# Withcare++: a data acquisition and analysis technology platform for diabetes management

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# Abstract

Type-1 diabetes is a chronic disease without a cure at the moment. Patients with type-1 diabetes need to carefully manage their condition to avoid both short-term and long-term complications. Due to the complexity of diabetes management and the lack of efficient tools, many patients are struggling with their management. Furthermore, with the recent advances in data mining and artificial intelligence technologies, deep learning and neural networks have been proven useful to tackle healthcare problems. However, those technologies require large datasets to work with and there lacks an efficient facility for structured diabetes data collection.

The work in the thesis presents a novel design of a holistic tele-healthcare system and data-driven research platform for Type-1 diabetes. The thesis proposes a novel development process for front-end devices utilising the combination of the agile design approach with the minimum viable product approach. (Minor 1)The proposed system has gone through multiple studies: first, a usability test which recruited a group of 11 volunteers; Second, a single centre pilot study which recruited 12 patients and 5 clinicians from Sheffield Teaching Hospital for system usability and acceptability; Third, a multi-centre pilot study which recruited 66 patients and 10 clinicians across three centres in the UK and resulted in significant improvement in medical outcomes. Furthermore, the proposed system is adopted by a large randomised clinical trial in 2019.

This thesis demonstrates the usage of the proposed system for data-driven research. The usage statistics of a commercial bolus advisor is collected and analysed. A bolus advisor checking and reviewing tool is designed for patients' adherence checking and bolus advisor settings optimisation.

I would like to dedicate this thesis to my parents for their love and unconditional support.
This journey wouldn't be possible without them...

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# Table of contents

# List of figures

# List of tables

# List of Abbreviations

**AI** Artificial Intelligence

**AP** Artificial Pancreas

**APP** Acquisition, Processing and Presentation

**ATT** Attribute Protocol

**BA** Bolus Advisor

**BERTIE** Beta Cell Education Resources for Training in Insulin and Eating

**BG** Blood Glucose

**BI** Basal Insulin

**BLE** Bluetooth Low Energy

**BMI SDS** Standardised Body Mass Index

**CDE** Certified Diabetes Educators

**CF** Correction Factor

**CGM** Continuous Glucose Monitoring

**CHO** Carbohydrate

**CPU** Central Processing Unit

**CRC** Cyclic Redundancy Check

**CRUD** Create, Read, Update and Delete

**CSII** Continuous Subcutaneous Insulin Infusion

**DAFNE** Dose Adjustment For Normal Eating

**DIA** Duration of Insulin Action

**DID** Diabetes Interactive Diary

**DKA** Diabetic Ketoacidosis

**EEPROM** Electrically Erasable Programmable Read-Only Memory

**FDA** Food and Drug Administration

**FIFO** First In First Out

**GAP** Generic Access Profile

**GATT** Generic Attribute Profile

**GDM** Gestational Diabetes Mellitus

**GSM** Global System for Mobile Communications

**Hb** Haemoglobin

**HbA1c** Haemoglobin A1c

**HHS** Hyperosmolar Hyperglycaemic State

**HTML** Hyper Text Markup Language

**ICR** Insulin to Carbohydrate Ratio

**ICT** Information and Communication Technology

**IDF** International Diabetes Federation

**IOB** Insulin On Board

**IoT** Internet of Things

**IrDA** Infrared Data Association

**ISF** Insulin Sensitivity Factor

**ISO** International Organization for Standardization

**L2CAP** Logical Link Control and Adaptation Protocol

**LL** Link Layer

**MAC** Media Access Control

**MCU** Micro-Controller Unit

**MD5** Message-Digest 5

**MDI** Multiple Daily Injections

**MDMA** Mobile Diabetes Management Application

**MTU** Maximum Transmission Unit

**MVP** Minimum Viable Product

**MW** Medical Workstation

**NFC** Near Field Communication

**NHS** National Health Service

**NICE** National Institute for health and Care Excellence

**OAD** Over the Air Download

**ORM** Object-Relational Mapping

**PCB** Printed Circuit Boards

**PHY** Physical Layer

**PID** Product ID

**PS** Physiologic State

**PU** Patient Unit

**PWM** Pulse Width Modulation

**QA** Quick Acting

**RCT** Randomised Clinical Trial

**RFCOMM** Radio Frequency Communication

**ROM** Read Only Memory

**RT-CGM** Real Time Continuous Glucose Monitoring

**SPI** Serial Peripheral Interface

**SRAM** Static Random Access Memory

**SMBG** Self Monitoring Blood Glucose

**SMS** Short Message Service

**SSL** Secure Sockets Layer

**SSID** Service Set Identifier

**STH** Sheffield Teaching Hospital

**T1D** Type 1 Diabetes

**TB** Time Block

**TLS** Transport Layer Security

**UART** Universal Asynchronous Receiver/Transmitter

**USB** Universal Serial Bus

**UUID** Universally Unique Identifier

**VID** Vendor ID

**WHO** World Health Organization

**WPS** WiFi Protected Setup

**WSD** Whole System Demonstrator

**XID** Exchange Station Information

# Chapter 1

# Introduction

Diabetes mellitus is a chronic disease with a series of clinical symptoms caused by an absolute or relative insulin shortage [1]. It is one of the four major non-communicable diseases in the WHO's (World Health Organization) non-communicable diseases report together with cancers, cardiovascular disease, and chronic respiratory disease [2]. The main symptom for diabetes mellitus is hyperglycaemia. Prolonged hyperglycaemia will damage various organs, especially eyes, kidneys, heart, blood vessels and nerves and leads to chronic complications such as cardiovascular disease, diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, and diabetes-related foot problems [3]. The causes of the hyperglycaemia are either the patients cannot produce enough insulin by themselves, or they become insulin resistant and their cells fail to respond to insulin properly. The former is known as type 1 diabetes and the latter is known as type 2 diabetes [4]. The third main form of diabetes is gestational diabetes, which occurs in pregnant women. Type 1 diabetes affects 10% of the diabetic population [5]. Patients with type 1 diabetes commonly suffer from diabetic ketoacidosis, a life threatening complication which is not common in type 2 diabetes patients. This form of diabetes is more likely to affect people at a young age, but can also affect adults. The cause of type 1 diabetes mellitus remains unknown and there is no cure for type 1 diabetes mellitus. Patients with type 1 diabetes mellitus need to carefully manage their condition to avoid chronic complications.

## 1.1 Current management of type 1 diabetes

The goal of type 1 diabetes management is to maintain a good glycaemic control. To keep the glucose level in "target", patients are normally advised to take at least four blood glucose measurements a day including before breakfast, lunch, dinner and bed. In addition, patients need to take more blood glucose measurements – up to 10 times a day – if they are having hypoglycaemia, illness, exercise, a poor glycaemic control or about to drive [6]. After taking the blood glucose test, patients inject insulin to manage their blood glucose level, this is known as insulin therapy. If the test is taken before a meal, patients need to inject fast acting insulin in proportion to their carbohydrates intake. If their blood glucose is above the target , they are often required to correct their blood glucose by injection of more insulin. If their blood glucose is below the target, they are required to reduce the amount of insulin injected. In the meantime, they also need to take their insulin on board (active insulin in the blood) into consideration if they have injected insulin within 5 hours.

There are two main types of glucose monitoring: continuous glucose monitoring (CGM) and self-monitoring of blood glucose (SMBG). When using SMBG technology, patients need to prick their finger with a lancing device and apply a small blood sample to a test strip, while CGM only requires the patients to attach a small patch to their body (i.e arm) for interstitial glucose measurement. Both methods have their pros and cons, every SMBG taken requires finger pricks which can be painful and annoying to some patients, while CGM has problems is less accurate, costly and requires calibration [7]. The National Institute for Health and Care Excellence (NICE) only recommends using CGM if the patient meets certain criteria [6]. Patients with CGM are also required to take SMGB when they are going to correct their glucose or consume food, (minor C1.1)only few new models do not require SMGB test before consuming food such as Dexcom G6. Those blood glucose measurements and insulin injections become patients' daily routine after being diagnosed with type 1 diabetes. In addition to the daily diabetes management, patients are asked to visit their healthcare centre every 3-6 months. During the visit, a laboratory test is done to measure the glycated haemoglobin (also known as HbA1c) in the blood. Haemoglobin is a type of proteins inside a red blood cell. When joined with glucose, haemoglobin becomes glycated. Because the normal lifespan of haemoglobin is three months, the measurement of glycated haemoglobin is a good reflection of the average blood glucose level of a patient in the last three months [8]. As diabetes patients have more glucose in their blood, the numbers of glycated haemoglobin in the red blood cell will be higher than non-diabetic people. The HbA1c target for diabetes patients to aim for is $48mmol/mol$ (6.5%) [9], but individual targets are set by the healthcare professionals for individual patients. The HbA1c is also a good indicator of how well the patients are managing their diabetes and whether they are going to have complications in future. Patients with a high HbA1c are more likely to develop diabetes-related complications such as cardiovascular disease, diabetic nephropathy, and diabetic retinopathy.

