SALURATE

STUDY PROTOCOL

SALURATE

Validation of salivary uric monitoring for early prediction of hypertensive disorders of pregnancy

Protocol Version: 4
Date: 04 July 2024
IRAS Project ID: 337290

Protocol Sign Off

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

For, and on behalf of, the Study Sponsor

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Position: CEO, Morgan Innovation & Technology Ltd.

Signature:  Date: 17th August 2023

Chief Investigator

Name: Baskaran Thilaganathan

Position: Professor and Director, Fetal Medicine Unit, St. George's University Hospitals NHS Foundation Trust

Signature:  Date: 17th August 2023

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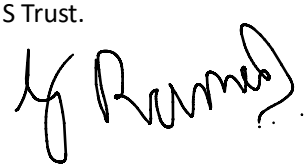
Signature:  Date: 9th April 2024

Compliance Statement

This protocol describes the Salurate Study only. The study will be conducted in compliance with the approved protocol, UK Policy Framework for Health and Social Care Research, Medicines for Human Use (Clinical Trials) Regulations 2004, the Data Protection Act 2018 and the principles of Good Clinical Practice (GCP) as set out in the UK Statutory Instrument (2004/1031) and subsequent amendments thereof. Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.

Reference Numbers

IRAS Project ID:	337290

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Confidentiality Statement

The information in this document is privileged and confidential and may not be disclosed unless required by law. The information in this document may be disclosed only to those persons involved in the conduct of the study. These restrictions on disclosure will apply as well to all future information supplied under this Protocol. The confidentiality of this material is further protected by the terms of the Confidentiality Agreement entered into by the Parties.

1 Contents

2 List of Abbreviations and Acronyms

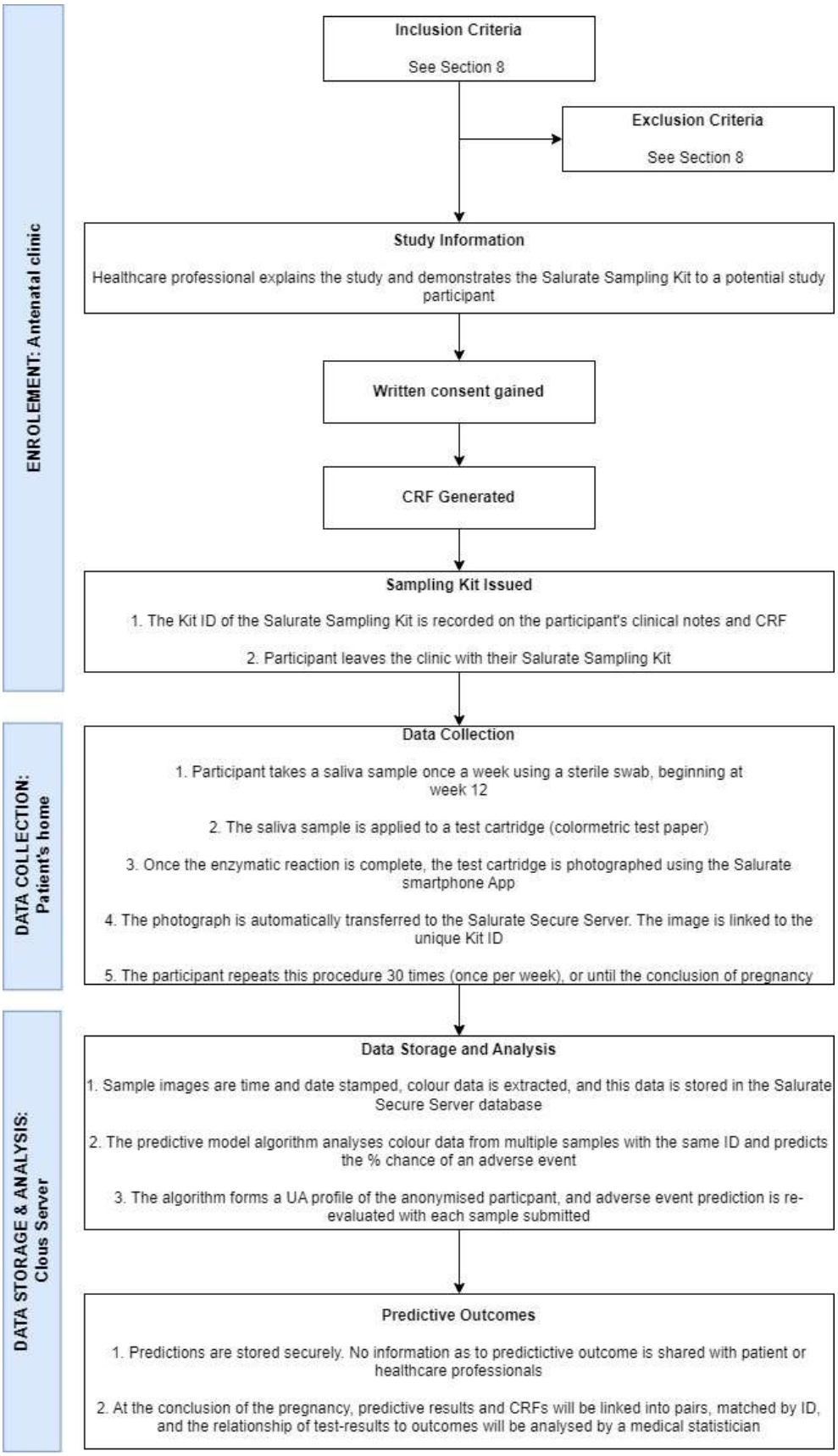
AE	Adverse Event
AR	Adverse Reaction
AWS	Amazon Web Services, Inc.
CI	Chief Investigator
CRF	Case Report Form
CVD	Cardiovascular Diseases
FGR	Fetal growth restriction
FSN	Field Safety Notice
GCP	Good Clinical Practice
GDM	Gestational Diabetes Mellitus
HDP	Hypertensive Disorders of Pregnancy
HELLP	Haemolysis, Elevated Liver enzymes, and Low Platelets
IFU	Instructions for Use
IUGR	Intrauterine Growth Restriction
MHRA	Medicines and Healthcare products Regulatory Agency
MIAT	Morgan Innovation & Technology Ltd.
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
NIH	National Institute of Health
NIHR	National Institute for Health Research
NPV	Negative Predictive Value
REC	Research Ethics Committee
PE	Pre-eclampsia
PI	Principal Investigator
PPV	Positive Predictive Value
SAE	Severe Adverse Event

SGA	Small for Gestational Age
SUA	Salivary uric acid
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSC	Trial Steering Committee
UA	Uric Acid

3 SALURATE STUDY SUMMARY

Study Title	Validation of salivary uric acid remote self-monitoring for early prediction of hypertensive disorders of pregnancy.
Short Title	The Salurate Study.
Objective	To clinically and logistically validate a novel remote self-monitoring screening system that uses the measurement of salivary uric acid to identify women who are at risk of developing hypertensive disorders of pregnancy (HDP) several weeks earlier than current methods.
Study design	A multi-center observational, analytical cohort study conducted over a period of 18 months with health economics evaluation. The Salurate Study is non-interventional; data collected will not result in any changes to the participants' care pathway.
Study Centres	St. George's University Hospitals NHS Foundation Trust Epsom and St. Helier University Hospitals NHS Trust
Sample size	n=4000 pregnant women
Eligibility criteria (overview)	Inclusion criteria: Pregnant women from age 16, with a viable singleton pregnancy at >12 weeks' gestation and able to provide informed consent. Full list section 8.1. Exclusion criteria: Physical incapacity, lack of access to a smartphone and/or the internet data at home, language or educational barriers that would cause an inability to read the instructions for use (IFU) or use the App. Full list section 8.2.
Outcome Measures	Primary Outcome: a) Clinical diagnosis of HDP to include; gestational hypertension, pre-eclampsia, and chronic hypertension with superimposed pre-eclampsia Secondary outcomes: b) To assess whether Salurate could detect other important placentally-mediated adverse outcomes for the woman and baby including but not limited to fetal growth restriction (FGR) and gestational diabetes (GDM). c) To assess the cost effectiveness of routine Salurate testing compared to current care methods. d) To assess the degree of compliance of pregnant women to a self-sampling weekly test regimen. e) To assess the algorithm efficacy in a demographically diverse population.

3.1 Study Schema



4 BACKGROUND AND RATIONALE

4.1 Hypertensive Disorders of Pregnancy

Hypertensive disorders of pregnancy (HDP) are serious medical conditions that affect approximately 10% of pregnancies worldwide [1]. HDP are classified into four types; gestational hypertension, chronic hypertension, pre-eclampsia, and chronic hypertension with superimposed pre-eclampsia. HDP are amongst the leading causes of maternal and fetal morbidity and mortality worldwide [2].

