[Non-Invasive Blood Glucose Monitor using Photoplethysmography]

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I. Introduction

- give some background of the investigated problem

Diabetes has emerged as a significant health concern over the years, necessitating regular monitoring of blood glucose levels using a glucometer, a common device for treatment purposes. Traditional glucometers involve invasive procedures such as pricking the skin to collect blood samples, which can be painful, lead to skin changes, and increase the risk of infection.

In response to these concerns, there is a growing demand for the development of an economical, simple, and non-invasive blood glucose monitoring device that eliminates the need for repeated skin pricking. Non-invasive techniques, including optical, transdermal, and thermal methods, have been explored as alternatives. Optical techniques utilize the interaction of glucose with light properties, transdermal techniques measure blood glucose using electricity or ultrasound, and thermal techniques detect physiological indicators of metabolic heat generation to estimate blood glucose levels [1].

One essential aspect of diabetes management is monitoring glycated hemoglobin (HbA1c) levels. HbA1c, a type of hemoglobin bound to glucose, provides a measure of average blood glucose levels over a period of time [2]. By considering the impact of factors such as mealtime, HbA1c readings serve as a reliable indicator of blood glucose levels, unaffected by immediate factors like exercise or food intake.

Photoplethysmography (PPG) has gained prominence in wearable devices, such as smartphones, smartwatches, and fitness trackers, for various health monitoring functions, including heart rate, blood pressure, and blood oxygen saturation levels (SpO2) [3]. PPG technology holds immense potential for detecting and monitoring diabetes among individuals. Leveraging machine learning algorithms, PPG signals can be utilized to estimate blood glucose levels, offering a promising avenue for future applications.

The objective of our investigation project is to explore the application of Photoplethysmography (PPG) and machine learning techniques to classify subjects as either diabetic or non-diabetic. Our proposed design involves placing the device on the finger and wrist, utilizing a light projector and detection unit to observe blood volume fluctuations over time. By analyzing the light absorption values obtained, we aim to estimate blood glucose levels. In order to validate our measurements, we will compare them with data collected using an invasive glucometer and HbA1c checker, employing the AFE4404 EVM and ADI Study Watch.

To ensure accurate analysis, we will employ filtering techniques to minimize noise and motion artifacts that can disrupt the PPG signal. Extracting relevant features related to blood glucose levels and the area under the curve for HbA1c representation, alongside body mass index (BMI), we will train machine learning models. The classification model will be trained and tested using the Clinical Database specifically collected for this investigation project, which provides the necessary information for our investigation project.

- list some pain points and how the clinical trial can assist your project to solve the existing problem

Pain Points	How the Clinical Trial Can Assist

Invasive and painful procedures	Evaluate non-invasive techniques, such as Photoplethysmography (PPG), to provide a pain-free alternative for blood glucose monitoring.
Skin changes and infection risks	Assess the safety and effectiveness of non-invasive methods to minimize skin changes and reduce the risk of infections associated with invasive procedures.
Compliance and convenience	Evaluate the usability and convenience of non-invasive monitoring devices to ensure they are user-friendly and easy to incorporate into daily routines, improving overall compliance.
Cost-effectiveness	Assess the cost-effectiveness of non-invasive devices, considering long-term maintenance costs and potential healthcare savings associated with reduced complications from invasive procedures.
Accuracy and reliability	Evaluate the accuracy and reliability of non-invasive monitoring devices compared to invasive methods, establishing their performance through rigorous clinical evaluation.
Real-time monitoring and data analysis	Explore the capabilities of non-invasive devices in providing real-time data on blood glucose levels and investigate advanced data analysis techniques, such as machine learning algorithms, to enhance accuracy and predictive capabilities.

II. Aims, hypothesis, and potential benefit

- Use point form to list out the objectives of the clinical trial (can have primary aim and secondary aim)

Primary aim:

1. Develop a non-invasive glucose measurement device using Photoplethysmography (PPG) with specific wavelengths.
2. Apply machine learning methods, utilizing the hospital database, to train and improve the accuracy of the non-invasive device in estimating blood glucose levels.

Secondary aim:

3. Assess the usability and user acceptance of the non-invasive glucose measurement device among participants, including factors such as ease of use, comfort, and overall satisfaction.

- Write down the hypothesis

Hypothesis:

The error of the machine learning-based non-invasive glucose measurement device is lower than the standard error rate of 15% currently observed with typical household-used glucose monitoring devices.

- What are the benefits after the validation from the clinical trial?

