine, cystatin, liver function tests, amylase, lipase, HbA1C and cholesterol, metabolomic profile and plasma and serum samples for freezing)
- urine test (ACR), urine sample for freezing, and pregnancy test*
* all pregnancy tests will be excluded if the study buddy is male
Samples for freezing with be processed immediately and then stored at -80°C for future measurements.
- urinary dipstick (protein/ glucose/leucocytes)
- Transthoracic echocardiogram (where available)
- Electrocardiogram (where available)
- ophthalmic assessment (where available)
- pulse wave velocity measurement (where available)
- concomitant medication check
- adverse event check
To facilitate baseline, visit attendance, travel expenses will be reimbursed, onsite childcare will be provided where possible and there will be flexibility in scheduling these visits.

Participants and study buddies will be asked to register with EPIC MyChart (or local patient electronic portal). The 'Home-Lab tests and assessments' will be explained alongside the provision of written and online materials explaining how to undertake the assessments/tests the frequency of testing and instructions on data entry.

Postpartum participants and study-buddy pairs will be randomised according to information provided in section 7.7(b). If randomised to the intervention, dapagliflozin will be provided in the study pack that the participant will receive at week 2. Participants and study buddies will receive a supply (see first pack below) every two months and dapagliflozin will be discontinued immediately if the participant becomes pregnant.

From this point in the protocol, study buddies will be referred to as participants as all their activities will be the same. Participants in Part B will be contacted by health champions every 4-6 weeks to maintain contact, build trust and enhance research team awareness of the timing of delivery.

Home Tests

Each participant will receive a study pack delivered to their home address, or given on-site, separated into three packs.

The first pack will be for participants in the treatment arm. It will have the first two months' supply of the IMP (dapagliflozin/tirzepatide). This will be supplied at week 2.

The second pack will include all that is required for the 4-weekly home assessments: BP monitor, weighing scales, urine dip kits (urinalysis measuring: protein/glucose/leucocytes) and pregnancy test (urine test measuring beta Human Chorionic Gonadotrophin).

The third pack will comprise of capillary blood kits and urine sample kits which will be sent to participants at weeks 2,14 and 38.

- Urine samples will be used for ACR testing and urinary amylase. Participants will send samples to King's College Hospital research team (via a prepaid return kit provided by the research team) and the research team will take them to Synnovis laboratory for analysis.
- Capillary blood kits will be analysed for creatinine, HbA1C, lipid profile (LDL, Non- HDL, HDL, total cholesterol, triglycerides), and liver function tests (total protein, albumin, globulin, alanine aminotransferase, GGT, alkaline phosphatase). Participants will send samples to Thriva https://thriva.co/ (via a prepaid return kit provided by the research team).

Participants will be asked to record their results (or reasons for uncompleted or unsuccessful testing) within EPIC MyChart (or local patient electronic portal) (via photographs or manual entry) or on paper, at the discretion of the participant.

26-week assessment – onsite

Onsite assessments for participants and study buddies will include:
- physical examination (weight, height, BP, anthropometric measures - waist, hip and upper arm circumference)
- blood test (full blood count, creatinine, cystatin, liver function tests, amylase, lipase, HbA1C, cholesterol, metabolomic profile and plasma and serum samples for freezing)
- urine test (ACR) urine sample for freezing and pregnancy test. Blood and urine samples for freezing with be processed immediately and then stored at -80°C for future measurement
- urinary dipstick (protein/ glucose/leucocytes)- Transthoracic echocardiogram (where available)
- Electrocardiogram (where available)
- ophthalmic assessment (where available)
- pulse wave velocity measurement (where available)
- Concomitant medications will be reviewed.
- PHQ-9.

IMP adherence in the intervention arm will be assessed by pill-counting at 26 weeks visit (**or 4 weekly photographs of blister packs). Participants will also be asked to complete the medication adherence report scale – 5 (MARS-5) to assess reasons for poor adherence.
Any adverse events will be recorded and reported.

52- week/final assessments - onsite

Onsite assessments will include:
- physical examination (weight, height, BP, anthropometric measures - waist, hip and upper arm circumference)
- blood test (full blood count, creatinine, cystatin, liver function tests, HbA1C and cholesterol, and plasma and serum samples for freezing)
- urine test (ACR) and pregnancy test

Blood and urine samples for freezing with be processed immediately and then stored at -80°C for future measurement.
- Urinary dipstick (protein/ glucose/leucocytes)
- Transthoracic echocardiogram (where available)
- Electrocardiogram (where available)
- ophthalmic assessment (where available)
- pulse wave velocity measurement (where available)
- PHQ-9

Concomitant medications will be reviewed, and photographs of pill packets checked. Any adverse events will be recorded and reported. Study resource use will be assessed at this point in terms of contacts with health champions, time for health champion training, expenditure on printing (£), time (hours) on recruitment and data extraction, home testing kit use (at 26 weeks and 52 weeks) (recorded in study logs in local site files).

All study equipment and any unused IMP (or empty blister packs) will be returned. Data entry will be reviewed and completed where possible and the end-of-study survey provided.

Quantitative and qualitative exploration of acceptability and participant experience
All participants will be invited to complete an End of study questionnaire (at 52 weeks), which will incorporate the Patient Health Questionnaire (PHQ-9), capturing all aspects of participation including engagement materials, support from postpartum health champions and study buddies, home-lab testing and assessments and data collection methods.

- A representative subgroup of participants (approximately 10 participants and up to 10-study-buddies from each site) who have completed their 26-week visits will be invited to the focus group which will last 1-2 hours in duration. During this focus group recommendations for raising future engagement and health awareness will be explored.