## 1.2 Challenges in current type 1 diabetes healthcare

The current system is facing a number of challenges. Without tele-healthcare, the patients need to have face to face appointment with their care giver. According to the NICE guideline[6], it is recommended that the patient have their HbA1c measurement every 3-6 months. It also recommend that patients with type 1 diabetes to set up an individual care plan and review it annually. However, this kind of appointment can be time-consuming and may not be suitable to everyone. According to [10], 8% of the diabetes patients did not attend the general follow-up hospital outpatient appointments. Another challenge is the healthcare professionals have no access to patients' glucose records before they visit the healthcare centre. Without the patient's blood glucose readings, it will be difficult for healthcare professionals to know the patient's condition, let alone provide assistance. In addition, during the visit, the healthcare professionals need to analyse patients' glucose records on site. It could be time-saving, if they can analysis the records in advances. If the patients forget to bring their meter or dairy with them during the outpatient appointment,it would be difficult for the healthcare professional to make valuable healthcare decisions. The current system is clearly lacking an efficient two-way communication between the patients and healthcare professionals.

## 1.3 Tele-healthcare for effective management of T1D

To overcome those challenges, researchers have proposed various kinds of the tele-healthcare systems which allow patients to share their data with the healthcare professionals. Most systems are based on popular communication technologies such as SMS and internet to establish a two-way communication channel between the patients and healthcare professionals. Those systems usually consist of two parts, a front-end device and back-end server. The patients are usually given a front-end device or use their smartphone to collect data from their glucose meter then send the data to the back-end server. With the data provided by the front-end device, patients can share their blood glucose, carbohydrates intake and insulin injection records with their healthcare professionals on a weekly even daily basis. There are generally two types of back-end design, one is called a healthcare professional centred system, where only healthcare professionals have access to the data, they are responsible to analyse those data and give advice to the users. Another type of system is patient-centred system where patients also have access to their data, a good back-end system will provide educational tools to help patients understand their diabetes and empower patients in their daily diabetes management. However, few proposed systems have moved into a randomized clinical trial stage, as they have overlooked certain important aspects such as usability. For example, there is not a shared standard among meter manufacturers. The communication protocol used by the meters varies. The latest meters may use the Bluetooth 4.0 while some old meters are still using serial port and infrared. Those different technologies may be easy for an engineer to understand, but in reality, patients have different education and IT skills. The designs working within a laboratory environment do not necessarily work with the real population. With the recent advances in communications technologies (commercial electronics) patients now have higher expectations from a diabetes management system. The front-end part of the tele-healthcare system is no longer a simple data acquisition device but also a diabetes management tool. This tool should provide functionality to help patients to improve their daily glycaemic control such as carbohydrates counting and bolus advisor. The challenge for designing the front-end is how to design a device that can communicate with the most of the popular meters while remaining low cost and user-friendly. In addition, tools like carbohydrates counting and bolus advisor should be included, to help patients achieve a better glycaemic control[11].

## 1.4 Research questions

1. How to design and develop a tele-healthcare system which will be adopted by clinical trial
2. How to improve the usability of the system that can cover different types of population (i.e. technologically literate and illiterate) and encourage them to manage their diabetes.
3. How to design a scalable and maintainable system that can be used in large clinical trials and real life situation.
4. What is the state-of-the-art bolus advisor and its usage among patients? How to improve the current bolus advisor to help patients to improve their glycemic control.

## 1.5 Thesis aims and scope

The aim of this thesis is to develop and implement the WithCare++ tele-healthcare system, a user-friendly, flexible and expandable platform for type-1 diabetes management. The

WithCare++ system also will work as a platform for researchers for collecting and analysing anonymous diabetes data and developing new algorithms to achieve better understanding of diabetes. From the patients' perspective, the system is aimed at supporting and improving their diabetes management while meeting their various requirements by providing a stand-alone solution (WithCare++ Box) and smartphone based solution (WithCare++ App). This thesis describes the implementation of this system and the feedback from both patients and healthcare professionals.

From the researchers' point of view, this system is designed for efficiency of data collection and analysis. By implementing a modular and future-proof design, this system can be expanded by adding seamlessly new sensors to the system to collect new type of data after the system is distributed to the patients. With the recent advances of machine learning technology, an efficient way of collecting data is more important than ever. Currently, there is a lack of platforms for healthcare professionals and data scientists to obtain and analyse diabetes related datasets. This thesis describes how the WithCare++ system is developed and fitted into that purpose.

Furthermore, the thesis reviewed different implementations of the-state-of-the art bolus advisors and demonstrates how the collected data is used to examine the usage of the bolus advisor among patients. A set of tools were developed to help with reviewing patients' adherence and optimising bolus advisor's settings

## 1.6 Key contributions

The motivation of this research is to design a tele-healthcare management system for type-1 diabetes to improve patients' diabetes management. The main contributions of the thesis is to design, develop and test the WithCare++ tele-healthcare system. A novel design process is proposed of the WithCare++ tele-healthcare system combining both the agile design approach and the minimum viable product approach.

Two front-end devices: WithCare++ Box and WithCare++ Widget, were developed all the way to prototypes using the proposed design process. The WithCare++ Box device was tested by 78 patients in two pilot studies for two years and achieved a score of 83.75 in the system usability scale (SUS) questionnaire [12]. The WithCare++ Widget device was designed based on a small and low cost Bluetooth Low Energy (BLE) micro-controller which only costs a fraction of the Box device while keeping the same functionalities. Both front-end devices support downloading multiple type of glucose meters with different interfaces.

An Android App was developed to cooperate with the WithCare++ Widget and help the patients with their daily management.

The proposed tele-healthcare management system is adopted by a large randomised clinical trial in 2019 which will recruit 600 patients in 14 centres across the UK.

An important contribution of the thesis is demonstrating the potential of the proposed system as a data-driven research platform. Indeed, the system is employed to collect usage data of a commercial bolus advisor which is then analysed, using developed tools, to help with reviewing patients' adherence and optimising bolus advisor's settings.

## 1.7 Thesis structure

Chapter 2 presents an introduction to diabetes and the benefits of a tele-healthcare system for type-1 diabetes management. The chapter further discusses the barriers of adopting such a system, and the requirements of developing a better tele-healthcare system.

Chapter 3 reviews the state-of-the-art tele-healthcare systems for type-1 diabetes from both research and commercial sectors. Then it describes the design process of the WithCare++ system and the implementation of the WithCare++ box. Furthermore, Chapter 3 analyses the usage of the system and the feedback from both users and healthcare professionals. It also describes the difficulties of adopting this system in a real life large scale clinical trial and how the system is designed to tackle those problems.

Chapter 4 reviews the smartphone based tele-healthcare systems. It describes an alternative solution to the WithCare++ Box mentioned in Chapter 3. (Minor 4.1)It presents the WithCare++ mobile solution which is a system that keeps the same functionalities as the WithCare++ Box and utilize patient's own smartphone while being less costly and portable. This chapter describes the software and hardware implementation of the WithCare++ widget. Furthermore, it discusses the different interface used by the currently popular glucose meters and how to design a widget that works with different meters and various interfaces.

Chapter 5 reviews the state-of-the-art implementation of bolus advisors, and demonstrates how the WithCare++ system is used as a research platform to analyse the usage of the bolus advisor among patients. (Minor 3.3)It also presents a tool for clinicians to evaluate patient adherence of multiple Daily injection treatment.

Chapter 6 concludes the thesis with recommendations for future works.

## 1.8 Publications

As a result of the presented research in the thesis, the following publications are to be submitted.

- Front-end system for tele-healthcare platform in chronic disease management : a case study for type 1 diabetes, IEEE biomedical and health informatics
- A low-cost responsive mHealth system for efficient multi-interface support of type-1 diabetes technologies, IEEE biomedical and health informatics
- The usability and efficacy analysis of bolus advisors for effective adjustment and optimisation of diabetes care, Diabetes Technology & Therapeutics

# Chapter 2

# Background

This chapter reviews the literature that focuses on diabetes mellitus, its economic costs, and its management, and analyses the state-of-the-art technology in tele-healthcare systems for diabetes healthcare.

## 2.1 Overview of diabetes mellitus

Diabetes mellitus is a common chronic disease where prolonged periods of high blood sugar is experienced due to an absolute or relative insulin shortage. Insulin is a hormone produced by beta cells of the pancreas that regulates the process of carbohydrate and fat metabolism. It controls the glucose balance by converting the blood glucose into either glycogen or fat. The reasons for lacking insulin can classify diabetes into different types.

There are three major types of diabetes:

- Insulin-dependent diabetes mellitus: commonly referred to as type 1 diabetes
- Non-insulin dependent diabetes mellitus: also known as type-2 diabetes

- Gestational Diabetes Mellitus

The most obvious characteristic of diabetes is an abnormally high blood glucose (blood sugar) level referred to as hyperglycemia. Hyperglycemia leads to increased hunger and thirst, frequent urination and weight loss. If untreated, patients with hyperglycemia will develop both short-term and long-term complications. Diabetic ketoacidosis (DKA) and hyperosmolar hyperglycaemic state (HHS) are two of its short-term complications. Both short-term complications are life threatening and can cause loss of consciousness or death in the worst scenario if left untreated[13]. With regard to long-term complications, diabetes can cause retinopathy, cardiovascular disease, nephropathy, and neuropathy. These long-term complications can reduce patients' life expectancy and lead to disability.