The worldwide incidence rate of HDP continues to increase. Changes in socioeconomic conditions in India, Asia, Africa, and South America has led to conception at an older age and increasing obesity rates [3]; these are both established risk factors for HDP.

Not only does HDP present a serious risk to mothers and babies during and immediately after birth, but as summarised by Giorgione et al., there is an established link between HDP and a propensity for women to develop cardiovascular diseases in the decades postpartum [4]. There is evidence to demonstrate that HDP can cause persistent left ventricular diastolic dysfunction and abnormal geometry, which may explain this predisposition to cardiovascular diseases (CVD) [5] [6]. Prior to developing CVD, women who have previously been diagnosed with HDP exhibit risk factors including chronic hypertension, diabetes, and dyslipidaemia [7].

Meads et al. reviewed 19,500 published reports of 27 candidate tests and concluded that none was clinically useful [8].

4.2 Salivary uric acid

Salurate is a novel monitoring device which detects elevated levels of Salivary uric acid (SUA) and identifies pregnant women at risk from developing HDP.

Using salivary biomarkers for disease detection and monitoring has potential implications for a variety of conditions [9]. Sampling is simple, non-invasive and does not require clinical involvement, making it ideal for remote monitoring. Two different studies demonstrated that elevated SUA in pregnant women correlates with an increased risk of developing complications associated with gestational hypertension such as pre-eclampsia [10].

The National Institute for Health Research (NICE) guidelines for monitoring the conditions associated with HDP are equivalent [11], yet also not particularly effective [12]. MIAT propose that a remote monitoring system to detect elevated SUA could predict which women are at risk from developing HDP more effectively than current protocols (blood pressure, proteinurea, fundal height).

4.3 Study Rationale

4.3.1 Significance of Hypertensive Disorders

HDP are major obstetric complications that pose significant risks to maternal and fetal health. These conditions are associated with severe maternal and fetal morbidity and are amongst the leading causes of maternal and perinatal death [13]. Early prediction and timely intervention are crucial to improving maternal and fetal outcomes and reducing the burden on healthcare systems.

4.3.2 Potential Benefits of Early Risk Assessment

The Salurate pregnancy monitoring system offers a novel and innovative approach to predicting HDP. By continuously monitoring various physiological parameters and utilising advanced algorithms, Salurate aims to provide early risk assessments for the development of these complications before the onset of clinical symptoms. Early identification could facilitate targeted interventions, personalised care plans, and

appropriate management strategies to mitigate the severity of complications and improve pregnancy outcomes.

4.3.3 Addressing Current Diagnostic Limitations

Traditional methods for diagnosing HDP rely on clinical signs and symptoms that may not become apparent until the disease has progressed significantly [11]. This delay in diagnosis can lead to missed opportunities for early interventions. Salurate's potential to provide predictive information before symptoms appear could fill a critical gap in current clinical approaches, allowing for proactive and timely management.

4.3.4 Potential to Improve Maternal and Fetal Outcomes

If the study demonstrates Salurate's predictive capabilities are reliable and accurate, its implementation could lead to improved maternal and fetal health outcomes. Early detection of high-risk pregnancies may enable healthcare providers to initiate appropriate interventions promptly, reducing the incidence and severity of HDP, and ultimately leading to improved maternal and neonatal health.

4.3.5 Advancements in Prenatal Care

The Salurate pregnancy monitoring system marks a significant stride forward in prenatal care, leveraging technological innovations to improve risk assessment throughout pregnancy. Salurate has the benefits of being convenient, simple, pain-free, and non-invasive. Serving as a remote monitoring tool, Salurate effectively minimises the burden of hospital visits for expectant mothers and fosters seamless communication between women and healthcare professionals. Undertaking this study will add to the expanding pool of evidence supporting the adoption of technology-driven healthcare solutions, especially in obstetrics. Early prediction of pregnancy complications remains crucial, and Salurate offers a promising approach to address this vital aspect of maternal well-being.

4.3.6 Clinical and Public Health Implications

The findings from this study have the potential to influence clinical practice and public health policies. If Salurate proves to be effective in predicting HDP, it could be integrated into routine prenatal care protocols, enabling healthcare providers to offer more personalised and proactive care to pregnant women.

5 AIMS AND OBJECTIVES

5.1 Study Aim

To assess the efficacy of the Salurate pregnancy remote self-monitoring system in predicting the onset of HDP. By comparing the Salurate system with traditional diagnostic methods, this study aims to determine the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of Salurate in identifying pregnant women. Additionally, the study aims to evaluate the time-to-diagnosis using the Salurate system in comparison to conventional diagnostic approaches.

5.2 Primary Objective

a) To test the hypothesis that the inclusion of the Salurate pregnancy remote self-monitoring system in a pregnant woman's care pathway would predict the subsequent development of HDP prior to is currently possible using traditional methods.

5.3 Secondary Objectives

a) To assess whether Salurate could detect occurrence of other important placentally-mediated outcomes such as fetal growth restriction (FGR) spontaneous preterm birth (sPTB), stillbirth and GDM.
b) To assess the cost effectiveness of Salurate testing compared to current care methods.
c) To assess the degree of compliance of pregnant women to a self-sampling weekly Salurate test regimen.
d) To assess the algorithm efficacy in a demographically diverse population.

Note: the current care methods to diagnose HDP involve assessing blood pressure, proteinuria (diagnosed via urinalysis/24 hour collection), blood test results and/ or PIGF levels.

6 Salurate System

Salurate is a non-invasive, home-use self-sampling system.

A weekly saliva sample is taken in the morning before eating, drinking, or brushing teeth. This sample is applied to a colorimetric test paper (test cartridge). An enzymatic reaction occurs, which producing a purple colour of varying intensities. The intensity of colour change is directly proportional to SUA concentration.

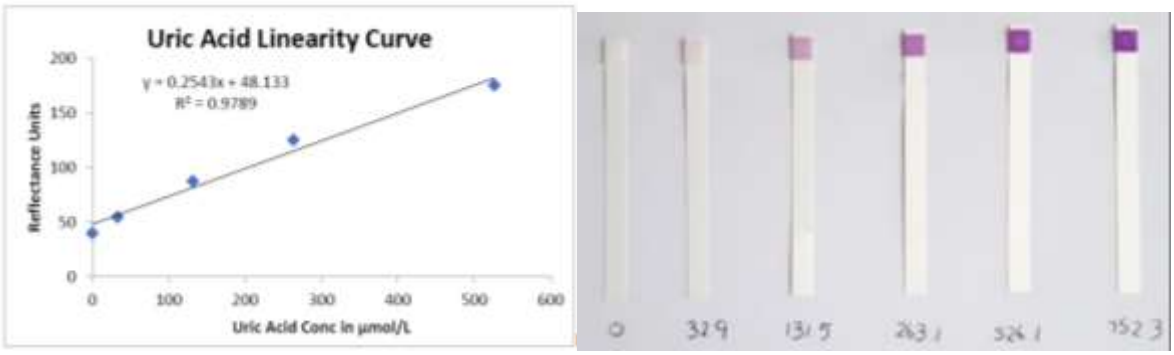


Figure 1. Uric acid linearity and colour intensity

A custom developed smartphone app, used in conjunction with a cloud server, receives the image from the smartphone app and extracts the relevant data. This data is combined with previous weeks' data and presented to the prediction algorithm.

The prediction algorithm is designed to detect patterns in the data that identify whether a hypertensive event is likely to occur in the pregnancy.

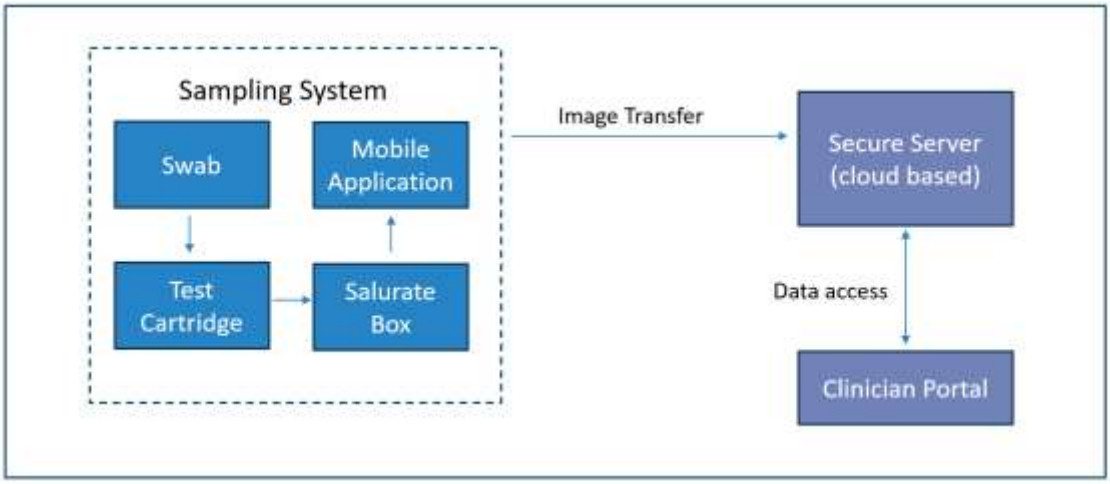


Figure 2. Salurate System Overview

6.1 Salurate System Components

The Salurate System is comprised of 6 key components.