- A separate focus group of postpartum health champions across each site to discuss material development, champion recruitment methods, barriers and facilitators to study engagement and optimal use of peer-educator support (e.g. prior to, during or after testing) in under-served communities.

  Focus groups with participants and study buddies, and separately with health champions, will be conducted at 26 weeks and 52 weeks. Separate focus groups will be held for participants with a study- buddy and participants without a study- buddy. Details of focus group conduct are provided in Appendix 1.

All focus groups will be facilitated by a trained member of the research team, audio-recorded and transcribed verbatim by Devon Transcription, fully anonymised, and analysed using NVivo 12.

Health economic data
- Study resource use will be recorded in study logs in local site files:
- Resources for printing (£)
- Contacts with health champions
- Time taken for health champion training
- Time taken for recruitment
- Time taken for data extraction
- Home testing kit use (at 26 and 52 weeks)

8.2. Laboratory Tests

All samples (blood: analysis of full blood count (haemoglobin), creatinine, cystatin, liver function tests (total protein, albumin, globulin, alanine aminotransferase, GGT, alkaline phosphatase), HbA1C, cholesterol; Urine: analysis of ACR) taken for Part B: at baseline, 26 weeks and at 52 weeks will be sent to local laboratories for analysis. For Part B, serum amylase and serum lipase will also be sent at baseline and 26 weeks to local laboratories for analysis. All samples (blood: creatinine, cystatin) taken for Part A: at baseline, 2 weeks and 16 weeks will be sent to local laboratories for analysis. For Part A at 16 weeks a urine sample (analysis of albumin creatinine ratio) will also be sent to local laboratory for analysis.

For Part B, at baseline, 26 weeks and 52 weeks additional plasma and serum blood samples will be taken, processed immediately and then stored at -80°C for future measurements. At these timepoints a mid-stream urine sample will also be taken, processed immediately and then stored at -80°C for future measurements. Pseudoanonymised plasma, serum, and urine samples will be stored in the HTA approved freezers for up to 10 years after study completion.

For Part B at baseline and at 26 weeks, serum and plasma blood samples and urine sample will be taken for metabolomic analysis. These samples will be taken at these two onsite visits and sent for analysis.
Blood results will be recorded on EPIC (or local electronic system) with a comment stating that results have been reviewed and are normal, or any results are noted and have been acted upon. Abnormalities will also be noted on the eCRF. All out-of-range results will be assessed as either clinically significant (CS) or not clinically significant (NCS), and any clinically significant results will be documented as adverse events.

Participant at-home testing will be analysed for creatinine, HbA1C, lipid profile (LDL, Non-HDL, HDL, total cholesterol, triglycerides) and liver function tests (total protein, albumin, globulin, alanine aminotransferase, GGT, alkaline phosphatase). Participants will send samples to Thriva https://thriva.co/ (via a prepaid return kit provided by the research team). All laboratory tests are trial-specific. Full details are included in the laboratory manual for the Thriva laboratory.

9. Assessment of Efficacy

Section not applicable given as the study is a feasibility study.

10. Assessment of Safety

10.1. Specification, timing and recording of Safety

The results of all investigations (blood pressure readings, blood test results, urinary results, cardiac investigations (transthoracic echocardiogram, electrocardiogram), ophthalmic assessment and metabolomic results) will be reviewed by an appropriately trained doctor who will counsel the patient, request repeat testing, inform general practice or referral to secondary care specialty as deemed clinically appropriate.

As tirzepatide may cause weight loss, a body mass index (BMI) of 27kg/m^2 or above is required as an inclusion criterion and tirzepatide will be stopped if BMI falls to less than 20kg/m^2.

In order to ensure the safety of all participants during the study duration, adverse events will be reported throughout Part A and Part B from the time the consent form is signed. The healthcare champions will contact the participants each month following randomisation and will inform the research team of any adverse events. At onsite visits throughout Part A (week 2, week 16) and Part B (week 26 and week 52) participants will be asked about adverse events. This will include any retrospective adverse events.

The following safety parameters will be recorded in the eCRF at the scheduled visits.
Urine Tests:
Beta-HCG shall be measured at baseline and at 4- weekly to ensure the medication is not taken during pregnancy. Urinalysis and blood tests will also provide assessments from a safety perspective. The four-weekly urine dipstick will reveal the presence of leucocytes and protein which could indicate infection and would prompt further testing. Urinary amylase will also be performed on urinary home samples sent by participants to screen for pancreatitis.

Blood Tests:
The risk of toxicity is also increased in renal impairment and liver impairment so the testing of both kidney function (cystatin, creatinine) and liver function (total protein, albumin, globulin, alanine aminotransferase, GGT, alkaline phosphatase) will also provide a safety mechanism.

Serum amylase and serum amylase will also be tested at weeks 0 and 26 which would detect pancreatitis. The kidney function testing in the form of cystatin and creatinine will be performed onsite at baseline, 26 weeks and 52 weeks. Creatinine testing alone will be performed at weeks 2, 14 and 38. Liver function testing (total protein, albumin, globulin, alanine aminotransferase, GGT, alkaline phosphatase) will also be performed on home testing at weeks 2, 14 and 38.
At each onsite review following the commencement of the IMP, the participants will be asked about side- effects and throughout will be encouraged to contact the research team with any concerns

10.2. Procedures for recording and reporting adverse events

The Medicines for Human Use (Clinical Trials) Regulations 2004 and Amended Regulations 2006 give the following definitions:

- **Adverse Event (AE)**: Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
- **Adverse Reaction (AR):** Any untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.
- **Unexpected Adverse Reaction (UAR)**: An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information from:
  The summary of product characteristics (SmPC) for that product
- **Serious adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR):** Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that**:**
  - results in death;
  - is life-threatening;
  - required hospitalisation or prolongation of existing hospitalisation;
  - results in persistent or significant disability or incapacity;
  - consists of a congenital anomaly or birth defect.