1. Improved patient experience: The non-invasive device eliminates the need for invasive procedures, resulting in a more comfortable and convenient experience for individuals during blood glucose monitoring.
2. Enhanced Accuracy: By integrating advanced machine learning techniques and training the device on the hospital's subject database, the accuracy of blood glucose estimations can be substantially improved, leading to highly reliable and precise results.
3. Personalized diabetes management: The accurate estimation of blood glucose levels using the validated device can enable individuals to make timely and informed decisions regarding medication, diet, and lifestyle modifications, facilitating personalized and optimized diabetes management.

4. Potential for wider adoption: Successful validation of the non-invasive device with improved accuracy can pave the way for its wider adoption in clinical practice, benefiting a larger population of individuals with diabetes.
5. Research and innovation: The clinical trial will contribute to the advancement of non-invasive glucose measurement technologies and machine learning techniques, fostering further research and innovation in the field of diabetes management.

III. Research Plan

1. Timeline

Proposed start date: 20 Sep 2023
Proposed end date: 20 Sep 2024

2. Recruitment: Selection of Subjects

a) Inclusion criteria

- What age of subjects are involved?
Age of subjects: Subjects included in the study are older than 15 years old.

- What kind of diseases or health conditions of subjects are involved?
The study encompasses a wide range of health conditions within the study population, including but not limited to various diseases, disorders, and general health conditions.

b) Exclusion criteria

- What kind of diseases or health conditions should be excluded of subjects involved?
The exclusion criteria for subjects involved in the study will be based on incomplete data rather than specific health conditions. Subjects with incomplete data will be excluded from the analysis to ensure the integrity and reliability of the study results.

c) Number of planned subjects/ Sample Size

- Can be arranged in different phrases
- Estimate with buffer, i.e. better report a larger sample size initially
The planned sample size for the study is estimated to be 1000 subjects. Each subject will undergo PPG (Photoplethysmography) and BG (Blood Glucose) measurements both before and after breakfast, with each measurement session expected to take approximately 20 minutes per subject. Specifically, 10 minutes will be allocated for measurements before breakfast, and another 10 minutes will be allocated for measurements after breakfast.

d) Study identification (optional)

- Is the subjects from a specific study pool or cohort?
e.g. Subjects are recruited from neurology clinic and a cohort of small vessel disease in Prince of Wales Hospital, Hong Kong, with brain MRI scan to identify the grade of its white matter hyperintensity.
No. The study does not involve a specific study pool or cohort.

3. Study Design & Measurements

- Is it a one-off trial or a follow-up study? Details?
It is a one-off trial where data will be collected for a specific time period from each subject.

- Any Screening?
There is **no specific screening procedure** involved in the study.

- Study measurements:

- “The subjects will be consented according to the inclusion and exclusion criteria.”
- The apparatus and devices involved, with their corresponding measurements, which may include Intermittent Measurement and Continuous Measurement

Intermittent Measurement:

Invasive Blood Glucose Measurements: The Contour Plus ELITE blood glucose meter is used for invasive blood glucose measurements. This involves pricking the subject's finger and collecting blood for analysis.

HbA1c Measurements: The A1CNow+ system is used for measuring HbA1c levels. HbA1c provides an indication of average blood glucose levels over a period of time.

Continuous Measurement:

PPG (Photoplethysmography) Measurements: PPG signals are measured using the prototype PPG device and substitute devices, including the AFE440 EVM and Analog Devices Study Watch. The measurements involve multiple wavelengths, including infrared (950 nm), red (660 nm), green (530 nm), and blue (only available in the Analog Devices Study Watch).

4. Study Procedures/Sampling Procedures/Sampling Analysis Plan

- Methodology

1. **Data Collection:** The first step in the study procedures is to collect raw data from the subjects. This may involve obtaining PPG waveforms, blood glucose measurements, and any additional relevant parameters.
2. **Hypotheses:** The study's hypotheses will include evaluating the accuracy of PPG signal acquisition using a 3-wavelength PPG device design. Additionally, the study aims to assess the correlation between PPG waveforms and glycated hemoglobin (HbA1c) to enable continuous blood glucose measurements.
3. **Selection of Sensitive Sites:** To optimize PPG waveform acquisition, two sensitive sites will be chosen. These specific sites will be carefully determined based on their potential to provide accurate and reliable PPG signals.
4. **Data Analysis:** Machine learning algorithms, specifically Random Forest (RF) and XGBoost, will be employed for data analysis. These algorithms will be utilized to process and analyze the collected data, extract meaningful features, and identify patterns or correlations between PPG waveforms and glycated hemoglobin (HbA1c).

- Preparation

1. Inclusion and exclusion criteria will be established to determine the subjects for the study.
2. Consent will be obtained from the participants, ensuring their understanding of the study's purpose, procedures, risks, and benefits.