1. The **Swab**: A pre-packaged, sterile swab commonly used for saliva collection. Single use, manufactured from a non-hazardous polyurethane foam.

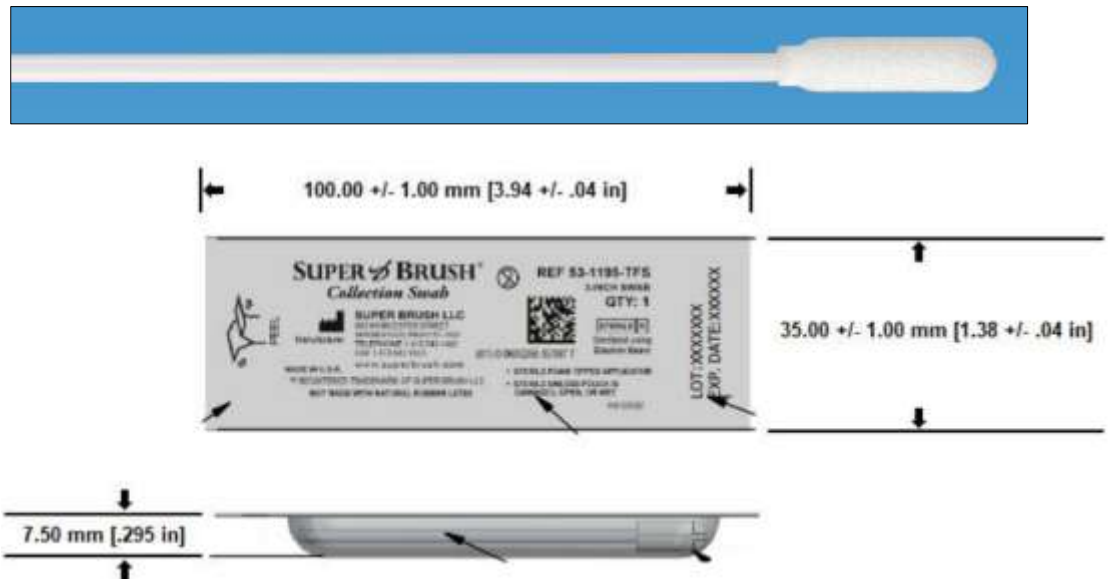


Figure 3. Swab and packaging

2. **Test Cartridge**: A bespoke enzymatic uricase colorimetric test assay. The intensity of the purple colour formed is directly proportional to the concentration of uric acid in the saliva sample. The test paper is encapsulated into a single-use test cartridge.

Figure 4. Test Cartridge

3. **Salurate Box**: Contains all equipment required to take a sample. The top of the box includes a designated test cartridge area for the purposes of facilitating image capture. The box top is also labelled with the Study ID in alphanumeric and QR form, and includes a simple colour chart (RGB). The colour chart is used by the Salurate Server to:
    - Adjust for differing lighting conditions
    - Adjust for a wide range of camera phone hardware

Figure 5. Salurate Box

Figure 6. Salurate Box Test area

4. **Mobile Application:** 'The Salurate App' is a custom designed smartphone app that participants will install on their smartphone. It's main features;
    - Facilitates the photographing of the colorimetric test paper (test cartridge)
    - Guides the participant through the Sampling process
    - Transmits this image to the Salurate Secure Server in a secure way
    - Reminds the participant when to take their sample
    - Displays relevant notifications and updates to participants
    - Provides a source of information about the study

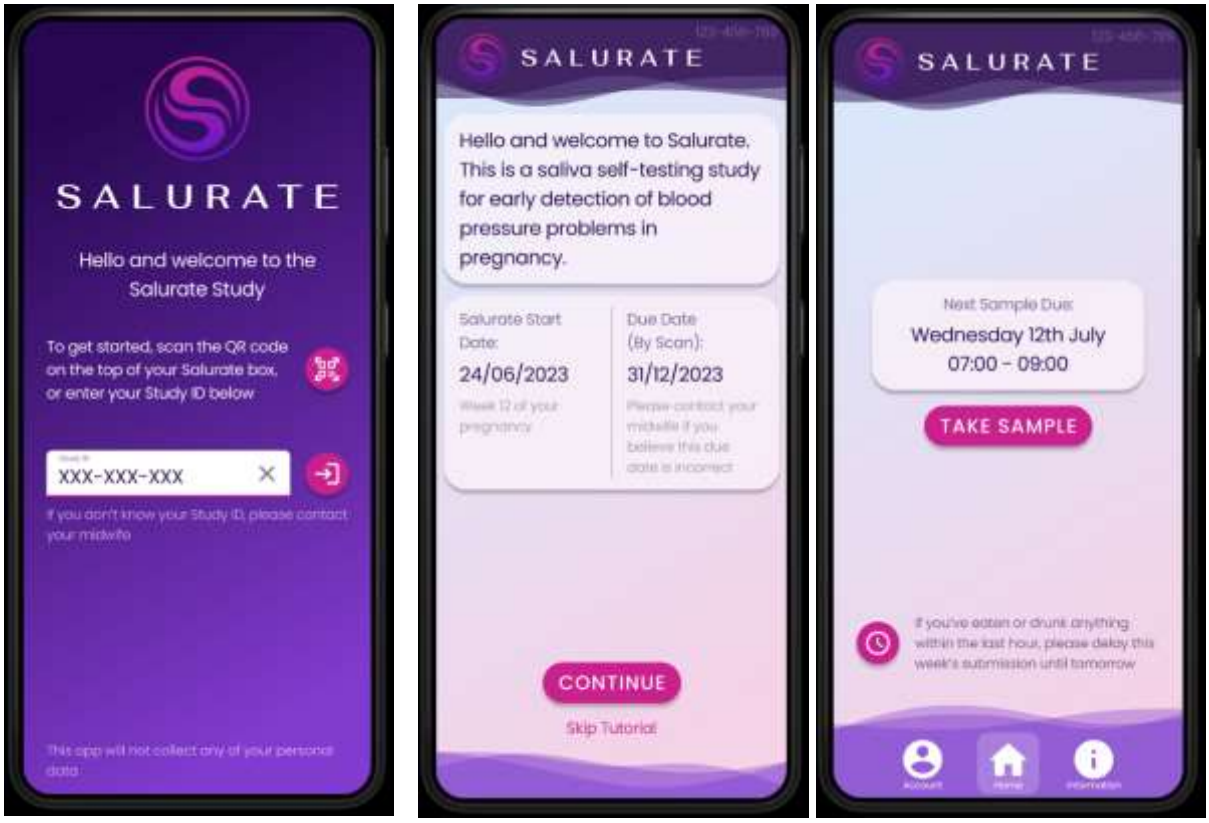


Figure 7. Salurate App; Login, Welcome and Start screens

5. **Salurate Secure Server:** A cloud-based server system that utilises the AWS platform. It will be designed by MIAT, and subject to independent security testing at regular intervals. The Salurate Secure Servers' primary functions;
    - To receive images transmitted from the Salurate App
    - To identify and extract colorimetric data from these images, and to generate predictions based on this extracted data
    - To act as a database of test kits, storing information including (but not limited to);
        - Anonymised participant ID number
        - Test kit batch information
        - Test kit Inventory and location
        - Information relating to recruitment centres and recruiters
    - To control and issue notifications to participants and recruiters

6. **Clinician Portal**: A means of viewing, updating, and extracting data from the Salurate Secure Server. Clinician Portal access is password controlled, with access permissions granted by the Sponsor. The primary functions;
    - To facilitate the registering of test kits during the recruitment process
        - The KIT ID is entered into the Portal, thereby informing the Salurate Server that this kit is activated. This creates an anonymous link between the participant, and data held by The Sponsor
    - To facilitate the control of inventory

- To allow low and high-level administrative access to data
    - Low level; Midwife access, Operations access. High level; Data controller