- **Important Medical Events (IME) & Pregnancy:** Events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above should also be considered serious. Although not a serious adverse event, any unplanned pregnancy will also be reported via the SAE reporting system

Reporting Responsibilities
Co-sponsors, King's College Hospital NHS Foundation Trust and King's College London have delegated the delivery of the Sponsor's responsibility for Pharmacovigilance (as defined in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004 to the King's Health Partners Clinical Trials Office (KHP-CTO).

All SAEs, SARs and SUSARs (excepting those specified in this protocol as not requiring reporting) will be reported immediately by the Chief Investigator (and certainly no later than 24hrs) to the KHP-CTO in accordance with the current Pharmacovigilance Policy.

The KHP-CTO will report SUSARs to the relevant ethics committee and to the regulatory authorities (Medicines and Healthcare Products Regulatory Agency, MHRA).

Reporting timelines are as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the sponsor is first aware of the reaction. Any additional relevant information must be reported within a further 8 days;

- SUSARs that are not fatal or life-threatening must be reported within 15 days of the sponsor first becoming aware of the reaction.

The Chief Investigator and KHP-CTO (on behalf of the co-sponsors) will submit a Development Safety Update Report (DSUR) relating to this trial IMP, to the MHRA and REC annually.

10.3. Adverse events that do not require reporting

Immediately upon becoming aware all AEs will be reported for participants from part A and part B, from the time the consent form is signed, on the Source Data Worksheets and then subsequently on the eCRF. The Principal Investigator will assess the relationship of the adverse event to the study drug and the Chief Investigator will assess the expectedness. In order to ensure the safety of all participants during the study duration, adverse events will be reported throughout Part A and Part B from the time the consent form is signed.

10.4. Premature termination of the trial

The trial may be prematurely discontinued by the co-sponsors, Chief Investigator or Regulatory Authority on the basis of new safety information or for other reasons given by the Trial Steering Committee, Regulatory Authority or Ethics Committee concerned. Treatment will also be stopped immediately if there is a positive urinary pregnancy test.

If the trial is prematurely discontinued, active participants will be informed, and no further participant or baby data will be collected. The Competent Authority and Research Ethics Committee will be informed within 15 days of the early termination of the trial.

11. Statistics

11.1. Sample Size

In order to progress to a definitive trial, parameters need to be defined for calculating sample size. In particular, the standard deviation of the primary outcome. All analyses will follow the intention to treat principle, i.e. all randomised participants will be analysed according to the treatment they were allocated to irrespective of the treatment they received or whether they received any treatment at all.

All baseline characteristics will be summarised to ensure that minimisation was successful, separated into two groups: those randomised to the intervention arm and those not. Counts with percentages will be used for categorical variables, means with standard deviations will be used for normally distributed continuous variables and medians with interquartile ranges for non-normal continuous variables. Those that do not follow a normal distribution will also be log-transformed.

As a feasibility study, it is not powered to find a statistically significant difference in clinical outcomes but will provide information on possible effect of SGLT2i and GLP-1 on BP and HbA1C to inform future sample size calculations. To calculate a standard deviation of BP or HbA1C for the definitive efficacy study, sample sizes of 36 in each arm are recommended from estimates described in a recent simulation study (Teare, Dimairo et al. 2014).

Across the three recruitment sites, there are approximately 15,000 deliveries per year. Assuming 10% have HDP (5%) and GDM (5%), there will be at least 1500 individuals eligible for recruitment per year.

With a sample size of 162, a recruitment rate of 80% will be estimated within a 95% confidence interval of +/7.7%. Allowing for a 33% drop-out/pregnancy rate (Ormesher, Higson et al. 2020), 54 individuals in each arm will be recruited. 162 participants (+ study-buddies) will also allow exploration of differences in BP/HbA1C.

The participation of study-buddies is exploratory and sample size calculation is not possible, but impact of SGLT2i and GLP-1 on study-buddy outcome parameters will also be analysed. The total sample size will be 324 (162 participants and 162 study-buddies).

11.2. Randomisation

A web-based randomisation system will be designed, using the bespoke KCTU randomisation system. The randomisation system will be created in collaboration with the trial analyst/s and the CI and maintained by the King's Clinical Trials Unit for the duration of the project. It will be hosted on a dedicated server within KCL.

Part A: Following informed consent participants recruited during pregnancy will be randomised to receive recommended postpartum care of enalapril or other antihypertensives safe for breastfeeding if required (1:1 ratio) to minimise the impact on BP control and renal outcomes between groups. Minimisation (A) will be performed based on site, type of hypertension (chronic hypertension (defined as blood pressure systolic BP ≥ 140 and/or diastolic BP ≥ 90 mmHg measured in the office or clinic pre-pregnancy at or <20 weeks' gestation)/gestational hypertension/no hypertension and severity (0/ 1-2/ ≥3 antihypertensive agents).

Part B: Once pregnancy and breastfeeding are completed participants will be re-screened and if they remain eligible, consent will be reconfirmed and participant and study-buddy pairs (if co-recruitment selected by the participant) will be randomised in a 1:1:1 ratio to either: 26-weeks SGLT2i, 26-weeks GLP-1 or standard care. Minimisation (B) will be performed based on site, last antihypertensive agent taken (current, or previous RAAS blockade agent (taken for at least two weeks postpartum)/ other antihypertensive agent/ no antihypertensive agent required postpartum) and presence of gestational diabetes in recent pregnancy (according to local guidelines).