### 2.1.1 Type 1 diabetes mellitus

Insulin-dependent diabetes mellitus usually referred to as type 1 diabetes. Pancreas' lack of insulin production results in diabetes patients experiencing higher blood glucose levels than the non-diabetic people. In type 1 diabetes, the immune system attacks the underlying mechanism, namely the beta cells. However, the reason that triggers the attacks is still unclear; this can be related to genes and environmental factors [4]. Symptoms of type 1 diabetes often develop within weeks of the onset date. There is no cure or prevention for type 1 diabetes at the moment. Patients need insulin therapy to maintain a normal glucose level, otherwise will suffer both short-term and long-term complications. According to the International Diabetes Federation (IDF) data released in 2017 the world has around 42.5 million type 1 diabetic patients [14]. Only up to 10% of cases of diabetes are type 1 diabetes, however, it is important to mention that 95.1% of the children who have diabetes are type 1 diabetes[5].

### 2.1.2 Type 2 diabetes mellitus

Type 2 diabetes mellitus is caused by insulin resistance and relative lack of insulin. Unlike type 1 diabetes mellitus, type-2 diabetes mellitus is not caused by the attacking of the immune system to the beta cells of the pancreas. Type-2 diabetes is related to the patients' lifestyle. It is usually a result of poor diet, obesity and lack of exercise [15, 16]. Type-2 diabetes mellitus can be hereditary, however, it is less likely for a person to develop type-2 diabetes if they keep a healthy lifestyle such as healthy diet and regular exercise. Type-2 diabetes develops slowly and gradually, in contrast to type 1 diabetes, patients can have type-2 diabetes for several years before noticing it. Type-2 diabetes mellitus is the most common type of diabetes, making up about 90% of all diabetes. Type-2 diabetes is more common in adults, only 1.9% diabetic children are type-2 diabetes[5].

### 2.1.3 Gestational diabetes mellitus

Gestational diabetes is another type of diabetes, in which a non-diabetic woman develop hyperglycaemia during pregnancy. Gestational diabetes only affects 3–9% of pregnant women and especially common during the last stage of pregnancy [17]. Gestational diabetes can affect both the mother and child if poorly treated. (minor 2.2)The mother with poor gestational diabetes management can have a higher risk of getting preeclampsia and depression[18, 19, 20]. Children born to that mothers are more likely to be too large, have low blood sugar after birth, and jaundice. Both mother and children have an increased risk of developing type 2 diabetes [21]. Gestational diabetes can be treated and prevented. A healthy weight and exercising before pregnancy is a good prevention of developing gestational diabetes[22]. Treatment is usually done by a diabetic diet, exercise, and occasionally insulin injection. Blood glucose level needs to be carefully monitored during pregnancy if the mother is having gestational diabetes.

### 2.1.4 Diabetes mellitus prevalence

According to International Diabetes Federation's report, in the year 2017, the estimated diabetes prevalence for adults between the ages of 20 and 70 was 424 million worldwide. This report estimated that the number of diabetic patients worldwide will reach 628 million in 2045 [14]. In the UK, there are almost 3.3 million diagnosed diabetes patients and 0.59 million estimated undiagnosed diabetes patients in the year 2014 [5]. Among all the diabetes patients in the UK, there are 31,500 children and young people with diabetes. 95.1% of those children and young people have Type 1 diabetes and about 1.9% have Type 2 diabetes. They are mostly diagnosed between the age of 9 to 14 years old. Comparing to the year 1996 in which only 1.6 million people have been diagnosed with diabetes, the number of diabetes patients are almost doubled in 20 years. By 2025, the estimated diabetes prevalence in the UK is about 5 million [5].

### 2.1.5 The economic impact of diabetes mellitus in the UK

Diabetes costs the NHS £14 billion each year which equals 10% of the NHS budget for England and Wales [23]. However, the direct cost of treatment for diabetes is relatively cheap compared to the cost of the treatment for diabetes complications. According to a 2012 report from the London School of Economics, the cost for the treatment of diabetes complications is 3-4 times of prescribing diabetes medication [24]. The cost of diabetes drugs is £1.056 billion, in which £0.344 billion is for type 1 diabetes and £0.712 billion is for type 2 diabetes. Given that the proportion of patients with type 1 diabetes and type 2 diabetes is 1:9, the cost of diabetes drug for type 1 diabetes per patient is higher than type 2 diabetes per patient. That is because most type 1 diabetes patients rely on insulin therapy, and the cost of analogue insulin is higher than the metformin which is a medicine for type 2 diabetes patients. However, the major cost of diabetes care is not the cost of drugs, the cost of drugs only occupy 7.8% of the total diabetes care cost. The largest cost of diabetes treatment is inpatient cost which makes up 65.8% of the total cost, followed by non-diabetes drugs, outpatient (excluding drugs), and other (including social service), making up 15.2%, 9.7%, and 1.7% respectively [24]. There are several long-term and short-term complications arising from poor diabetes control. The treatment of those long-term and short-term complications makes up the most part of the inpatient cost. In additional, those complications will also introduce indirect cost. For example, early retirement is one of the indirect cost. Some long-term diabetes complications will result in disability. Diabetic retinopathy is one of the most common complications of diabetes that could cause disability, it will cause blindness if untreated. Diabetic neuropathy is another complication arising by diabetes that could cause disability. A patient with diabetic neuropathy has a reduced ability to feel pain, thus makes minor wound harder to discover. In the worst case scenario, those wounds will be infected and a lower limb amputation may be necessary. Other indirect cost includes absenteeism and social benefits which are £8.4 billion per year and £0.152 billion respectively [25].

### 2.1.6 Type 1 diabetes mellitus daily management

Type 1 diabetes mellitus is a chronic disease which cannot be cured. Patients need to manage the disease carefully every day to avoid both short-term and long-term complications. The goal of daily diabetes mellitus management is maintaining the blood sugar levels in a normal range for the most of the day and prevent any prolonged hypoglycaemia (low levels of blood sugar) or hyperglycaemia (high levels of blood sugar) while possible.

#### Blood glucose measurement

Patients perform blood glucose test by using a glucose meter. A glucose meter is a portable electronic device that can measure blood glucose level using a test strip. The accuracy of blood glucose meters in the UK should meet the guideline 95% of the time set by the International Organization for Standardization (ISO) [6]:

- Within ± 0.83$mmol/L$ of laboratory results at concentrations of under 5.6 $mmol/L$
- Within ± 15% of laboratory results at concentrations of 5.6 $mmol/L$ or more

Daily diabetes management requires close monitoring of blood glucose levels. (minor 2.2)Patients are advised to have a blood glucose test at least 4 times a day and up to 10 times a day [6].

### Insulin therapy

With the taken blood glucose measurement, patients need to perform a blood glucose correction if necessary. If the glucose level is above the patient's personal target (hyperglycaemia), the patient needs to inject the correct amount of fast acting insulin to lower their blood glucose level to the normal range. This injected insulin is often referred to as correction insulin [26]. If the glucose level is below the patient's personal target (hypoglycaemia), the patient needs to treat the hypo with $15-20g$ of fast-acting sugar, such as glucose tablets, fizzy drink or fruit juice. In addition to correction insulin, the patient needs to inject carbs related insulin when they are going to have meals. Both correction insulin and carbohydrate (CHO) insulin are called bolus insulin. Another type of insulin are basal insulin, basal insulin also referred to as background insulin is used to keep blood glucose levels stable during periods of fasting. Mixed bolus insulin and basal insulin regimen helps patient achieve better diabetes management [27].

### Carbohydrate counting

Carbohydrate counting (or carb counting) is another important skill that used in type 1 diabetes patients daily management. Carb counting is a way of better understanding how carbohydrates affect patients' daily diabetes management. For type 1 diabetes patients, carbohydrate counting is a way to calculate insulin requirements for the amount of carbohydrate intake.

For diabetes patients, learning carb counting requires patience and diligence. Several techniques and tools can be used for carbohydrate counting.

- Food labels, scales and calculators

  Food labels can help patients understand the nutritional values of the food. Most pre-packed foods have nutritional labels. These include information on energy, fat, carbohydrate, sugars, protein and salt. These are displayed either per 100 grams or per serving. When provided in per 100 grams format, a scale and a calculator can be used to help with the calculation. Some smart kitchen scales have that nutrition information embedded, patients can keep track of their carbohydrate intake with ease when using this kind of scales.

- Recipe books and online resource

  Recipe books are another source of carbohydrate information. Many recipe books include detailed carbohydrate information. This is particularly useful compared to calculating the total carbohydrate based on the raw materials. Because some foods have a different amount of carbohydrate depending on the way of the food is cooked, it is better to follow the recipe books than using the food labels on the raw material. Carbs and Cals is an App provides visualised food reference with the associated nutrition information [28].