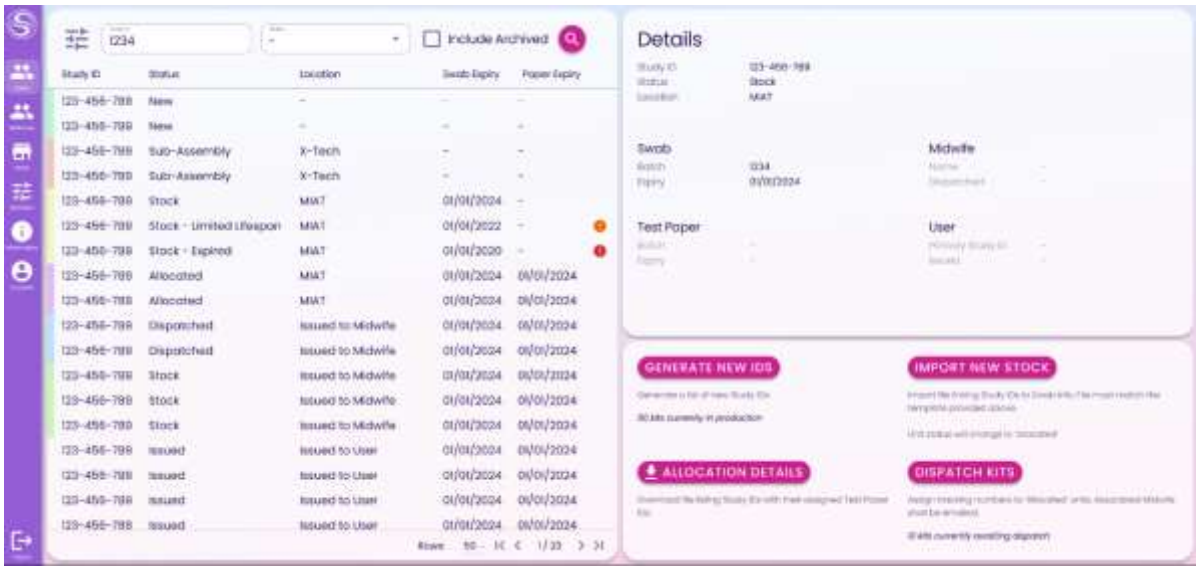


Figure 8. Clinician Portal; inventory information

6.2 Sampling Procedure Overview

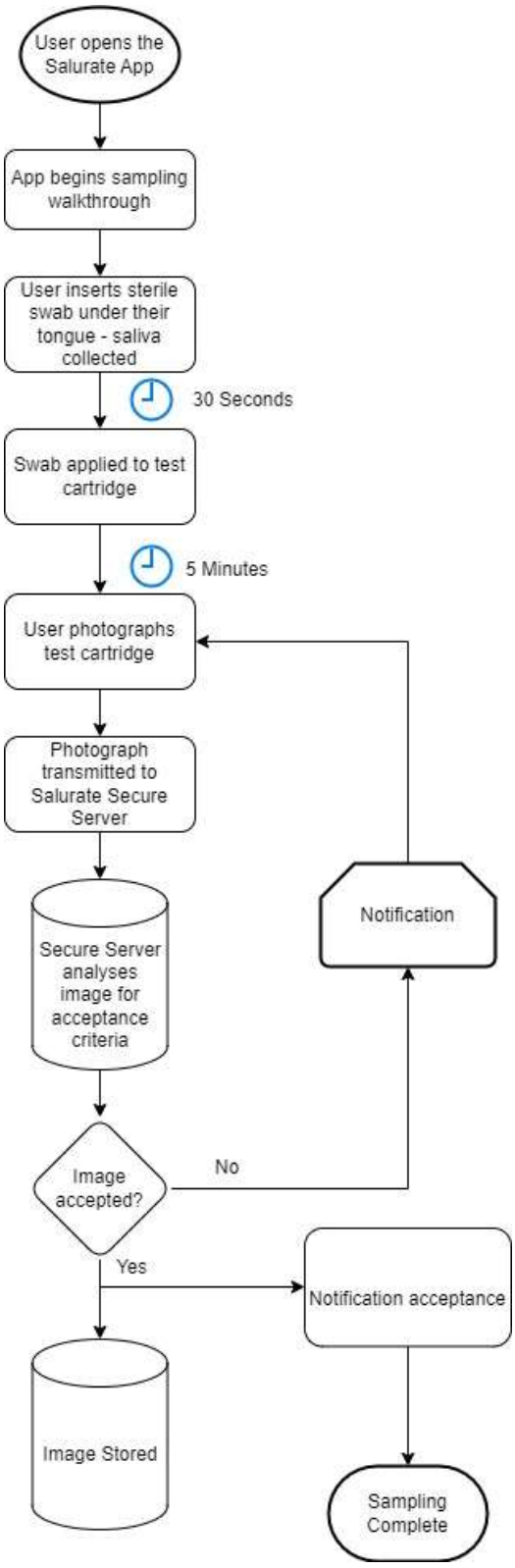


Figure 9. Sampling process, overview

7 STUDY DESIGN AND SETTING

7.1 Trial Design

A multi-center observational, analytical cohort study conducted over a period of 18 months with health economics evaluation.

7.2 Trial Setting

St. George's University Hospitals NHS Foundation Trust
St George's Hospital,
Blackshaw Road
Tooting, London
SW17 0QT

Epsom and St. Helier University Hospitals NHS Trust
Epsom & St Helier NHS Trust
East Wing, Epsom Gateway
Ashley Avenue
Epsom, Surrey
KT18 5AL

7.3 Identification Of Participants

Participants will be recruited by the clinical team as they present at a clinic for their routine first trimester scan at 10-14 of gestation. Recruitment and participation involve no additional appointments or travel for the woman, but could extend the duration of their clinic visit by up to 30 minutes.

The potential participant will be shown information about the Salurate Study, as well as introduced to the sampling kit. They will be advised that participation is entirely voluntary and that they may withdraw at any time. It will be made clear that inclusion in the study (or subsequent withdrawal) will not affect their usual care.

Potential participants will be advised that results will not be accessible to their clinical team, and that no additional clinical intervention will take place as a result of participation in the study.

The clinical team maintain the right to exclude potential participants if they consider the Study to potentially interfere with or compromise the delivery of care to the pregnant woman.

7.4 Side Effects / Participant Inconvenience

The Salurate Study does not involve pharmaceuticals, revealed test results, medical intervention, and there are no known side-effects linked to the collection of saliva.

The only procedure outside of standard antenatal practice is that once per week, on the same day, at the same time and before drinking, eating, exercise or teeth cleaning, the participant will take a saliva sample and test it on the disposable device.

Participation in the Study causes no risk of physical hurt, embarrassment, or pain to the participant.

Participation involves no manual handling, physical exercise, or physical activity from which there is a risk of accidents occurring.

7.5 Biobank

No research biobank is involved.

8 ELIGIBILITY

8.1 Inclusion Criteria

1. Women, 16 years old or over with a singleton pregnancy
2. Viable intrauterine pregnancy on the 10-14 week scan
3. High risk (≥1:100) of HDP as determined by the ASPRE [14] algorithm[1]
4. Medium risk of HDP as defined by an ASPRE risk between 1:100 and 1:300
5. Able to provide informed consent
6. Gestation at enrolment ≤16 weeks

8.2 Exclusion Criteria

1. Any significant medical co-morbidities which may potentially interfere with participation in or achieving the objectives of the study
2. Presence or history of severe mental illness that means the participant is unable to use Salurate independently
3. Any significant learning disability that means the participant is unable to use Salurate independently
4. Educational status or language barrier that influences capacity to use the App or understand the IFUs
5. Women who are physically incapacitated such as to make manipulation of the sampling system uncomfortable or impractical, as judged by the recruiter
6. Women who do not have access to a smartphone and/or internet data at home
7. Women who have been diagnosed with severe gingivitis or periodontal disease
8. Women who have been diagnosed with oral cancer

8.3 Contraindications

1. The potential participant suffers from severe nausea and vomiting in pregnancy.
2. The potential participant has infected, inflamed, cut/scraped or painful areas in their mouth.

9 INFORMED CONSENT

It is the responsibility of the research team to obtain informed consent for each trial participant.

Informed consent will be obtained during the early scan appointment. The recruiting clinician will allow the potential recruit sufficient time to read consent form *HR-P-51, Consent Form* and will have an opportunity to ask questions. If they decide to proceed and join the study, they will be asked to sign the Consent Form. This form will be scanned and stored with the participants' documentation on the EDGE database. Copies of the consent form will be given to the participant and stored in the participant's medical record. Reford of consent will also be entered onto the CRF (Doc: HR-P-55).

[1] Risk assessment based on: maternal factors, Mean Arterial Pressure, Uterine Artery Pulsatility Index, maternal serum pregnancy-associated plasma protein – A and placental growth factors

10 SCHEDULE OF EVENTS

10.1 Preparation

MIAT and its subcontractors will secure components, materials, and will assemble approximately 5000 Salurate test kits, each containing sufficient components to submit 30 samples. Each kit will be issued with a unique Kit ID number, which in turn will be linked to a batch number for traceability purposes.