Data entry
Randomisation will be undertaken by study team onto the randomisation system by going to www.ctu.co.uk and clicking the link to access the randomisation system. A full audit trail of data entry will be automatically date and time stamped, alongside information about the user making the entry within the system.

Security
The CI or delegate will request usernames and passwords from the KCTU. System access will be strictly restricted through user-specific passwords to the authorised research team members. It is a legal requirement that passwords to the randomisation system are not shared, and that only those authorised to access the system are allowed to do so. If new staff members join the study, a user-specific username and password must be requested via the CI or delegate (e.g., Trial Manager) from the KCTU team and a request for access to be revoked must be requested when staff members leave the project. Study site staff experiencing issues with system access or functionality should contact the CI or delegate (e.g., Trial Manager) in the first instance.

Participant initials and date of birth will be entered on the randomisation system. Whereas NHS number, email addresses, participant names and addresses and full postcodes will not be entered into the randomisation system. No data will be entered onto the randomisation system unless a participant has signed a consent form to participate in the trial.

Data Quality Processes
The CI team will undertake appropriate reviews of the entered data for the purpose of data cleaning. No data can be amended in the system, however CI or delegate (e.g., Trial Manager) may request King's Clinical Trials Unit to add notes against individual subject entries to clarify data entry errors.

Database Lock
Upon request, KCTU will provide a copy of the final exported dataset to the CI in .csv format and the CI will onward distribute as appropriate.

11.3. Analysis

A detailed Statistical Analysis Plan (SAP) will be developed in-house and agreed by the Trial Steering Committee (TSC) before the analysis is undertaken. The analysis and presentation of results will follow the most up-to-date recommendations of the CONSORT group. Analyses will be completed in Stata 17.0.

Baseline data
All demographic and clinical data for individuals recruited into the cohort (Part A and Part B) will be summarised with counts (and percentages) for categorical variables, means (and standard deviations) for normally distributed continuous variables and medians (and interquartile or simple ranges) for non-normal continuous variables.

Primary outcome analysis
Recruitment rates will be assessed by calculating the number of participants recruited out of all eligible postpartum individuals who were deemed to be eligible. The rates will be calculated with a 95% confidence interval. This will be assessed by comparing screening and enrolment logs. Individual counts as well as the percentage recruited will be reported. An overall recruitment rate will be calculated as well as a recruitment rate for each of the three study sites.

Secondary outcome analysis
Retention of study buddies: Recruitment rate of 'study-buddies' will be assessed by calculating the number of people recruited out of all those who were deemed to be eligible.

Retention of Postpartum participants: The count and percentage lost to follow-up will be reported for the whole cohort, as well as stratified by treatment group and site.

Additional outcomes: The count and percentage for the number of blood pressures, weights, pregnancy test results, urine-dip results and urine and blood tests recorded the whole cohort, as well as stratified by treatment group will also be reported. The mean (SD) or median (IQR) will also be reported for these variables over time.

Adherence to daily SGLT-2 inhibitors and weekly GLP-1 injections for the intervention arm will be assessed by the total proportion taken during the study period. For each participant, the total number of SGLT-2 inhibitors or GLP-1 injections that should have been taken throughout the study period will be calculated. This denominator will be calculated separately for each

participant. The numerator, how many SGLT-2 inhibitors were actually taken, will be measured based on self-reporting by participant. The mean and standard deviation (or median and IQR if non-normal) of these proportions will be calculated to determine the average adherence for the intervention arm. These will be calculated for total time of the trial. The trend across study visits will be tested to identify any changes in adherence throughout the follow-up period. Both the total number of SGLT-2 inhibitors and GLP-1 injections taken and proportions will be reported.

Longitudinal changes in clinical parameters for participants and study-buddies between study arms. Pregnancy rate during study period and pregnancy outcomes will be reported.

Time needed for study and analysis
Time needed for study will be calculated from the first participant recruited until 52 weeks after the last participant is recruited.

Missing data
Missing data as a result of a participant being lost to follow-up are expected to be low. Any missing data present will be summarised using counts and percentages. Characteristics between the missing and non-missing groups will be compared to identify any non-random patterns of missingness. Where missingness is at random, missing data will be imputed and a sensitivity analysis will be conducted. The results of this will be compared to the original results.

Analysis of outcomes
Quantitative: Number of eligible individuals and recruitment rates will be assessed by comparing screening and enrolment logs. A CONSORT flow diagram will provide additional detail on the flow of participants and make up on those enrolled.

Baseline demographics of randomised participants and study-buddies will be summarised using summary statistics according to the data's distribution. Delta change/variability in capillary blood tests and urine ACR home-testing will be reported and subgroup analyses undertaken for entry risk factors and use of ACEi..

Qualitative analysis: Focus group discussions and interviews will be analysed separately, stratified by participant type then triangulated to enhance understanding of complex phenomena. Thematic framework analysis (Gale, Heath et al. 2013) will be used to demonstrate patterns among different groups in order to better understand contextual factors likely to affect trial implementation and acceptability of intervention components from postpartum participants, study-buddies and postpartum health champions.