- Diabetes education courses

Many structured diabetes education courses include carbohydrate counting as part of their course. In the UK, nationwide diabetes education course such as DAFNE, X-PERT and BERTIE have carbohydrate counting course for their target population. DAFNE which stands for Dose Adjustment for Normal Eating is designed for type 1 diabetes patients. BERTIE (Beta Cell Education Resources for Training in Insulin and Eating) is another education courses targets at type 1 diabetes patients [29, 30]. X-PERT is a diabetes education course that is designed for not only type 1 diabetes patients but also patients with other forms of diabetes [31]. In addition to that course, healthcare professionals in the UK can provide dedicated one-to-one guidance on carbohydrate counting if a patient is struggling with this aspect of their daily diabetes management.

## 2.2 Tele-healthcare

Tele-healthcare which is also called telemedicine and e-health is the use of information technologies to support remote healthcare related services [32]. Tele-healthcare has different forms when used in different disease. For example, remote diagnose and video conference between clinicians [33], a robotic surgery performed by remote professionals [34], home monitoring by sending patient health data from home based sensors [35], remote consultant with healthcare provider. Although the rapid development of information technology has only occurred in recent decades, the earliest tele-healthcare instance was reported in the Lancet in 1879 [36]. In mid of 1900s, tele-healthcare was used in space and military sectors, tele-healthcare system was used by NASA to monitor their astronauts in space [37]. After the year of 2000, with the development of information and communication technologies (ICT), several randomised controlled trials were carried out to explore the potential of tele-healthcare [38]. In the year of 2008, Department of Health in the UK carried out a randomised controlled trial of telehealth and telecare which is called Whole System Demonstrator(WSD). It is believed to be the largest randomised control trial of tele-healthcare in the world at that date [39]. Although the study showed a reduction in mortality and hospital admissions [40], it neither showed significant improvement in quality of life nor improvement in cost-effectiveness [41, 42] With population growth and population ageing, the demands of tele-healthcare is rapidly increasing nowadays. The main purpose of tele-healthcare is to provide an efficient communication between patients and their healthcare provider in order to meet the desired clinical targets and reduce the cost of healthcare.

### 2.2.1 Tele-healthcare for diabetes management

In the management of chronic diseases, tele-healthcare enables the remote patient monitoring and minimises the need for outpatient visits. In the area of diabetes mellitus management, tele-healthcare is often used as a tool for home monitoring and remote consultation. The former allows patients to record their glucose reading, carbohydrate intake, insulin injection, health state, physical activities into a digitalised log instead of using hand written diaries. The latter allows patients being consulted by healthcare professionals without visiting the clinic in person.

### 2.2.2 Benefits of tele-healthcare

A well-designed tele-healthcare system can be beneficial in both economic and clinic aspects. In the clinic aspect, the benefits include reduced cost, elective admissions and bed days, A&E visits, emergency admissions, and mortality rates. For example, the early findings of the Whole System Demonstrator (WSD) programme showed it achieved a 14% reduction in both elective admissions and bed days. It also reduced A&E visits by 15% and emergency admissions by 20%, Last but not least, it indicated a 45% reduction in mortality rates [40]. For diabetes related tele-healthcare projects, additional outcomes can be measured by number of hypoglycaemic events, number of hyperglycaemic events, quality of life and HbA1c.

In terms of economic benefit, the Whole System Demonstrator (WSD) programme also claims that it achieved an 8% reduction in tariff costs in its early findings report. However , the detailed cost of the Whole System Demonstrator still needs to be fully analysed. The overall costs of intervention for patients in hospital care (including emergency admissions, elective admissions and outpatient attendances) over 12 months, were £188 per patient less than the control group. And that cost does not include the hardware cost of those tele-healthcare kit given to the intervention group at the beginning of the trial [43]. The initial cost of a tele-healthcare could be high because of the initial deployment cost. However, the overall cost-benefit analysis should be based on long-term rather than short-term.

### 2.2.3 Barriers of tele-healthcare adoption

Although evidences from research show that tele-healthcare can be beneficial to both health-care provider and patient, but barriers exist for both of them to fully adopt tele-healthcare.

From a patient's point of view, their main concerns when using telemedicine systems are the technical skills required to operate the device, the loss of identity threats, loss of independence, and service interruptions [44]. Lehoux[45] also mentioned that some patients worried about the tele-healthcare system requiring them to change their personal life trajectory. Otherwise, the tele-healthcare system would become a burden to a patient. Gitlin et al.[46] highlight that the tele-healthcare system should be perceived to support rather than undermine their sense of identity.

(minor 2.4c)From healthcare provider point of view, cost is one of the important factors when evaluating a tele-healthcare system. Henderson et.al suggests some system could not be cost effective comparing to standard support and treatment[42]. Economic impact of tele-healthcare is not convincing enough for policy-makers to invest in telemedicine. Another barrier that stops healthcare providers from adopting tele-healthcare is conventional healthcare has not been optimised to work with tele-healthcare. There is a steep learning curve for both healthcare provider and patients to fully understand how to use tele-healthcare and embrace its benefits.

### 2.2.4 Requirements of tele-healthcare

Tele-healthcare projects need to meet the needs of healthcare providers and patients to overcome the barriers and improve healthcare outcomes.

Healthcare provider would require the tele-healthcare projects to be efficient, secure, cost-effective and robust. An efficient tele-healthcare system should provide more information and be easily integrated into existing healthcare system without bringing extra workloads to the healthcare providers. A robust tele-healthcare system needs to be able to provide secure and sustainable service with self-diagnosed system to ensure reliability. Low cost or cost-effectiveness is another requirement of developing a tele-healthcare, otherwise it would be unlikely to be used in clinic practice [37]. Security is another concern that patients have when introduced to a tele-healthcare project.

From the perspective of the patient, a tele-healthcare should be user-friendly, secure and robust. Some patients would reject adopting tele-healthcare project, because they feel that engaging with the technological equipment would be difficult for them [44]. Thus, user-friendly design is one of the most important requirements for tele-healthcare project. Especially, the elderly population would be the main population that will benefit from adopting tele-healthcare project because of the ageing problem. A tele-healthcare system also needs to be robust, technical failures can lead to data transmission failures and reduce user confidence in tele-healthcare.

## 2.3 Conclusion

In this chapter, the background of diabetes is presented. Diabetes is a chronic disease which cannot be cured at this moment. The prevalence of diabetes is rapidly increasing globally. The rapid growth of diabetes not only increases the economic burden but also increases the workload of healthcare professionals. In the UK, not all diabetes patients are receiving enough support. The goals of the NHS is hardly met due to all the challenges in diabetes management. Those challenges include long waiting time for each visit. Patients have to wait at least three months before each visit, which may increase the likelihood of developing a complication if they were having a poor diabetes management. These complications will reduce the patient's quality of life and life expectancy and cause massive costs for NHS.

Through the analysis of the current status of diabetes management in the UK, the need for a tele-healthcare system is introduced. It is clear that some of those challenges can be solved with tele-healthcare, but there are also some barriers that stop adopting the tele-healthcare system. In this chapter, the barriers that stop adopting tele-healthcare are discussed as well. With the analysis of those barriers, the possible solutions to the barriers and the requirements of developing a state of art tele-healthcare system were discussed. Hence, a tele-healthcare system which has been designed for diabetes management and adopted by DAFNEplus program is proposed in this thesis[47]. (Minor 3.8)The DAFNEplus program is aiming at re-develop and evaluate the current DAFNE course which is an educational course for managing type 1 diabetes and offered by 76 different diabetes centres throughout the UK and ROI[48].

Next Chapter will focus on describing the architecture, design, implementation, verification of the proposed system. A pilot trial of the proposed system was carried out, and its outcome would be discussed in the next chapter as well.

# Chapter 3

# WithCare++ Tele-healthcare System

## 3.1 Introduction

This chapter reviews the literature regarding tele-healthcare, explains the architecture and design of WithCare++ front-end devices and evaluates its deployment and user feedback. The project WithCare++ was initially designed by two PhD students Anastasios Kanakis and Bilal Ahmad Malik. The original project carried out a pilot trial with six patients on 2013 and ceased to work within two weeks due to faulty device and schedule related issues. Since the original design was outdated and did not meet the new requirements of healthcare professionals and patients, the author of this thesis continued the project and redesigned the entire system. This thesis is focused on the front-end design. The motivation for redesigning WithCare++ was to provide an up to date solution for tele-healthcare with state of art information technologies. (Minor 1)The system has been designed in collaboration with the Sheffield Teaching Hospital (STH), and has been tested under an usability test with 11 volunteers and an initial pilot trial with 17 volunteers(12 patients and 5 clinicians) recruited by the University of Sheffield. After the usability test and the initial pilot trial, this system was tested in three locations in the UK including Sheffield Teaching Hospital, King's College Hospital, and Norfolk and Norwich University Hospital. Finally, this work are adopted by DAFNEplus project and will be used in a randomised controlled trial in 2019. In order to develop a state of art system, the author of the thesis applied the agile design approach and worked closely with both healthcare providers and patients and improved the system through several iterations.

## 3.2 Literature Review

In this section, a range of tele-healthcare system in both academic and commercial sectors were reviewed. Both academic researchers and healthcare related industries has spent great effort to explore the potential of tele-healthcare. A significant amount of literature regarding tele-healthcare system has been published covering different aspects such as design, cost, barriers to adoption, benefits, and usability.