These kits will be dispatched to recruiting locations in pre-agreed quantities, and will be refrigerated upon arrival[2].

10.2 Screening

Prior to the 10-14 week dating scan, the clinical team will have assessed the pregnant woman with regards to her risk of developing HDP. This risk category (Low/Medium/High) will be recorded on her clinical notes and will be used by the recruiting clinician to determine study inclusion.

10.3 Enrolment; 10-14 Week dating scan

Subject to eligibility criteria detailed in section 7, and following consent, the clinician will retrieve a Salurate sampling kit from storage and guide the participant through the process of taking a sample.

The clinician will login to the Salurate Portal and 'register' the kit with the Salurate Secure Server by entering the unique KIT ID. The clinician will enter this same ID onto the CRF and participants' clinical notes – thereby creating the pseudo anonymous link between results and participant.

10.4 Data collection; 10-14 Week dating scan

The following will be recorded on the CRF as part of the Dating Scan:

- Study ID
- Maternal age (at booking)
- Ethnicity
- Height (at booking)
- Weight (at booking)
- Smoking
- Obstetric history (parity, FGR, stillbirth, PE, PTB)
- Medical history (CHT, cardiac, renal or autoimmune disease)
- Blood pressure (MAP - and date taken)
- PAPP-A (MoM - and date taken)
- CRL (mm – and date taken)
- Estimated due date (by scan)
- Uterine Artery PI (left - and date taken)
- Uterine Artery PI (right - and date taken)
- ASPRE risk for PE <37 weeks

10.5 Data collection; Salurate Testing, Week 12 – Conclusion of pregnancy

Each participant submits weekly samples from enrolment $\leq$16 weeks of gestation until conclusion of pregnancy.

Should a test kit be destroyed or otherwise misplaced during the study, replacement kits will be issued and Kit ID information updated accordingly.

[2] Subject to resources available at each facility, MIAT may supply refrigeration equipment to ensure preservation of product

10.6 End Points (Primary Outcomes); Conclusion of Pregnancy

Clinical diagnoses of the following outcomes will be collected and recorded on the participant's CRF for a period of **6** weeks following the conclusion of pregnancy. Definitions 10.6.1 to 10.6.3.2 based on NICE Clinical Knowledge Summaries. The Salurate study's primary outcome is to predict HDP, the primary conditions of which are defined below.

10.6.1 Gestational hypertension

New hypertension presenting after 20 weeks, *without* significant proteinuria

10.6.2 Pre-eclampsia

New onset hypertension presenting after 20 weeks, *and* the coexistence of 1 or more of the following new-onset conditions.

New onset of hypertension (over 140 mmHg systolic or over 90 mmHg diastolic) after 20 weeks of pregnancy and the coexistence of 1 or more of the following new-onset conditions:

- Proteinuria
- **Other maternal organ dysfunction:**
    - Renal insufficiency (creatinine 90 micromol/litre or more, 1.02 mg/100 ml or more).
    - Liver involvement (elevated transaminases [alanine aminotransferase or aspartate aminotransferase over 40 IU/litre] with or without right upper quadrant or epigastric abdominal pain).
    - Neurological complications such as eclampsia, altered mental status, blindness, stroke, clonus, severe headaches or persistent visual scotomata.
    - Haematological complications such as thrombocytopenia (platelet count below 150,000/microlitre), disseminated intravascular coagulation or haemolysis
    - Uteroplacental dysfunction such as fetal growth restriction, abnormal umbilical artery doppler waveform analysis, or stillbirth.

10.6.2.1 HELLP Syndrome

Haemolysis, Elevated Liver enzymes, and Low Platelets

10.6.2.2 Eclampsia

The occurrence of one or more seizures in a woman with pre-eclampsia

10.6.3 Chronic hypertension with superimposed pre-eclampsia

Characterized by;

- New-onset proteinuria (≥300 mg/24 h) in a woman with hypertension but no proteinuria before 20 weeks' gestation *and,*
- A sudden increase in proteinuria or BP, or a platelet count of less than 100,000/mm^3, in a woman with hypertension and proteinuria before 20 weeks' gestation [15].

10.6.4 Additional Primary Outcomes

- Adverse maternal outcomes
- Adverse perinatal outcomes
- Mode of delivery

10.7 End Points (Secondary Outcomes); Conclusion of Pregnancy

Data on the following secondary study outcomes will be collected.

10.7.1 SGA

Neonates whose birth weight is less than the 10th percentile for that particular gestational age or two standard deviations below the population norms on the growth charts. The definition considers only the birth weight without any consideration of the in-utero growth and physical characteristics at birth.

10.7.2 Gestational Diabetes

Any degree of glucose intolerance with onset or first recognition during pregnancy. Developed during the second and third trimester of pregnancy, characterized by a marked insulin resistance secondary to placental hormonal release.

10.7.3 Sampling Adherence

Data relating to the following will be collected and analysed;

- Frequency of missed samples
- Dropout rate
- 'Dry' samples received

10.7.4 Definition of HDP

Blood Pressure

- Systolic blood pressure ≥130 mm Hg on 1 or more occasions
- Diastolic blood pressure ≥80 mm Hg on 1 or more occasions

Urine

- Urine protein dipstick test 1+ or more
- Urinary protein/creatinine ratio ≥0.30 mg/mg
- Urinary protein ≥300 mg per day in timed collection

Bloods

- New-onset low platelet count ≤100,000 x 109/L
- New onset elevated serum creatinine ≥1.0 mg/dL
- New-onset transaminase elevation above limits of normal for local laboratory

Symptoms

- New-onset headache unresponsive to medication and not accounted for by alternative diagnoses
- New-onset visual symptoms

Fetus

- Fetal growth restriction with AC/estimated fetal weight ≤10th percentile

11 ADVERSE EVENT REPORTING

11.1 Safety Reporting

11.1.1 Adverse Event Definitions

Adverse Event (AE)	An event in which care resulted in an undesirable clinical outcome – an outcome not caused by underlying disease – that prolonged hospital care, caused permanent

	harm or requires lifesaving intervention or contributed to death.
Adverse Reaction (AR)	An untoward and unintended response resulting from an intervention related to the use of an investigational product.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity Other 'important medical events' may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial methodologies or treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	Any events suspected to be caused by the investigational product, but which are not consistent with information about the investigational product.

11.1.2 Safety Reporting Window

Participants will be monitored for adverse events while they are enrolled on the study, and given contact details (telephone number and email address) to report any adverse events that may occur. Once their involvement in the study has ended, they will have an additional 6 weeks in which to contact the Investigators with details of any adverse events that become apparent after they have been unenrolled. Therefore, the Safety Reporting Window will be from enrolment until 12 weeks after disenrollment.

11.1.3 Assessment of Causality

The relationship of each adverse event to the trial intervention must be determined by a suitably qualified individual according to the following definitions:

- Related: The adverse event follows a reasonable temporal sequence from the trial investigational product. It cannot reasonably be attributed to any other cause.
- Not Related: The adverse event is probably produced by the participant's clinical state or by other modes of therapy administered to the participant.

Due to the low-risk nature of the device the assessment of causality will be deemed by the Principal or Chief Investigator as suitably qualified healthcare professionals.

11.1.4 Procedure for Reporting Adverse Events

All AEs occurring during the safety window for the trial as defined above that are observed by the Investigator or reported by the participant, will be recorded during visits on the participants electronic

health record as source data and recorded on the CRF for the purposes of the study, whether or not attributed to the Salurate device.

The following information will be recorded on the CRF: description, date of onset and end date, severity, assessment of relatedness to investigational product, other suspect drug or device and action taken. Follow-up information should be provided as necessary until the AE has resolved or stabilised.

The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.

Non-serious AEs considered related to the study intervention as judged by the Principal or Chief Investigator or the Sponsor will be followed up until resolution, or the event is considered stable.

It will be left to the Investigator's clinical judgment to decide whether an AE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what they perceive as an intolerable AE. If either of these occurs, the participant will be thanked for their involvement and followed up by telephone until the AE is resolved or considered stable. All withdrawals must be recorded using document *HR-P-62 - Early Withdrawal Form*.

11.1.5 Procedure for Reporting Serious Adverse Events

All SAEs must be reported to the Sponsor using document *HR-P-60 - SAE Reporting Form* immediately upon the Site Study Team becoming aware of the event being defined as serious. An assessment of Expectedness will be made by the Principal or Chief Investigator at the point of reporting.

It will be left to the Investigator's clinical judgment to decide whether an AE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what they perceive as an intolerable AE. If either of these occurs, the participant will be thanked for their involvement and followed up by telephone until the AE is resolved or considered stable. All withdrawals must be recorded using document *HR-P-62 - Early Withdrawal Form*.