Health economic data capture
Components relevant to a future evaluation will be assessed including:
- Identification of resources used for material development, postpartum health champion training and home-testing for future costing
- Resource required to extract and analyse data
- Identification of appropriate future economic outcome

12. Trial Management Group (TMG)

The TMG will include the Chief Investigator and trial staff. The TMG will be responsible for overseeing the trial. The group will meet regularly, approximately monthly, and will send updates to PIs.

The TMG will review recruitment figures, SAEs and substantial amendments to the protocol prior to submission to the REC and/or MHRA. All PIs will be kept informed of substantial amendments through their nominated responsible individuals.

We recognise that this is a rapidly changing field and there are likely to be new relevant findings within the study period. Any relevant data or findings will be reviewed within the monthly TMG meetings, with immediate escalation to the Trial Steering Committee who will decide if there is a need to stop, pause or amend the study documents to communicate new risks.

13. Trial Steering Committee

The role of the Trial Steering Committee (TSC) is to provide overall supervision of the trial. The TSC will recommend any appropriate amendments/actions for the trial as necessary. The TSC acts on behalf of the funder(s) and Sponsor.

A Trial Steering Committee (TSC) will be established and meet prior to study start via teleconference, and thereafter every 6-months (and at request of the TSC, interim meetings maybe organised), to assess scientific and ethical conduct and oversee study progress and safety. Membership will comprise an Independent Chair, two Independent Members, two PPI Members, Chief Investigator and the trial statistician. The TSC will fulfil the function of a Data Monitoring Committee during this feasibility study and will make an overall recommendation about proceeding with future trials based on study results.

14. Direct Access to Source Data and Documents

The Investigator(s) will permit trial-related monitoring, audits, REC review, and regulatory inspections by providing the co- sponsors, Regulators and REC direct access to source data and other documents (including blood test results).

15. Ethics & Regulatory Approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of Good Clinical Practice and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework and the Medicines for Human Use (Clinical Trial) Regulations 2004, as amended in 2006 and any subsequent amendments.

This protocol and related documents will be submitted for review to Health Research Authority (HRA), Research Ethics Committee (REC), and to the Medicines and Healthcare products Regulatory Agency (MHRA) for Clinical Trial Authorisation. Any subsequent protocol amendments will be submitted to the REC, HRA and Regulatory Authorities for approval as appropriate.

Prior to site recruitment the Chief Investigator/Principal Investigator or designee must receive local site approvals e.g. NHS permission in writing from the Trust Research & Development (R&D) known as confirmation of capability and capacity.

The Chief Investigator will submit a final report at conclusion of the trial to the KHP-CTO (on behalf of the Sponsor) and the REC within the timelines defined in the Regulations. The KHP-CTO or delegate will upload the final report to a publicly registered database on behalf of the Sponsor.

16. Quality Assurance

Monitoring of this trial will be to ensure compliance with Good Clinical Practice and scientific integrity will be managed and oversight retained, by the KHP-CTO Quality Team.

17. Data Management

A web based electronic data capture (EDC) system will be designed, using the InferMed Macro 4 system.

Data entry
The EDC will be created in collaboration with the trial analyst/s and the CI and maintained by the King's Clinical Trials Unit for the duration of the project. It will be hosted on a dedicated server within KCL. Source data will include electronic clinical notes and laboratory results from EPIC (or local electronic notes, paper questionnaires and PHYLLIS specific data work sheets. Data from onsite visits and virtual visits (including adverse events) will be recorded in data worksheets (which will be drafted to match the eCRF) and then the data will be transcribed from these worksheets by authorised staff onto the EDC by going to www.ctu.co.uk and clicking the link to access the MACRO 4 EDC system. To maximise the completeness of the data, participants will be phoned by the PHYLLIS research team and the healthcare champion for that individual participant if measurements have not been uploaded to EPIC MyChart (or local electronic patient portal), or if onsite appointments have been missed. As not included in EDC, sites will need to keep a standard screening log and need to record demographics of participants attending focus groups.

A full audit trail of data entry and any subsequent changes to entered data will be automatically date and time stamped, alongside information about the user making the entry/changes within the system.

Security
The electronic source data will be held in hospital, under hospital regulations, including password-protection, ensuring confidentiality and following GDPR guidelines. The participant data will be pseudo-anonymised before being entered into the trial database. King's Clinical Trials Unit will manage the study database using eCRFs using the database, MACRO. Members of the study team will have unique login details to access Macro, and they will input source data to the database. It is a legal requirement that passwords to the EDC are not shared, and that only those authorised to access the system are allowed to do so. If new staff members join the study, a user-specific username and password must be requested via the CI or delegate (e.g Trial Manager) from the KCTU team and a request for access to be revoked must be requested when staff members leave the project. Study site staff experiencing issues with system access or functionality should contact the CI or delegate (e.g., Trial Manager) in the first instance.

Participant date of birth will be entered on the EDC. Whereas NHS number, email addresses, participant names and addresses and full postcodes will not be entered into the EDC system. No data will be entered onto the EDC system unless a participant has signed a consent form to participate in the trial. Paper source data (PHYLLIS specific data worksheets, eligibility logs and paper questionnaires) and the trial master file will be locked in a secure filing cabinet in King's College London, Department of Women's Health, Weston Education Centre, Cutcombe Road, London SE5 9RS. The Chief Investigator will act as custodian for the trial data.

Data Quality Processes

The CI team will undertake appropriate reviews of the entered data, in consultation with the project analyst for the purpose of data cleaning and will request amendments as required. The KCTU will provide the study team with Data management plan for Elsevier InferMed MACRO EDC once the system is made live and ready for use.

Database Lock
At the end of the trial, the site PI will review all the data for each participant to verify that all the data are complete and correct. At this point, all data can be formally locked for analysis.