- Detailed procedures of the on-site clinical trial

1. **Subject Recruitment:** A targeted recruitment process will be initiated to enroll 1000 subjects for the on-site clinical trial.
2. **Quality Control Measures:** Rigorous quality control measures will be implemented to ensure the selection of high-quality PPG signal segments for analysis. This may involve visual inspection and signal quality assessment to identify and exclude segments with significant artifacts, noise, or technical issues.
3. **Feature Extraction:** Feature extraction will be performed on the selected PPG signal segments. This process will involve examining the first derivatives of the PPG waveforms to capture important features such as pulse amplitude, pulse rise time, and other relevant characteristics. These extracted features will be used for further analysis.
4. **Dataset Composition:** The final dataset will consist of more than 800 segments and their corresponding extracted features. The dataset will include both healthy patients and individuals with

diabetes to capture a range of physiological variations. Additionally, the majority of the data will be acquired before mealtime to minimize the influence of postprandial effects on the PPG signals.
5. **Extracted Features:** The features extracted from the PPG signals will include heart rate (beats per minute), mean amplitude (average magnitude of the PPG waveform), various time intervals within the PPG waveform (e.g., pulse duration, systolic duration, diastolic duration), area under the curve (AUC) representing the overall pulsatile activity, body mass index (BMI), and HbA1c-related AUC, which provides insights into glucose control over a specific time period.

- Follow-up of each subject
As the study is a one-off trial using cross-sectional data, there will be no follow-up of the subjects.

- Any risk and safety monitoring measures
1. Appropriate ethical considerations and guidelines will be followed to ensure participant safety and well-being.
2. Adverse events, if any, will be monitored and documented.
3. Measures will be implemented to minimize potential risks associated with the study procedures.

5. Data Analysis

- What analysis will the data/samples be done after collection?
1. **Raw data analysis:** The collected raw data from the prototypes, including PPG waveforms, will undergo thorough analysis. This analysis will involve examining the important parameters of PPG, such as systolic and diastolic peaks, dicrotic notches, and baseline drift. The stability and reproducibility of the recorded signals will be assessed.
2. **Comparison analysis:** Various comparisons will be made to evaluate the impact of different factors on PPG signal characteristics. This includes comparing before-meal and after-meal data to identify any changes in PPG waveforms. Additionally, the measurements taken from different locations (wrist and finger) will be compared to determine the suitability of each site for PPG signal acquisition.
3. **Blood glucose and HbA1c analysis:** The blood glucose and HbA1c tests conducted before and after eating will be analyzed to understand the relationship between PPG signals and glucose levels. The data obtained from invasive measurements will be used as reference values to assess the accuracy of the results obtained through training and regression modeling.
4. **Machine learning analysis:** Machine learning models, specifically the Random Forest (RF) and XGBoost algorithms, will be utilized for classification and regression tasks. These models will be trained and tested using the extracted features to predict or estimate relevant parameters, such as HbA1c levels. The accuracy and performance of the models will be evaluated, and the impact of additional features, such as BMI and AUC, on the models' accuracy will be assessed.

- Post-collection data analysis in lab for samples
1. **Signal filtering:** The collected signals will undergo filtering processes, such as Chebyshev and moving average filters, to correct baseline drift and reduce noise.
2. **Feature extraction:** Features will be extracted from the filtered signals, and their patterns will be examined. Key features, such as the area under the curve (AUC) values, will be analyzed for stability over time and differences between diabetic and non-diabetic subjects.

- How the data will be used?
1. The data will be used to gain a deeper understanding of PPG signal characteristics, their relationship with blood glucose levels, and the accuracy of machine learning models in predicting relevant parameters.
2. The findings from the data analysis will contribute to the overall objectives of the study, providing insights into the potential applications of PPG in assessing glucose levels and monitoring health conditions.

IV. References

- References for the background, details, methodology, etc., for the whole clinical trial.

[1]LIN T, GAL A, MAYZEL Y, HORMAN K & BAHARTAN K, Non-invasive glucose monitoring: a review of challenges and recent advances, Current Trends in Biomedical Engineering & Biosciences, 6(5), 2017, pp 1-8. https://doi.org/10.19080/ctbeb.2017.06.555696

[2]KWON TH & KIM KD, Machine-Learning-Based Noninvasive In Vivo Estimation of HbA1c Using Photoplethysmography Signals, Sensors, 22(8), 2022, 2963. https://doi.org/10.3390/s22082963

[3]PARK J, SEOK HS, KIM SS & SHIN H, Photoplethysmogram Analysis and Applications: An Integrative Review, Frontiers in Physiology, 12, 2022, 2511. https://doi.org/10.3389/fphys.2021.808451