11.1.5.1 Exceptions for SAE reporting

Hospitalisation for a pre-existing condition, including elective procedures planned prior to study entry, which has not worsened, does not constitute a serious adverse event.

11.1.6 Procedure for Reporting SUSARs

In the unlikely event of a SUSAR occurring, it must be reported on document *HR-P-60 – SAE Report Form* to the Sponsor immediately on the Investigation Team becoming aware of the event being defined as serious. An assessment of Expectedness will be made by the Principal Investigator at the point of reporting.

It will be left to the Investigator's clinical judgment to decide whether the SUSAR is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what they perceive as an intolerable serious adverse reaction. If either of these occurs, the participant will be thanked for their involvement and followed up by telephone until the AE is resolved or considered stable. All withdrawals must be recorded using document *HR-P-62 – Early Withdrawal Form*.

11.1.7 Clinical Responsibility

Overall clinical responsibility for all participants enrolled onto the study will lie with the Chief Investigator, professor Baskaran Thilaganathan, who will review AEs as they are reported and provide clinical guidance for participants' safety through involvement as their treating clinician and in the oversight committee.

Professor Baskaran Thilaganathan is the Director of Fetal Medicine at St George's Hospital since 1999. He has authored over 400 peer-reviewed publications in indexed journals. His major research interest is placental dysfunction leading to pre-eclampsia, fetal growth restriction and stillbirth. He has led on the implementation of algorithm-based screening at St Georges which has led to an 80% reduction in preterm pre-eclampsia and a 30% reduction in perinatal death.

12 DATA HANDLING AND RECORD KEEPING

The data controller will be nominated by the Sponsor at the beginning of the study. Data processing will be by employees of the Sponsor under the direction of the data controller. The data will be used only for the purposes indicated in the currently-proposed Study. All data collected for the study will be subject to the General Data Protection Regulation and Data Protection Act 2018. The data collected will be anonymised and stored securely by Morgan Innovation & Technology Ltd, the data controller for the Salurate Study, and by the St George's clinical research archive, for a maximum of 15 years. This is for the purpose for processing the data, protection of IP and to ensure regulatory and legal requirements are evidenced when obtaining approvals.

Hospital-based. For the following functions:

1. Signing and storage of Consent Forms
2. Registration of Participants
3. Generating Study IDs, linked to Participant's ID
4. Clinical event data

These can be executed as paper-based hard copy, with attendant lock-and-key storage of documents, or electronically, on a software module written for the purpose and residing on a hospital-based system, and password controlled by the Investigator. Access to the hospital site is tightly controlled.

Also executed at the Hospital site, by clinical staff under the direction of the investigator, will be the creation, and storage of CRFs.

Sponsor's data-centre. For the following functions:

1. Receipt of compressed image data;
2. Calculation of results from image data;
3. Validation and storage of results;
4. Receipt and storage of CRFs identified only by Participant Study ID;
5. Linkage of Prediction-results and CRFs by Participant Study ID;
6. Statistical analysis

Two sets of Participant data relate; the sequential results of weekly self-testing for uric acid by each Participant, and the CRF of selected data from the Participant clinical records. Both sets shall be stored in separate areas: The weekly uric acid data shall reside in a Cloud-based system under the control of the data controller in the United Kingdom. The CRF will be stored on physical Servers owned by the sponsor and under the control of the data controller in the United Kingdom.

Data Protection: Test Results

- Recruitment will be carried out by a qualified medical professional approved by the Investigator and trained in Good Clinical Practice and the obligations of Researchers towards protection of the rights of volunteer participants, including personal data protection.
- Candidate participants will be advised that they will be asked to provide and test saliva samples, and to agree to the results being matched with certain data from their clinical records. These requirements are noted in the Participant Information Sheet (Doc:HR-P-53), in the oral recruitment interview, and in the Consent Form (Doc: HR-P-51) which they will be asked to sign.
- Upon giving informed consent, the subject's Consent Form will be registered on the Participant Register by the recruiter and assigned an individual Participant Study ID. The Register file linking Subject's Identity with Participant Study ID, either hard-copy or electronic, will be held by the Investigator. Staff of the Sponsor shall have no access to this linkage.
- Upon testing her sample, the participant will use their smart-phone app take an image / photo of the test cartridge. This image will then be compressed along with a time / date stamp and Participant Study ID. The compressed data is then transmitted to the Sponsor-held algorithm.
- These functions will be encoded in an application developed for the purpose by the Salurate supplier (which, in the case of the Trial, will be the Sponsor). The participant associated with each result will be identified only by their Study ID. Data transmitted will be encrypted by the smart-phone's communication protocol(s).
- The algorithm will convert the image to a digital uric acid concentration value.
- Test results will be validated and stored on a Cloud-based database managed by the Sponsor. The security levels and physical redundancy back-up facilities of reputable Cloud-system suppliers are generally much more robust than could realistically be provided by a stand-alone system.
- It should be noted that the sequence of uric acid test results for a pseudonymised participant would be entirely meaningless to an unauthorised observer.

Data Protection: Clinical Data

- At registration of a participant the linkage of participant Identifiable Information to Participant Study ID will be known only to the recruiter, and will be stored securely by the Investigator, either in a hard-copy register under lock-and-key or electronically under password protection. On completion of the Trial the register of linkage of participant Identifiable Information to Participant Study ID will be destroyed.
- As set out above, the participant will be well informed prior to her consent of the intention to extract certain clinical information from the records of every participant, and record them in a CRF on conclusion of the pregnancy. It will be emphasised that the data extraction will be done by a medical professional, and that the participant whose data goes in the CRF will be identified only by Participant Study ID.
- The information to be included in the CRF will be the presence or absence of any of the targeted end-points related to HDP, as defined in this Protocol. These will simply be characterised to the subject as "information relating to the progress and outcome of her pregnancy", but the detailed end-points can be made known on request.
- The completed CRF, identified only by Participant Study ID, will be generated electronically by clinical staff directly into the Sponsor-held data-base, and matched by Participant Study ID with the test-results already on file for the subject holding that Participant Study ID.

At no point will persons other than the participants' clinicians be aware of the subject's ID, or of any clinical information other than that specified in the CRF. The CRF information for a participant pseudonymised by Study ID would be meaningless to an unauthorised observer.

13 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Site Set-up and Initiation

The Chief Investigator must sign an agreement to document the expectations of the clinical team and the sponsor – MIAT. The agreement document must be completed before participation. The Chief Investigator (CI) is required to sign a Clinical Trials Task Delegation Log, which documents the agreements between the CI and MIAT. All PIs will be asked to sign the necessary agreements, including a Site Signature & Delegation Log between the PI and MIAT, and supply a current CV and GCP certificate to the sponsor. All site staff who are performing trial-specific tasks are required to sign the Site Signature and Delegation Log, which details all functions that have been delegated to them by the PI. Prior to commencing recruitment, each recruiting site will undergo a process of initiation, either a meeting or videoconference, at which critical members of the site research team are required to attend, covering aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will receive an investigator's site file, instructions, and other documentation required to conduct the trial. The sponsor must be informed immediately of any change in the site research team.

13.2 Sampling System Integrity

The device manufacturer adheres to a QC regime which includes verification, by Lot Number of: Wet-reagent component concentrations, Blank test-paper colour, Accuracy of finished device on Uric Acid Standards, Reproducibility of finished device on UA Standards, with records available for inspection.

Integrity of patient/kit ID as well as resulting sampling data are assured by unique design and verification of the Device, App, and Server.

Time-stamping of photograph and then receipt by database will allow identification of diurnal variation and the subject will be automatically advised to adhere to same-time-each-day procedure.

Plausibility of each colorimetric result is controlled by the correlation of two optical parameters, saturation and luminance, in the assay algorithm. If the two results differ by a defined margin, a request for a repeat-test will be sent to the subject.

Accuracy of CRF data excerption from Patient Records will be controlled by a monthly spot-check of 10% of CRFs by a qualified independent individual from another hospital, with any required corrective action identified.

13.3 Risk Assessment

A risk assessment has been completed in line with St George's University Hospitals and Epsom and St Helier University Hospitals standards and policies. A risk management file was developed for the clinical trial to identify issues that participants and trial staff may face that might affect the study's quality. The file is available for consultancy. No unacceptable risk was identified that could compromise the physical or mental well-being of people involved in the trial.

13.4 Monitoring (onsite and central monitoring)

St George's University Hospitals and Epsom and St Helier University Hospitals Research Teams will monitor study processes and data collection after the first cohort has been processed. The Research Teams may also undertake spot checks for monitoring purposes at any point throughout the entire study, as issues regarding poor data quality, deviation of the protocol and GCP will raise extra monitoring visits.