### 3.2.1 Literature review of commercial tele-healthcare systems

Diasend®tele-healthcare system is currently being used in Sheffield Northern Hospital by the healthcare professional. Diasend®[49] is a commercial product provided by Glooko©. The company provides two versions of Diasend®, Diasend®Clinic which is a cloud based solution for uploading and managing patient diabetes data in clinic, and Diasend®Personal which is a cloud based solution for patients. Diasend®Clinic provides a small box to clinics for data uploading. The small box contains a GSM (Global System for Mobile Communications) unit which talks to the back-end server owned by Glooko©. Three LEDs on the front panel of the Diasend box indicate the working status of the Diasend®box. The healthcare professionals use different cables provided by Diasend®to download glucose data from patients' meter. Diasend®Personal is a software made by Glooko©for Windows and Mac. This software allows patient to upload their diabetes data from a computer. Patients have to purchase extra hardware from meter manufactures to support their meter. Diasend®is free for patients and NHS pays a subscription price to use their service.

Tidepool is an open source, a not-for-profit company providing support for diabetes patients, clinicians, and researchers to easily access diabetes data. For patients, Tidepool provides an application written in Electron to upload their readings. The application supports about 15 different kind of meters including normal blood glucose meters and CGM (Continues Glucose monitoring) meters.Unlike Diasend®, this system requires no extra hardware to download the diabetes data from the meter, as a result only USB meters are supported. The company also provides iOS and Android applications which allows users to view their diabetes data. However, uploading diabetes data with the smartphone application is not supported. Tidepool also provides services for clinicians and researchers. For clinicians, Tidepool allows them to view their patients' diabetes data via a remote web portal. In addition ,Tidepool shares anonymised diabetes data with their data partners.

MySugr is another commercial tele-healthcare system for diabetes. Unlike the other two, mySugr only has a smartphone application for diabetic patients. The healthcare professionals cannot access diabetes data of their patients in this system. However, mySugr provides a coach service as their tele-healthcare system solution. By subscribing to their premium service, patient will receive advise from their highly trained CDEs (Certified Diabetes Educators). However, this business model does not fit into UK's NHS system. MySugr only supports a few Bluetooth glucose meter. Patient who uses non-Bluetooth meters has to enter their diabetes data manually.

### 3.2.2 Literature review of academic tele-healthcare studies

Chase et al. [50] evaluated the effect of transmitting blood glucose data in their study. A total of 70 adolescents who have been diagnosed with type-1 diabetes mellitus were recruited for the study. 33 of them were randomised into the Acculink group and the rest of them were in the control group. The Acculink group were provided with an Acculink modem which is a modem made by Roche to transmit readings from their Accu-Chek Complete meter. The control group were under regular diabetes cares with clinic visit every 3 months while the Acculink group omitted the clinic visit. There was no website for the participants in the Acculink group to view their data, a group of healthcare professionals reviewed participants' data and discussed the treatment over the telephone. At the end of that study, there was no statistically significant difference between the Acculink group and the control group in terms of HbA1c. However, Chase et al claim that there was a significant difference ($P \leq 0.001$) between the two groups in terms of cost. The average cost of the control group was $305 per person, while in the Acculink group the cost per person was $163. The cost for the control group includes $246 for a 3-month clinic visit and $59 for additional costs (parking, meals, mileage, hotels, etc.). The costs for the Acculink group includes $17 for Modem cost, $35 for Modem (and meter) training, $50 for internet provider, $48 for patient time (estimated at $15.00/h), $3 for phone expenses, 3 and $10 for designated computer.

This study shows that tele-healthcare can help healthcare provider to maintain the current level of healthcare outcome while reducing cost. The drawback of this study is patient in Acculink group has been isolated from their diabetes management. They cannot access their own data in the system, and their diabetes management relies on the reviews from their tele-healthcare provider. It would be beneficial if they can access their data in a graphic form. Another disadvantage is the meter and modem by Roche has been obsolete, and Roche stopped designing modem for tele-healthcare purpose as it does not fit their business model. Glucose meter manufacturers rely mainly on sales of meters and test strips for profit [51]. If a diabetes tele-healthcare system were designed to work with a single company or single meter only, it would be problematic when migrating the system to another company. This also exposes a problem that tele-healthcare for diabetes lack a standard protocol for transmitting diabetes data.

Roudsani et al.[52] have developed a web-based diabetes management system called DiabNet. The system consists of two parts: a Patient Unit (PU) and a Medical Workstation (MW). Each patient will have a PU which consists of a glucose meter, a handheld computer and a mobile phone or a wireless modem. The handheld computer was used to download readings from the glucose meter via an infrared interface then uploaded data to the medical workstation using a mobile phone or a wireless modem. The medical workstation is a web server hosted in the hospital, healthcare professionals can view patients' diabetes data via a web browser. A video conference system was also implemented in the system which allows tele-consultation between the doctor and the patient. They did not carry out any trial for their system instead a questionnaire was sent to different diabetes discussion groups and mailing lists to collect feedback of the described system. Since there was no trials or user testing for this system, the usability of the system remains unknown. They also mentioned that this system requires patients who are familiar with internet usage and has a certain level of computer literacy. The lack of trials and user testing suggests this system could be impractical in a real-world set-up. McMahon et al.[53] have demonstrated a web-based management system for patients with poorly managed diabetes . They recruited 102 patients with an HbA1c $\geq 8.8\%$ and randomly put into two groups, web-based care management group and education and usual care group. The patients in the web-based care management group were equipped with a notebook computer, a glucose meter and a blood pressure monitor. A software was pre-installed on the computer to read diabetes data from their meter and upload to a data centre hosted at Georgetown University. The data centre also provided a website that allowed patients to view their data in a graphic and tabular forms. Additional education resources were also included on the website. A two-way communication system was also included in the system which allows patients to send queries to their care manager. In addition to the care manager, there are an advanced practice nurse and certified diabetes educator to provide recommendations to participants and their care manager. The aim of this study is to investigate the effects of web-based care management in patients with poorly managed diabetes mellitus. It ran for 12 months and the outcome was measured every 3 months using HbA1c, systolic and diastolic blood pressure. At the end of this study, it showed a significant improvement on HbA1c in the web-based care management group compares to the education and usual care group. This web-based care management system demonstrated that a system which utilises the internet, remote healthcare care, two-way communication and education could have a positive impact on patients with poorly controlled diabetes. Patients with poorly controlled diabetes who adopt such a system are likely to derive important clinical benefits.

However, this demonstrated system has its limitations. Most of their study participants had no prior computer experience. Those participants needed a computer training for a mean total of 2.3 hours provided by the researchers and were provided with a pre-programmed computer. This indicates there could be a barrier that stops the system being adopted by non-computer-literate people. Providing each patient a computer is unpractical in a real situation and using patient's personal computer may counter some technical issues. Healthcare provider also requires training to use the system, not every clinical practice has access to fully trained healthcare professionals.

Farmer et al.[54] have presented a mobile-phone based tele-healthcare system for type 1 diabetes management . The system utilises a Motorola T720i phone as a data bridge to download readings from a OneTouch Ultra® blood glucose meter. After downloading the readings, the mobile phone sends all the glucose data to a secure server and displays summaries of glycaemic control on the phone. In addition, the patients were asked to record their carbohydrate intakes, activities and insulin injections before each time they were going to inject insulin. A randomised controlled trial of young adults with type 1 diabetes was carried out using this system. In this trial, out of 94 participants, 46 participants were put into the intervention group and used the system with full functionality [55]. The control group only had limited functionality of the system. They can upload their readings to the back-end server and view their blood glucose readings on a graphical summary for the previous 24 hours only. This study has demonstrated the feasibility of using a telemedicine system to support young adults with type 1 diabetes. But the study did not show a significant difference between the intervention and control groups in terms of HbA1c change. To achieve the real-time feature of the system, the participants needed to upload their data each time before an insulin injection which some participants found difficulties in fitting it into daily routines, or failing to remember to do so. In the paper, they also report that there was 59 data transmission related to technical problems occurrence and 94 occurrences of other technical problems including cable link, meter and phone.

Rigla et al.[56] evaluated their web-based tele-healthcare application DIABTel in a randomised crossover clinical study . Their system also utilises a handheld computer and Acculink modem to transmit diabetes data to remote server, in addition, an insulin pump was also integrated into the system to incorporate insulin delivery data. This trial concludes that by including insulin delivery data in a tele-healthcare system for diabetes can achieve better glycemic control. The author mentioned that there is a correlation between the decrease in HbA1c significantly and the number of treatment changes carried out by the patients. Non-compliance indicates that the patient may disagree with doctor's decision which is understandable. The designed system only transmits the glucose value, diet data and insulin delivery data. In reality, the amount of insulin should be injected also are affected by patients' physiologic state [26]. To make a better decision, physiologic state such as exercise, illness or hormone should also be included in a tele-healthcare system.

In 2009, Gema et al.[57] improved Rigla et al.'s work and added private assistant . The new version of the system kept all the features from the previous generation. The added private assistant in the portable device has a closed-loop algorithm implemented providing a real-time control of the insulin pump based on continuous glucose data. This private assistant can directly control the insulin pump to start or stop the delivery of insulin based on real-time glucose data from continuous glucose monitoring device. As a fact, the private assistant they described is an artificial pancreas (AP). However, it should be noticed that the private assistant is capable of delivering both bolus and basal insulin. It is questionable that whether it is safe to delivery bolus insulin without patient's confirmation. Let alone this private assistant is also connected to the internet. If there is a vulnerability in their software, the attacker could exploit it and deliver lethal quantity of insulin.