Upon request, KCTU will provide a copy of the final exported dataset to the CI in .csv format and the CI will onward distribute as appropriate.

18. Publication Policy

It is intended that the results of the trial will be submitted for publication by the Chief Investigator, with sponsorship knowledge, in a peer-reviewed scientific journal.

19. Insurance / Indemnity

King's College London holds insurance against claims from participants for harm caused by their participation in this clinical study. Participants may be able to claim compensation if they can prove that KCL has been negligent. KCL holds insurance for no-fault compensation for clinical trials. However, if this clinical study is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical study. King's College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

KCH will provide NHS indemnity cover for negligent harm, as appropriate and is not in the position to indemnify for non-negligent harm. NHS indemnity arrangements do not extend to non-negligent harm and NHS bodies cannot purchase commercial insurance for this purpose; it cannot give advance undertaking to pay compensation when there is no negligence attributable to their vicarious liability. The Trust will only extend NHS indemnity cover for negligent harm to its employees, both substantive and honorary, conducting research studies that have been approved by the R&D Department. The Trust cannot accept liability for any activity that has not been properly registered, and Trust approved. Potential claims should be reported immediately to the R&I Office.

20. Financial Aspects

This trial is funded by the National Institute for Health Research, an advanced fellowship for Dr Kate Bramham (nihr302513) and will apply to be part of the clinical research network portfolio.

21. Archiving

At the end of this trial, all trial data will be stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the 2018 Data Protection Act and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the Co-Sponsors Archiving Standard Operating Procedure (SOP).

22. Signatures

_____ 25th of June 2025

Chief Investigator Date

Print name Dr Kate Bramham

_____ 25th of June 2025

Statistician Date

Print name Professor Yanzhong Wang

REFERENCES

Batzias, K., A. S. Antonopoulos, E. Oikonomou, G. Siasos, E. Bletsa, P. K. Stampouloglou, C. V. Mistakidi, M. Noutsou, N. Katsiki, P. Karopoulos, G. Charalambous, A. Thanopoulou, N. Tentolouris and D. Tousoulis (2018). "Effects of Newer Antidiabetic Drugs on Endothelial Function and Arterial Stiffness: A Systematic Review and Meta-Analysis." J Diabetes Res **2018**: 1232583.

Coyne, I. T. (1997). "Sampling in qualitative research. Purposeful and theoretical sampling; merging or clear boundaries?" J Adv Nurs **26**(3): 623-630.

DeFilippis, E. M., B. L. Collins, A. Singh, D. W. Biery, A. Fatima, A. Qamar, A. N. Berman, A. Gupta, M. Cawley, M. J. Wood, J. Klein, J. Hainer, M. Gulati, V. R. Taqueti, M. F. Di Carli, K. Nasir, D. L. Bhatt and R. Blankstein (2020). "Women who experience a myocardial infarction at a young age have worse outcomes compared with men: the Mass General Brigham YOUNG-MI registry." Eur Heart J **41**(42): 4127-4137.

Díaz-Cruz C, González-Ortiz M, Rosales-Rivera LY, et al. Effects of dapagliflozin on blood pressure variability in patients with prediabetes and prehypertension without pharmacological treatment: a randomized trial. Blood Press Monit. 2020;25(6):3

Gale, N. K., G. Heath, E. Cameron, S. Rashid and S. Redwood (2013). "Using the framework method for the analysis of qualitative data in multi-disciplinary health research." BMC Medical Research Methodology **13**(1): 117.

Kitt, J. A., R. L. Fox, A. E. Cairns, J. Mollison, H. H. Burchert, Y. Kenworthy, A. McCourt, K. Suriano, A. J. Lewandowski, L. Mackillop, K. L. Tucker, R. J. McManus and P. Leeson (2021). "Short-Term Postpartum Blood Pressure Self-Management and Long-Term Blood Pressure Control: A Randomized Controlled Trial." Hypertension **78**(2): 469-479.

Kountouris, E., K. Clark, P. Kay, N. Roberts, K. Bramham and N. A. Kametas (2021). "Postnatal assessment for renal dysfunction in women with hypertensive disorders of pregnancy : A prospective observational study." J Nephrol **34**(5): 1641-1649.

Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001 Sep;**16**(9):606-13. doi: 10.1046/j.1525-1497.2001.016009606.x. PMID: 11556941; PMCID: PMC1495268.

Lytvyn Y, Kimura K, Peter N, Lai V, Tse J, Cham L, Perkins BA, Soleymanlou N, Cherney DZI. Renal and Vascular Effects of Combined SGLT2 and Angiotensin-Converting Enzyme Inhibition. Circulation. 2022 Aug 9;146(6):450-462.

Mori Y, Duru OK, Tuttle KR, et al. Sodium-glucose cotransporter 2 inhibitors and new-onset type 2 diabetes in adults with prediabetes: systematic review and meta-analysis of randomized controlled trials.J Clin Endocrinol Metab. 2022;108(1):221-231. doi:10.1210/clinem/dgac591

National Institute for Health and Care Excellence (2015). Diabetes in pregnancy: management from preconception to the postnatal period.

National Institute for Health and Care Excellence (2019). Hypertension in pregnancy: diagnosis and management.

National Institute for Health and Care Excellence (2024) CVD risk assessment and management: What are the risk factors? Accessed on 8th of January 2024 at https://cks.nice.org.uk/topics/cvd-risk-assessment-management/background-information/risk-factors-for-cvd/

Ormesher, L., S. Higson, M. Luckie, S. A. Roberts, H. Glossop, A. Trafford, E. Cottrell, E. D. Johnstone and J. E. Myers (2020). "Postnatal Enalapril to Improve Cardiovascular Function Following Preterm Preeclampsia (PICk-UP):: A Randomized Double-Blind Placebo-Controlled Feasibility Trial." Hypertension **76**(6): 1828-1837.