At the end of the study, a final monitoring session from the Research team will be undertaken to assess the conduct of the study and ensure good quality data. The sites will be monitored under the trial risk assessment and monitoring plan.

Between each cohort, the CI will discuss the performance of the Investigation Team and the cohort participants informally with the PI and the Investigation team to identify any practical and/or logistical difficulties during the cohort which may be improved for future cohorts or used to improve study design for future research projects. This will also be fed back to the Oversight Committee.

Trials staff will regularly contact the site research team to check on progress and address any queries they may have. Trials staff will check incoming ICFs and CRFs for compliance with the protocol, data consistency, missing data and timing. Sites will be sent DCFs requesting missing data or clarification of inconsistencies or discrepancies. Sites will be requested to send copies of signed consent forms and other documentation for in-house review for all participants providing explicit consent. This will be detailed in the monitoring plan.

13.5 Audit and Inspection

The CI will allow monitoring, audits, ethical review, and regulatory inspections to take place at clinical trial site. This means that direct access to source data and documents will be provided. The CI will fully comply with these visits and any necessary follow-up. Additionally, sites are requested to notify the sponsor of any relevant inspections.

By allowing these measures to take place, we can ensure the highest level of quality and safety for the trial. This will ultimately lead to better outcomes for the patients involved and help advance medical knowledge.

13.6 Medical Device Recall

The Sponsor is responsible for product recall.

The actions below shall be taken should a recall of the Salurate Sampling System be required;

- The Sponsor shall start an investigation with the CI supporting, to identify the route of the issue and the affected batch
- The sponsor shall immediately notify the MHRA regarding Field Safety Corrective Actions that will be carried out, and request MHRA advice
- The CI must inform the clinical trial team of all the sites involved in the study
- Depending on the recall class, as dictated by the MHRA (1-3), batches or the entire sampling inventory may be recalled.
- The CI shall confirm if the affected batch is in stock; if yes, it should be immediately quarantined until the Sponsor authorises either;
    - The release of the batch,
    - Return to the Sponsor/manufacturer
    - Destruction of the batch
- The PI or CI must identify participants with access to the affected batch for the information to be available when necessary. This task can be delegated to other members of the clinical team.
- A draft of the Field Safety Notice (FSN) must be shared with the MHRA for comments before an official FSN is released
- An FSN shall be submitted to the MORE Portal, and the recall initiated
- New stock will be ordered by the CI

13.7 Notification of Serious Breaches

It is imperative to promptly document any deviation from the Protocol in the HR-P-52 *Protocol Deviation Log*. This log will be shared with the Sponsor after each cohort. It is the Sponsor's responsibility to inform the licensing authority in writing within seven days of discovering any significant relating to the trial. Any deviation that may impact the physical and mental safety of participants or staff, or have an effect on the quality or integrity of the data, and subsequently the scientific value of the trial, must be treated with utmost seriousness. Serious breaches, they must be immediately recorded in the Protocol Deviation Log and reported to the Sponsor.

Promptly reporting any suspected trial-related serious breach of GCP and/or the trial protocol is mandatory and Trials office shall be informed. Where the Trials Office is investigating whether or not a serious breach has occurred, sites are also requested to cooperate with the Trials Office in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action.

Sites that exhibit serious and persistent non-compliance with the protocol and/or GCP and/or poor recruitment may be suspended from further recruitment. Any major problems identified during monitoring must be reported to the Trial Management Group, Trial Steering Committee, the site's R&D Department, and the REC. Serious breaches of GCP and/or the trial protocol also must be reported to the REC and MHRA. When reporting to the REC and/or relevant regulatory bodies, a copy of the documentation relating to serious breaches will equally be sent to the sponsor.

14 END OF STUDY DEFINITION

The end of the study will be the point at which 4000 complete datasets have been received. REC and MHRA will be notified within 90 days of the trial ending.

15 STATISTICAL CONSIDERATIONS

A cohort of 4,000 participant mothers would experience an estimated 460 events overall (PE/PIH/ IUGR) assuming a prevalence of 11.5%, and 100 cases of IUGR (the least prevalent of the conditions being studied), assuming a prevalence of 2.5%, based on observations from the Denmark study. This sized cohort would allow sensitivity of the Salurate algorithm to identify IUGR to be estimated with a 2-sided 95% confidence interval (CI) to within plus or minus 10% of the point estimate (if sensitivity was actually 50%, i.e. 95% CI 40% - 60%) and this would improve to a more precise confidence interval to within plus or minus 6% of the point estimate if the sensitivity proved to be around 90% (i.e. 95% CI 84% - 96%).

Additionally, a cohort of N=4,000 would allow sensitivity of the Salurate algorithm to identify any of the events of interest (prevalence 11.5%) to be estimated with greater precision, with a 2-sided 95% confidence interval to within plus or minus 5% of the point estimate (if sensitivity was actually 50%, i.e. 95% CI 45% - 55%) and this would improve to a more precise confidence interval to within plus or minus 3% of the point estimate if the sensitivity proved to be around 90% (i.e. 95% CI 87% - 93%). Specificity will be estimated to a much higher degree of precision because the majority of participants/babies in the cohort will not encounter adverse outcomes, and so they will comprise the much larger sample.

All analysis will be conducted by the study statistician Professor I. Reading, using StataSE v16.1 statistical analysis software.

The Salurate study is quantitative research (numerical outcome). The quantitative data for this study will be analysed and reported according to the relevant reporting guidelines (STARD, BMJ. 2015;351:h5527. PMID: 26511519 and TRIPOD BMJ 2015; 350:g7594. PMID: 25569120).

All clinical primary and secondary outcomes (maternal and neonatal) will be presented across the whole cohort as percentages with 95% confidence intervals, missing outcomes data will be presented. Women's characteristics at enrolment into the study will also be presented with percentages or summary statistics as appropriate. Salivary uric acid concentration (Salurate) observations will be presented graphically over time from the initial 10-14 week pregnancy record through to the end of study participation i) for the whole cohort, ii) by primary outcome (HDP present or absent), iii) for each secondary outcome, including adverse maternal or perinatal outcomes.

Numbers and percentages of missing Salurate reports will be presented by week of pregnancy with the number of women participating in the study as the denominator (which may vary in the last weeks of the study depending on when they give birth). This will be used to assess the degree of compliance of women to the testing regime. No multiple imputation or other forms of missing data replacement will be used to estimate missing values of Salurate. No missing data replacement will be employed for clinical outcomes or participant's characteristics at enrolment, and every effort will be made to record these data. We anticipate that rates of data missingness will be low.

Multilevel Logistic/Linear regression models, as appropriate, will be used to determine the relationship between Salurate results and the primary and secondary outcomes in this cohort. The Salurate algorithm will be employed and its sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) to identify the primary outcome will be presented with 95% confidence intervals. We will also determine how soon the primary outcome would be indicated using Salurate results and compare this with traditional prediction methods using standard NHS monitoring data.Subgroup analyses will explore whether the Salurate algorithm has greater diagnostic value in particular women according to baseline characteristics, although these analyses may not have enough statistical power to be definitive. Adverse Event and Serious Adverse Events details will be listed.

15.1 Missing Data

Every attempt will be made to collect full follow-up data on all trial participants; it is thus anticipated that missing data will be minimal.

16 HEALTH ECONOMICS ANALYSIS

The study outcomes will be incorporated into a Health Economics Evaluation, in particular a decision analytical model to evaluate the cost and health outcomes of Salurate from an NHS perspective by assessing the incremental changes as compared against the current care for screening patients at risk of n, pre-eclampsia. Uncertainties will be quantified by probabilistic sensitivity analysis.

17 TRIAL ORGANISATIONAL STRUCTURE

17.1 Sponsor

The Sponsor for this trial is Morgan Innovation & Technology Ltd.

17.2 Coordinating Centre

The trial coordinating centre (Trial Office) is St. George's University Hospitals NHS Foundation Trust.

17.3 Trial Management Group

The Trial Management Group will take responsibility for the day-to-day management of the trial and will include (but is not limited to) the CI, co-applicants, statistician, team leader and trial manager. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

17.4 Trial Steering Committee (TSC)

A TSC will be created for the Salurate Study.

Membership and duties/responsibilities will include;

- Overall oversight of the trial, including the practical aspects of the trial, as well as ensuring that the trial is run in a way which is both safe for the participants and
- To provide appropriate feasibility data to the sponsor and investigators.

The TSC will meet once a month (or as required) to review recruitment and study progress.

18 ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research and applicable UK Acts of Parliament and Statutory Instruments (and relevant subsequent amendments), which include, but are not limited to, the Medicines for Human Use Clinical Trials 2004; Data Protection Act 2018; Mental Capacity (amendment) Act 2019; Medical devices Regulations 2002 (UK MDR 2002).