Martínez-Sarriegui et al.[58] carried a two-month crossover randomised study to evaluate patients' behaviour when interacting with continuous monitoring based mobile telemedicine system . The tele-healthcare system they used was the DIABTel system described in the paper of Rigla et al.[56]. Unlike their previous study, in this study they used continuous glucose monitoring device. They recruited 10 volunteers in this study and divided the study into two phases, control phase and intervention phase. In the control phase, the participants were given a tele-healthcare system with a conventional glucose meter. In the intervention phase, a continuous glucose monitoring meter was given to every participant. In this study, they concluded that participants use the tele-healthcare system more intensively when using continuous glucose monitoring meter. They also mentioned that there are barriers to develop tele-healthcare system due to meter manufacturers do not follow any kind of protocol when designing their meter. However, in their study, they did not mention the difference between control group and intervention group in terms of medical outcomes such as HbA1c and average blood glucose. Given that the cost of using continuous glucose monitoring meters is much higher than using conventional glucose meters, it is very unlikely the continuous glucose monitoring meters will be adopted by the NHS if there are no clinical improvements presented.

Mackillop et al.[59] developed a real-time smartphone solution for the gestational diabetes . In this paper, a Bluetooth based device was developed to aquire the readings from a glucose meter via UART (Universal Asynchronous Receiver-Transmitter) link and send readings to a smartphone via Bluetooth. Due to the limitation of the meter they support, only blood glucose readings were recorded. Other diabetes data such as carbohydrate consumption and insulin intake were entered manually. The fact that this system only support one meter suggests the use of this system could be affected if the supported meter become obsolete. Medical outcomes were not measured in this study.

In 2018, Rigla et al.[60] demonstrated a smart mobile based telemedicine for gestational diabetes management . Comparing to the work of Mackillop et al., their design utilises Bluetooth technology to download data from Bluetooth enabled meters. Bluetooth enabled meters are becoming popular in recent years. But the disadvantage of using Bluetooth only solution is that most meters in the market are still not Bluetooth enabled, patients have to change their meter to use the system. It is better to support Bluetooth as well as other interfaces to get a better user coverage. In Rigla et al.'s study,twenty patients who diagnosed with gestational diabetes were recruited. At the end of the study, no significant improvements were shown in terms of average blood glucose or hyperglycaemic occurrences. But participants had a lower systolic and diastolic blood pressure at the end of the study.

## 3.3 Development process of the WithCare++ tele-healthcare system

The WithCare++ system is designed to be a user-centred tele-healthcare system. Medical device manufacturers tend to consult healthcare professionals during their development [61]. We believe the user in our system contains two different parties: the patients and healthcare professionals. (Minor 3.4)It is important to emphasize that a tele-healthcare system is not only used by the patients but also used by healthcare professionals. To meet the requirements of both parties, we utilised agile design approach and minimum viable product design pattern. Agile design is a design approach suitable for projects which requirement and solutions evolve through the collaboration between the system designers and end users [62]. A minimum viable product (MVP) is a product with minimal functionality that can released to the end user [63].

As discussed before, it is important to involve both the patients and healthcare professionals in the developing process. However, it is also challenging to involve both parties especially the patients in the development process.Comparing to consulting the healthcare professionals, it is more resource intensive to collect design requirements from patients in the early design stage [61]. To speed up the design process, we combine the minimum viable product design approach with agile design approach where the patients are excluded in the early design stage and included after the minimum viable product is developed. The illustration of the design process in shown in figure 3.1.

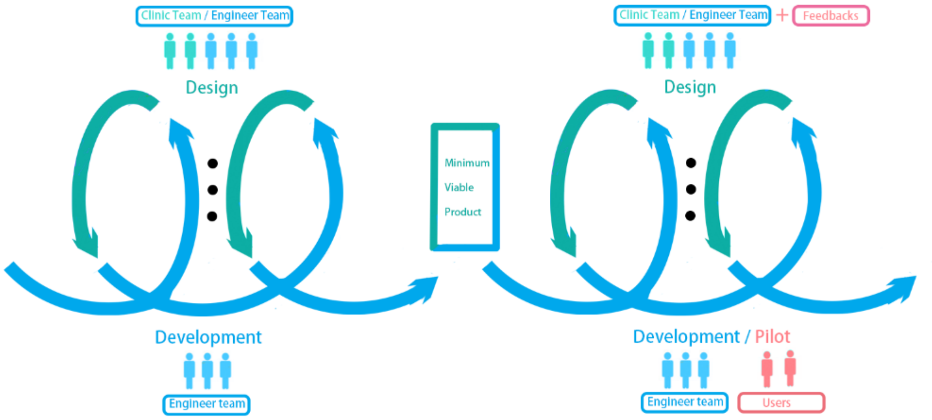



Fig. 3.1 WithCare++ agile design illustration

The overall development process of the WithCare++ system can be divided into two phases. The first phase is an initial design phase where system requirements are collected from both healthcare professional team and engineering team and a minimum viable product is designed. The second phase is the iteration phase where patients are recruited to test the minimum viable product and collaborate in the agile design process. Due to the natural of the agile design approach applied by this project, the requirements of this project would likely to change during each iteration. To enable an effective feedback collecting, mixed methods of feedback collecting are used in the development of the system such as semi-structured interview, focus group, and online questionnaire.

The requirements come from both the healthcare professional team and engineering team, it should be noted that two teams could come up with conflicting requirements due to their differences in understanding the system. It is important that all stakeholders meet regularly in an agile design process to discuss the feedback from previous iteration and the new requirements for the next iteration. Although patients are not included in the initial design phase, we conducted a home internet survey to help us understand the overall information technologies used by our targeted population.

### 3.3.1 Initial design phase

In the initial design phase, the requirements for the minimum viable product were collected. At the begin, the author of this thesis visited Sheffield Children Hospital and Northern General Hospital in Sheffield. During the visits, the author conducted semi-structured face-to-face interview with the two doctors in the clinic. The healthcare professionals in both hospitals were using Diasend®tele-healthcare system at the moment [49]. A few drawbacks were raised by the healthcare professionals about Diasend®. The main complains about the Diasend®from the HCP are cost and reliability. Firstly, Diasend®charges NHS £500 per month per device. To increase the likelihood of the system being adopted, the proposed system needs to be more cost effective than the current system. Secondly, the healthcare professionals mentioned that the system is not always reliable. The system suffers from uploading failure sometimes. The HCPs also demonstrated the operation of the system during the visit and provided a list of meters that are commonly used in their clinic. Due to the fact that none of the patients were using Diasend®from home, the HCPs suggest the system should be user-friendly and can be easily adopted by the patients without extra efforts. In addition to the semi-structured interviews, we also carried out a home internet survey to collect initial requirements regarding the technologies aspects.

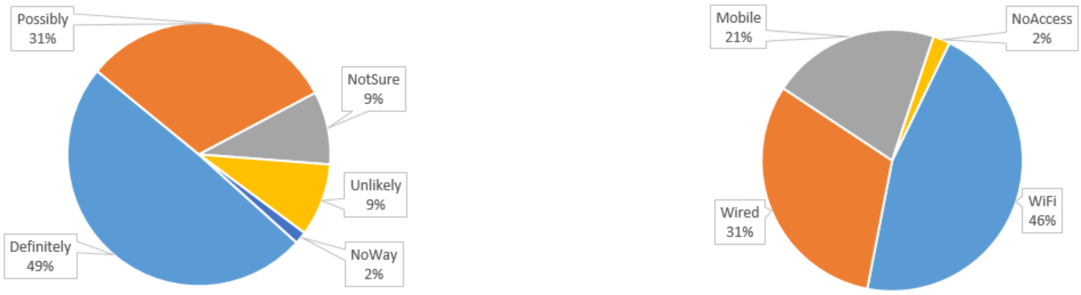
### Home internet survey

(Minor 1)A home internet survey was carried out to help the researchers evaluate the willingness and capability of patients to use a technology based intervention. This survey was covered by the ethic approval issued by the University of Sheffield. One hundred questionnaires were printed and were available for completion at the Diabetes clinic of the Northern General Hospital zin Sheffield. All the type-I diabetes patient in Northern General Hospital can attend the study voluntarily and anonymously. A statistic analysis was carried out two weeks after the start of the survey.

In the survey, 67 completed questionnaires from patients were received. As shown in Figure 3.2a, there are 31% of the surveyed patients possibly considering of using a tele-healthcare system and 49% of surveyed patients are definitely considering using a tele-healthcare system. 11% are unlikely or very unlikely to use a tele-healthcare system. 9% of them are still uncertain about using tele-healthcare.

Home broadband is the most economic home internet access compared to mobile network such as 3G and 4G. As shown in figure 3.2b, 77% of them have internet access at home, while 21% of them have mobile network. Only 2% of the targeted population do not have any form of internet access.