Rossing P, Inzucchi SE, Vart P, et al; DAPA-CKD and DAPA-HF Trial Committees and Investigators. Dapagliflozin and new-onset type 2 diabetes in patients with chronic kidney disease or heart failure: pooled analysis of the DAPA-CKD and DAPA-HF trials. Lancet Diabetes Endocrinol. 2022;10(1):24-34. doi:10.1016/S2213-8587(21)00295-3

Sabaner, M. C., R. Duman, M. Dogan, M. Akdogan, A. Vurmaz, E. Bozkurt and S. Beysel (2021). "Do SGLT2 inhibitors prevent preclinical diabetic retinopathy? A Prospective Pilot Optical Coherence Tomography Angiography Study." J Fr Ophtalmol **44**(8): 1159-1167.
Smith, G. N., J. M. Louis and G. R. Saade (2019). "Pregnancy and the Postpartum Period as an Opportunity for Cardiovascular Risk Identification and Management." Obstet Gynecol **134**(4): 851-862.
Teare, M. D., M. Dimairo, N. Shephard, A. Hayman, A. Whitehead and S. J. Walters (2014). "Sample size requirements to estimate key design parameters from external pilot randomised controlled trials: a simulation study." Trials **15**(1): 264.
Treweek, S., K. Banister, P. Bower, S. Cotton, D. Devane, H. R. Gardner, T. Isaacs, G. Nestor, A. Oshisanya, A. Parker, L. Rochester, I. Soulsby, H. Williams and M. D. Witham (2021). "Developing the INCLUDE Ethnicity Framework—a tool to help trialists design trials that better reflect the communities they serve." Trials **22**(1): 337.
Verma, S., C. D. Mazer, A. T. Yan, T. Mason, V. Garg, H. Teoh, F. Zuo, A. Quan, M. E. Farkouh, D. H. Fitchett, S. G. Goodman, R. M. Goldenberg, M. Al-Omran, R. E. Gilbert, D. L. Bhatt, L. A. Leiter, P. Jüni, B. Zinman and K. A. Connelly (2019). "Effect of Empagliflozin on Left Ventricular Mass in Patients With Type 2 Diabetes Mellitus and Coronary Artery Disease." Circulation **140**(21): 1693-1702.

APPENDICES

Appendix 1: Focus Groups with participants, study buddies and health champions

Contents

1. Overview

Face to face or virtual focus groups of individuals and study buddies who took part in PHYLLIS

The focus group topic guide will cover participant and study buddy experiences of: Home testing being/having a Study Buddy, the post-partum health champions as well as the experience of being randomised to SGLT2 inhibitors, and experience of taking SGLT2 inhibitor. Separate focus groups will be held for participants with a study- buddy and participants without a study- buddy.

2. Planning Focus Groups – organisation and recruitment

As part of the recruitment process for the clinical trial, it is explained that participants/SBs can volunteer to take part in the FGs.
One researcher, as FG lead, will coordinate recruitment to the FGs in their area. FG can be face to face or virtual. Face to face FGs will have a lead and a note taker. Virtual FG will have a reserve facilitator in case of technical difficulties, and the note taker will monitor the chat.
The FG lead will:

- Provide all study information to the FG participants including PIL, consent and confidentiality forms
- Act as a liaison with all FG participants for information and questions regarding FG and recruitment to the FGs
- Coordinate mutually convenient times for each FG and ensure maximum participation, considering childcare issues and other time constraints
- Organise a venue that is easy to access and will accommodate participants with their children
- If a virtual FG, ensure that all participants are familiar with the mode of discussion (e.g. Teams or zoom) and have access to the hardware necessary to participate in the FG as well as downloads as appropriate and passwords
- If a virtual FG, request that each participant can attend the FG in a comfortable and private space, to ensure the comfort and confidentiality of all participants

- Participation is entirely voluntary, and those volunteering will be asked to sign and return a consent form (in person or virtually) prior to the focus groups.

The focus groups will last up to 90 minutes, they will be audio recorded on an independent digital recorder, transcribed and all content will be anonymised to prevent disclosure of identifiable information. If a virtual FG, comments in the chat function will be saved, anonymised, and collated for data analysis using NVivo alongside the transcripts. For consistency the same researchers will carry out all FG in their area.

Transcripts from the staff focus groups will be subjected to thematic analysis process to understand the experience of taking part in PHYLLIS and how things could be improved in the future. A constant comparative technique will be used to evaluate both within and across group discussions. This provides a basis for understanding similarities and differences across the range of participants. Quantitative (the questionnaire) and qualitative (focus groups) data will be synthesised. This will drill down into understanding the experience of participating in PHYLLIS and what improvements could be made. A report of the focus group findings will be produced and then synthesised with the other strands of PHYLLIS.