The trial will also be conducted in accordance with the principles of the Declaration of Helsinki and ISO 14155:2020 Clinical investigation of medical devices in human subjects – Good Clinical Practice.

This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use Clinical Trials regulations and according to the Principles of Good Clinical Practice as set out in the UK Statutory Instrument (2004/1031; and subsequent amendments).

The protocol will be submitted to and approved by the REC prior to the start of the trial. All correspondence with the MHRA and/or REC will be retained in the TMF/ISF, and an annual progress report will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given by the REC, and annually until the trial is declared ended. A trial-specific risk assessment and monitoring plan will be developed before submission to the REC and will be reviewed regularly during the trial.

Before any participants are enrolled into the trial, the PI at each site is required to obtain the necessary local approval.

It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

19 CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018.

The participant's personal and clinical information is known only to the clinicians. They are known to the Sponsor by their KIT ID only. The participant's identity is not disclosed to the persons accessing the results, before, during, or after completion of the study.

Only pseudo anonymised linked pairs of test results and clinical outcomes, with Participants' KIT ID removed, will be subjected to statistical analysis and any publication derived therefrom.

20 FINANCE

The study is funded by Innovate UK. All costs related to this clinical trial, including additional charges, will be covered under this grant. As Sponsor, Morgan Innovation & Technology Ltd. does not exclusively

restrain its support to financial affairs. The Sponsor will also provide support in terms of technical expertise (project management, clinical advisor, quality assurance, regulatory affairs consultancy, and software engineering).

21 INSURANCE AND INDEMNITY

It is essential to ensure adequate provision is made for insurance or indemnity to cover any liabilities that may arise in relation to the design, management, and conduct of the research project. This will help to mitigate any potential risks and ensure that all parties involved in the research project are protected. Therefore, in addition to standard NHS indemnity protection, the Sponsor has taken out indemnity Insurance with Chubb European Group SE, via Tony Knight of KnightSure Insurance Brokers, subject to receipt, review and acceptance of applicable Patient Consent and applicable Protocol as follows:

Insurer:	Chubb European Group SE
Policyholder:	MORGAN INNOVATION & TECHNOLOGY LTD.
Period of insurance:	20/08/2024 - 20/01/2026 both days inclusive
Coverage:	Clinical Trials Liability
Territorial Limits:	United Kingdom
Limit of Liability:	GBP 1.000.000
Study Protocol Title:	Validation of salivary uric monitoring for early prediction of hypertensive disorders of pregnancy
Coverage:	Clinical Trials Liability

22 PROTOCOL APPROVAL & AMENDMENTS

Following Sponsor approval, the protocol, informed consent form, and participant information sheet will be submitted to the REC, MHRA, CI and PI for written approval. The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

23 POST-STUDY CARE

The Salurate Study is non-interventional and will cease with the end of pregnancy. Throughout the study and after, participants will receive standard medical care.

24 TRIAL RESULTS AND PUBLICATION

Trial results will be submitted for publication in a peer reviewed journal, with Chief Investigator as lead author. Publication will be attempted regardless of outcome.

25 PATIENT AND PUBLIC INVOLVEMENT

A range of PPI activities including surveys and focus groups with women and clinicians have guided our choice of participant population, software and test device design. Specific input has been provided from the Action on Pre-eclampsia Charity (APEC).

26 References

[1] C. V. Ananth , K. M. Keyes and R. J. Wapner, “Pre-eclampsia rates in the United States, 1980-2010:

age-period-cohort analysis," *BMJ 2013; 347 :f6564 doi:10.1136/bmj.f6564.*

[2] V. Garovic, W. White, L. Vaughan, M. Saiki, S. Parashuram, O. Garcia-Valencia and Et al., "Incidence and long-term outcomes of hypertensive disorders of pregnancy," *J Am Coll Cardiol,* vol. 75(18), 2020.

[3] R. Fox, J. Kitt, P. Leeson, C. Aye and A. Lewandowski, "Preeclampsia: Risk Factors, Diagnosis, Management, and the Cardiovascular Impact on the Offspring," *J Clin Med,* 2019 Oct 4;8(10):1625. doi: 10.3390/jcm8101625. PMID: 31590294; PMCID: PMC6832549..

[4] V. Giorgione, A. Khalil, J. O'Driscoll and B. Thilaganathan, "Peripartum Screening for Postpartum Hypertension in Women With Hypertensive Disorders of Pregnancy," *J Am Coll Cardiol,* pp. 11;80(15):1465-1476. doi: 10.1016/j.jacc.2022.07.028. PMID: 36202536, 2022.

[5] M. Countouris, F. Villanueva, K. Berlacher, J. Cavalcante, W. Parks and J. Catov, "Association of Hypertensive Disorders of Pregnancy With Left Ventricular Remodeling 322 Later in Life," *J Am Coll Cardiol,* pp. 77:1057-1068., 2021.

[6] F. McCarthy, J. O'Driscoll, P. Seed, A. Placzek, C. Gill and J. e. a. Sparkes, "Multicenter Cohort Study, With a Nested Randomized Comparison, to Examine the Cardiovascular Impact of Preterm Preeclampsia.," *Hypertension,* pp. 78:1382-1394., 2021.

[7] V. Giorgione, A. Kalafat, A. Khalil and B. Thilaganathan, "Incidence of postpartum hypertension within 2 years of a pregnancy complicated by pre-eclampsia: a systematic 312 review and meta-analysis," *BJOG,* pp. 128:495-503. doi:10.1111/1471-0528.16545, 2021.

[8] C. Meads, J. Cnossen, S. Meher and et al., "Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling," *Health Technol Assess,* 2008 12(6):iii-270.

[9] W. Giannobile, J. McDevitt, R. Niedbala and D. Malamud, "Translational and clinical applications of salivary diagnostics. 2011;23(4):375-380. doi:10.1177/0022034511420434," *Advances in Dental Research,* 2011;23(4):375-380. doi:10.1177/0022034511420434.

[10] Püschl, IC, Bonde, L, I. Reading and P. M. Maguire, "Salivary uric acid as a predictive test of preeclampsia, pregnancy-induced hypertension and preterm delivery: A pilot study," *Acta Obstet Gynecol Scand,* 2020; 99: 1339– 1345. https://doi.org/10.1111/aogs.13888.

[11] "Hypertension in pregnancy: diagnosis and management," NICE GUIDELINE [NG133], 17 April 2023. [Online]. Available: nice.org.uk/guidance/ng133.

[12] J. Allotey, K. L. E. Snell and Smuk, Melanie et al, "Validation and development of models using clinical, biochemical and ultrasound markers for predicting pre-eclampsia : an individual participant data meta-analysis," *Health Technology Assessment. ,* vol. 24, no. 72, 2020.

[13] E. A. P. Steegers, P. von Dadelszen, J. J. Duvekot and R. Pijnenborg, "Pre-eclampsia," *The Lancet,* 2010;376(9741):631-44.

[14] Rolnik DL, Wright D, Poon LCY, et al., "ASPRE trial: performance of screening for preterm pre-eclampsia," *Ultrasound Obstet Gynecol,* pp. Oct;50(4):492-495, 2017.

[15] K.-H. Lim and E. al., ""Preeclampsia"," Medscape, 18 Aug 2022. [Online]. Available: https://emedicine.medscape.com/article/1476919-overview#a2?form=fpf. [Accessed 07 Aug 2023].

27 APPENDICES

27.1 Appendix 1 – Related Documentation

ID Code	Title
HR-P-08	Salurate Instructions for Use
HR-P-51	Salurate Consent Form
HR-P-52	Protocol Deviation Log
HR-P-53	Participant Information Sheet
HR-P-54	Quick Start Guide
HR-P-55	Case Report Form
HR-P-59	Risk Management Review – Clinical Trial
HR-P-60	SAE Report Form
HR-P-61	Investigator's Brochure
HR-P-62	Early Withdrawal Form
HR-P-64	Laboratory Manual

27.2 Appendix 2 – Amendment History

Date	Amended by	Amendment Details	New Version Number
25/06/2024	C. Cacumba	- The patient population's minimum age has been revised to 16, in response to a request from the Research Ethics Committee. This change is intended to include 16 and 17-year-old participants in the trial, as they are considered adults and are legally able to provide consent. - Research Ethics Committee information was added in the table 'Administrative Information', after meeting with REC on the 18th of June 2024. - Exclusion and inclusion criteria were reviewed and updated.	2
25/06/2024	C. Cacumba	- On section 3, it was added a new secondary outcome. - On section 5.3, added the same secondary outcome added in section 3. It was also added a reference to current care methods to diagnose HDP.	3
04/07/2024	B. Chmielewska	- Statistical considerations were added on section 15.	4