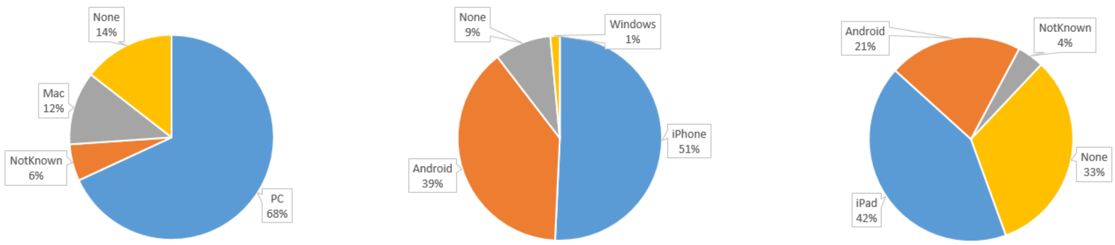
The following figures show the electronic device penetration rate among the participants. As shown in figure 3.3a, 86% of the participations have a desktop at home, in which 12% are Mac and 74% are running Windows or Linux operating system. In terms of smartphone, 91% of the participants are using smartphone. iPhone is the most popular smartphone among the participants, and Android phone is the second most popular. Only 54% of the participants




(a) Attitude of using tele-healthcare (b) Home internet penetration rate

Fig. 3.2 Attitude of diabetic population towards tele-healthcare and Internet access

have a tablet. Only one participant does not have any desktop, smartphone or tablet and does not have any kind of internet. All the participants that expressed interest in tele-healthcare have at least one of desktop, smartphone or tablet.




(a) Desktop (b) Smartphone (c) Tablet

Fig. 3.3 Electronic device penetration rate among the participants

This survey shows that most of the diabetic population are willing to use tele-healthcare system to help them to manage their diabetes. Home internet is sufficient to be used as the remote communication channel in the system. Other communication channels such as GSM and SMS(short message service) can be ruled out as they are not economically efficient. No single operating system dominates, which means that cross-platform solutions are best suited to cover the majority of the population.

After requirements are collected from healthcare professionals, we develop a minimum viable product and recruit patients to test the minimum viable product.

**Requirements for the minimum viable product**

After meeting with the healthcare professionals and consulting the results from the home internet survey. A list of requirements for the minimum viable product of our WithCare++ tele-healthcare system was composed. Those requirements are collected from and agreed between both teams which were focused on different aspects of the system. The requirements are mainly focused on the following aspects:cost, compatibility, expandability, ease of use, data visualization and security.

Table 3.1 Requirements for the Minimum viable product

| Requirement | Attribute |
|---|---|
| A browser-based web application provides 24/7 access to healthcare professionals and patients | Data visualization |
| A system supports Contour USB, Freestyle Optium Neo and Accu-Chek Aviva Nano | Compatibility |
| A system can support other meters in the future | Expandability |
| A system can collect and store other types of data i.e. activity | Expandability |
| A system should implement a proper security system such as a role-based authentication system | Security |

The requirements captured from this stage can be not detailed as non of the involved parties can see a whole picture of the end product, especially when the inputs from patients are missing. However, both the healthcare professional team and the engineering team have provided their own minimum requirements that can get the project started. The requirements from the healthcare professional team is more focused on the clinic usage aspect of the system, such as supporting certain meters and storing different types of data. While the engineering team is more engineering oriented, i.e. security. Using the inputs from the healthcare professional team allows the system designer to avoid missing some critical aspects due to incorrect assumptions. However, the patients are not involved in the initial design phase, their feedback were collected during the iteration phase.

### 3.3.2 Iteration phase

The iteration phase started when the first prototype of WithCare++ box was developed and 6 of those boxes were manufactured. Eleven volunteers were recruited in a usability pilot study and provided feedback at the end of that study via a system usability scale (SUS) questionnaire and a semi-structured interview. The detail of the study is in section 3.6. To enable effective feedback collection, we built an online feedback portal to allow the user to submit their feedback during the study. The author can improve the system in parallel without waiting for the result collected at the end of the studies. After the usability pilot study, the WithCare++ was used in pilot study at Sheffield Teaching hospital to test the system usage and acceptability . In this study, 12 patients and 5 clinicians were recruited. Feedback was collected from them using online feedback form during the study and focus group at the end of the study. Comparing to the previous study in section 3.7, this study recruited 5 clinicians alone with 12 patients and tested the system under its intended environment. Then the WithCare++ system was tested in a multi-centre pilot study, the DAFNEplus pilot trial which is mentioned in section 3.8. In this trial, 66 patients and 10 clinicians across three centres in the UK were recruited. This is the last trial before, the system was being evaluated by a large multi-centre randomized clinical trial [64]. During the iteration phase, we recruited 89 patients and 15 clinicians in total. The following table 3.2 summaries the methods they had used to submit feedbacks.

Table 3.2 Summary of feedback collection

| Stage | Study | Participant | Method |
|---|---|---|---|
| Initial | - | 2 doctors | Semi-structured interview |
| Initial | Home internet survey | 67 patients | Questionnaire |
| Iteration | Usbility pilot study | 11 patients | SUS Questionnaire, Semi-structured interview |
| Iteration | Single-centre pilot study | 12 patients, 5 clinicians | Semi-structured interview, focus group, online feedback form |
| Iteration | Multi-centre pilot study | 66 patients, 10 clinicians | Semi-structured interview, focus group, online feedback form |

## 3.4 WithCare++ Tele-healthcare system architecture

With all the requirements collected from the initial design phase, we proposed a system architecture for the minimum viable product. This section describes the architecture of WithCare++ Tele-healthcare System, including the high level abstractions of high-level components and connectors that defines the structure, behaviour, and views of this system. Among adopted architecture of some tele-healthcare systems is the PU (patient unit) - MW (Medical Workstation) architecture. In PU-MW architecture, a patient unit is designed for patient use and medical workstation is designed for healthcare professionals use. Patients and healthcare professionals share no common experience as they would not use the same device or interface. Tasks are clearly assigned in this architecture, patients are responsible for uploading data and healthcare professionals are responsible for analysing data and providing feedback. The popular system used in the NHS, Diasend®, uses a tele-healthcare architecture that does not have a clear line between patients and healthcare professional. This provides the patients with Diasend®Personal and healthcare professionals with Diasend®Clinic. In this architecture, both patients and healthcare professionals can upload and view diabetes data. The advantage of this architecture is the system can still provide a minimal functionality if one party have failed their responsibility. Unlike the PU-MW based architecture, the healthcare professionals can still upload the data if the patient fail to do so. And patients can view and manage their diabetes without the wait for the healthcare professionals to provide feedback. The disadvantage of this architecture is it is still a role based architecture. The patients and healthcare professionals use different devices to complete the same task. Not only healthcare professionals and patients cannot share the same experiences when using the system but also increases the burden of maintaining the system for the engineers.

In this thesis, the author propose a new architecture for tele-healthcare systems called APP (Acquisition, Processing and Presentation). Unlike the other architectures, APP is based on functionalities instead of roles. Patients and healthcare professionals use the same device and interface to engage with the system. As the name suggests, APP architecture consists of three layers: acquisition, processing and presentation.

- Acquisition

The acquisition layer is focused on collecting diabetes related data such as glucose value, carbohydrate consumption, insulin injection, activities, user comments and healthcare professionals feedback. The acquisition layer need to be user-friendly and reliable as it is the first layer presented to the users.

- Processing

  The processing layer is responsible for processing the data from the acquisition layer, store the data and process the data for the next layer. Data processing includes analysing the data, such as calculating the average blood glucose, generating weekly report and even performing artificial intelligence (AI) algorithm to help both patients and healthcare professionals in improving diabetes management. [65]

- Presentation

  The presentation layer is responsible for data visualisation. This layer allows both patients and clinicians to view the data in their preferred devices. It also provides useful resources to users such as diabetes education material.

The system architecture is illustrated in figure 3.4. (Minor 3.4)In the acquisition layer, the author designed WithCare++ Box and WithCare++ widget to collect glucose readings, insulin , CHO, ketone from patients' glucose meter if those devices record. In addition, the box and the widget also reads from activity trackers. Both the box and the widget has the capability of reading from Bluetooth enabled devices which means, with further development, the system can read data from other T1D healthcare related device i.e. scale, insulin pen, heart rate monitor. The 3 meters shown in figure 3.4 is for illustration purpose. The details of the WithCare++ box and the WithCare++ widget are in 3.5

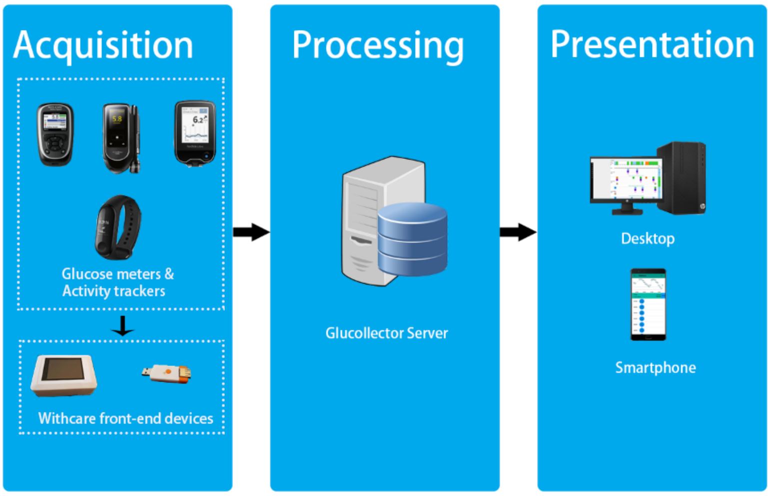



Fig. 3.4 Withcare+ system architecture

## 3.5 WithCare++ Box, the stationary solution

The WithCare++ box is a stationary solution for the acquisition layer of WithCare++ tele-healthcare system. Its main task is to reliably collect diabetes data. (Minor 1)This design has been tested through a usability test with 11 volunteers and a pilot trial with 76 volunteers. The results of these trials have demonstrated the reliability and usability of the system. Thus, this stationary design has been adopted by a major randomised controlled trial in 2019.