3. Conducting Focus Groups (including etiquette)

Standard welcome to include:

- Researcher introductions and roles – 1) facilitator and 2) observer/note-taker 3) 2nd facilitator if online, in case of tech failure
- Project summary
- Confirm information and consent process that has been completed
- Remind the group of the timings
- Remind the group that the session will be recorded and how (independent digital recorder) so that comments aren't missed, but any quotes used in reports/articles will be anonymised as per the details in the consent form.
- Ensure information sheet is read and consent form completed
- Ensure confidentiality agreement is signed and that everything said in the group must remain confidential to the group
- Participant introductions and ice breaking

FG etiquette;

- Remind participants to respect each other's opinions and that there are no right or wrong answers - it's expected they will have differing points of view. Encourage all views to be expressed even if they differ. Remind participants that there is no pressure to answer any questions they are uncomfortable with. Ask participants to avoid naming/identifying other people except in broadest terms (e.g. a friend, medical colleague, or other clinician).
- Encourage participants to follow up on what others have said, and not wait for the facilitator to 'give permission' – also the facilitator does not need to be addressed at all times – conversations can be held within the group.
- The facilitator's role is to ask questions, listen and make sure that everyone has a chance to contribute. As we are keen to hear from everyone in the group, please help to make sure that everyone has a turn to speak.
- Request that people speak one at a time so everyone can hear what is being said and to ensure that the session can be appropriately recorded.

4. Role of the Observer/Note-taker(s)

- Decide with the facilitator who will take responsibility for consent forms, FG notes and digital recorder.
- Monitor any chat function during the meeting if online
- Observe the FG rather than participate
- Take notes e.g. major themes, comments, observations and dynamics
- Debrief with the facilitator immediately after FG participants have left the meeting and review notes with the facilitator. Note down any further insights as a result of the discussion.

5. Difficult Situations

Awareness of potential upset/distress arising from experiences that may be recounted in discussion such as embarrassing experiences, stigma and conditions, stress relating to birth, illness and relationships.

If someone dominates the conversation:

Respectfully acknowledge and thank them for their input then encourage other participants to speak and emphasise that you are very keen to hear how others are feeling too. Could put questions to individuals if needed.

If no-one responds to a question:

Are people feeling uncomfortable? More likely to happen at the start of a focus group which is why building rapport at the outset is so important. Good idea to start with the easier/less sensitive topics for this reason.

It's fine to be quiet for a moment. People often need time to think. Don't feel you have to jump in with a probe/further question straightaway.

It might be that the question needs to be rephrased. Check in with the group re their understanding of the question if rephrasing it doesn't help. Are people nervous about talking about more sensitive aspects of their experiences? Building rapport and trying to reassure the group is important here. Move to another question then if it feels appropriate later in the discussion the question can be returned to, perhaps in a more gentle way if necessary.

People might simply have said enough on the topic, perhaps from a question/discussion before for example. You could invite people to make a final contribution to the discussion if they so wish so people are aware that you are about to move on.

If people start talking about irrelevant topics:

Thank them for the question/comment and suggest it is discussed at another time, in another forum. Suggest that a new item is moved onto, with a reminder of the time constraints of the FG and that you're keen to hear from everyone in the remaining time on a number of focussed topics.

6. Effective Focus Group Facilitation

An effective facilitator should have the ability to build rapport thereby creating a friendly environment and have adequate knowledge of the topic and potential sensitivities in addition to in-group power differentials. As well as excellent communication skills and a manner which facilitates open and honest conversations, they should have excellent listening skills whilst being able to draw out those who might be shy in the process as well as intervening if someone is dominating the discussions. Exercising impartiality and using pauses, probes and silence to facilitate elaboration is important. The facilitator should be able to effectively sum up the key points and ensure that people feel valued for their time and contributions. Keeping to

time – focus groups should not run over - and ensuring that people fully understand the focus group process is also vital.

7. **Recording Focus Groups**

All focus groups to be audio-recorded using an independent digital recorder. Recorders should be fully charged and checked prior to starting each focus group recording.

8. **Facilitator Checklist**

- Familiarity with research aims
- Familiar with focus group schedule
- Ensure early arrival with the observer/note-taker, meeting open and checking for participant emails to resolve any access issues
- Welcome focus group participants
- Introduce self and invite others to do the same
- Remind participants of: the purpose of the focus group; process of data collection; how data will be used; their rights and their right to leave the group at any time; how long the discussion will last for; that it will be audio recorded
- Explain any housekeeping information – confidentiality and online etiquette
- Ensure written consent has been received if it hasn't already
- At the end of the discussion, make sure people have the contact information of someone who can answer any questions they may have about the project in the future

9. Focus group discussion guide

1. Participant introductions and ice breaking

Point 3 of the focus group protocol re consent, confidentiality, etiquette etc.

Welcome by facilitator who introduces purpose of the FG – We would like to hear about your experiences of being part of PHYLLIS and also hear about how we could do things better.

Participants, SBs and facilitators introduce themselves.
SB relationship
When they had their baby?

2. Randomisation and study drug

What were your experiences of being randomised and of the study drug?

3. Home testing

Tell us about your experience of home testing.

- Urine and blood sampling
- Monthly monitoring (blood pressure, weighing scales, urine dip, pregnancy test)
- Recording data
- Clear what you had to do? Easy/hard to do?

4. Study Buddy

For study buddies: how did you find being a study buddy? Were there any benefits/drawbacks? Anything you didn't anticipate?

For participant: how did you decide on your study buddy? Did you find their support helpful regarding taking part and also staying on the study? Was there anything else that SB support helped with (unexpected benefits)?

5. Post partum health champions

Tell us about your PPHC. Introduction to the study, staying on the study. Anything unexpected.

6. In-person study visits

What were your experiences/thoughts on the 2 in-person study visits?

7. What can we do better?

What one small thing would you change to improve the experience of future participants/SBs?
Was there anything that was particularly interesting/easy? Was there anything that was especially difficult?
What would you say to future participants?

8. Review and opportunity for additional comment

Summary and opportunity for further comment.

Thank participants.