### 3.5.1 WithCare++ Box platform selection

The home internet survey and hospital visits summaries the requirement of the tele-healthcare system. It is important to choose the supportable technology to build the acquisition device for WithCare++ system. Due to the rapid advancements of the glucose meters, tele-healthcare system can become obsolete quickly. For example, previous WithCare++ system was based on A MCU (Microcontroller) and only support UART based glucose meter. Some tele-healthcare system which are discussed in the literature review also became obsolete because the meters they support are deprecated. In the literature review, the author of this thesis discussed different tele-healthcare systems. Those systems followed different design patterns. The following is a list of commonly used designs for data acquisition:

- Patient's computer based solution.

  This solution uses user's personal computer as an acquisition device. A software is provided by the designer of the system and installed on user's personal computer. The home internet survey shows that 86% of the population will be covered if this approach is used. The advantage of this approach is there is no extra hardware needed, thus the cost of this approach would be lower compared to other approaches that require extra hardware. This approach also has its disadvantages. For example, Tidepool[66] uses this approach and it only supports USB based meters. The designer also needs to deal with the compatibility issues. Writing a cross platform software can also be challenging when interacts with low level hardware such as Bluetooth and USB.

- Smartphone based solution

  This solution uses user's smartphone as an acquisition device. Same as the first solution, this solution requires extra hardware. But it is also limited to certain types of meters. In this case, this solution only supports Bluetooth enabled meters. For example, Diasend Mobile [67] can only support 10 Bluetooth enabled meters while their Diasend Transmitter can support more than 50 different meters. The latter can only be used in clinics. The USB interface on smartphones cannot be accessed due to security reasons. Thus, USB based meters cannot be accessed using the built-in USB port on smartphones unless they are certified [68].

- Smartphone and Widget based solution

  Similar to the previous solution, this solution uses patients' smartphone and a widget as an acquisition device. This widget normally uses Bluetooth to communicate with user's smartphone. This widget also will support meter's communication method. In previous WithCare++ system, the widget uses UART to download readings from user's meter. The widget is usually made of a MCU based system. A more complex system could have a core microcontroller and few co-microcontrollers. Although this design requires an extra hardware, the cost of this hardware is normally very low. The disadvantage of this approach is it requires longer development time.

- Stand-alone device based solution

  Few studies provide their participants with a stand-alone device for data acquisition [52, 57]. This solution will guarantee that all participants use the same equipment. By using the same hardware for data acquisition, system designers do not have to worry about compatibility issues that may arise when using user equipment. And the designers can customise the device based on different requirements of the healthcare professionals and patients, regardless of the limitations of the patient's personal computer and smartphone. The disadvantage of this solution is that the cost of stand-alone devices may be higher than other solutions.

The author of this thesis decided to use the stand-alone device based solution for the WithCare++ stationary solution based on the following reasons:

- Coverage

  According to the home internet survey, 14% of the participants do not have any kind of computer, 9% of the participants do not own a smartphone, 33% of the participants do not have a tablet. Providing the participants with a stand-alone device could achieve a higher coverage.

- Compatibility

  Using a stand-alone device can avoid compatibility issues that may arise when using the participant's own device. Therefore, shorter development time is needed.

- Customisation

  System designer could customise the stand-alone device to suit the needs of the healthcare professionals and patients. When using participants' device, some functionality may be restricted, i.e. USB cannot be accessed when using an iPhone.

Raspberry Pi was chosen as the platform for the data acquisition device. Raspberry Pi is an ARM Cortex™-A based small single-board computer. Its original role was to promote basic computer science teaching in schools and developing countries. This small single-board computer is affordable but powerful, and in addition to its original purpose, it makes it a suitable platform for other fields such as tele-healthcare and robotics.

### 3.5.2 WithCare++ Box hardware design

The hardware of the WithCare++ box consists of a Raspberry Pi, a PiTFT 2.8 inch touchscreen and an MCP2122 IrDA standard encoder/decoder. The PiTFT touchscreen is connected to the Raspberry Pi via a Serial Peripheral Interface Bus (SPI) .The MCP2122 IrDA standard encoder/decoder is connected to the Raspberry Pi via a UART interface. The cost of the whole device is approximately £90. According to the requirements, this device does not have to be portable, so no battery or any charge circuit is included. However, it is possible to power this device by a portable power bank.

The latest Raspberry pi has dual-band wireless adaptors and an Ethernet port that provides connectivity to back-end servers. This system supports three different types of communication. Those communication interfaces are widely used by the popular glucose meters in the UK.

- USB

  The system has four native USB ports which allow the device to read from USB glucose meters. USB is the most commonly used interface for glucose meters developed in recent years. Those meters not only use the USB to communicate with a PC but also use it to charge the meter itself. It should be noticed that, the first generation of Raspberry Pi has a 700mA limit on the USB port. When connecting some meters, the current spike will cause the Raspberry Pi to reboot.

In addition, if a USB to UART cable is added, this system could support UART based glucose meters as well. However, UART based meters are becoming obsolete.

- Bluetooth

  Raspberry Pi 2 and its later generations has a Bluetooth module embedded. This Bluetooth module allows the system to read data from Bluetooth enabled glucose meters. Some glucose meter manufactures now put Bluetooth Low Energy (BLE) in their latest meters.

- Infrared

  A MCP2122 IrDA standard encoder/decoder is added to the Raspberry Pi. The additional added IrDA module allows the device to read data from the infrared based meters. Infrared is not a popular communication method among the meters. However, most Roche meters are using infrared as their data transfer method. This interface was added to support those meters. This example also shows the advantage of providing a stand-alone device rather than using patients' device, adding an infrared reader to patients' device could be difficult and costly.

It is worth mentioning that at the beginning of the development of the system, the author designed the system on a Raspberry Pi 2 B+. By the time of the trial, Raspberry Pi 2 B+ has become obsolete. Because this design is device independent, this system can be easily moved to a newer platform without the need for changes in the design. Researchers sometimes overlook the importance of future-proofing aspect of telemedicine systems. Some tele-healthcare systems became obsolete after they finished their trial.

Fig. 3.5 WithCare++ Box

### 3.5.3 WithCare++ Box software architecture

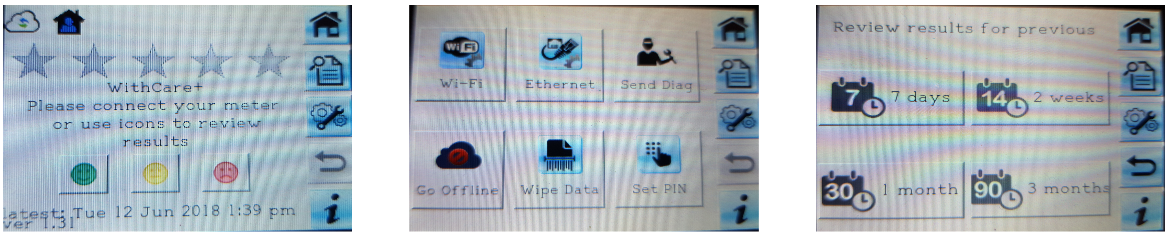
The WithCare++ box is built on a Raspberry Pi 2. It is running a Debian-based Linux operating system, Raspbian. The operating system was modified to suit the requirements of the system. Raspbian's original user interface, LXDE (lightweight X11 desktop environment) was stripped out of the operation system. A Qt based program was written to be used as a user interface and handling all the tasks of the system. Qt is a cross-platform application framework for developing graphical user interfaces programmes. The official language supported by Qt is C/C++. A bootloader was written in bash script to show a splash screen, checking for updates and start the Qt program.

### 3.5.4 WithCare++ Box software details

The key requirements of this system is ease of use and reliability. The design of the software ensures that this system requires minimal user interaction while providing a reliable and secure tele-healthcare data acquisition system.

#### User interface

The WithCare++ box is a Linux based device. The GUI (Graphical User Interface) is programmed in C++ using Qt framework. The touchscreen used on this device is a capacitive touchscreen with 320 * 420 pixels resolution. Although the screen size is relatively small compared to the current commercial electronic devices, some useful graphical user interfaces were built to help to improve the usability as shown in Figure 3.6.




(a) Main view (b) Configuration view (c) Review view

Fig. 3.6 WithCare++ Box user interfaces

The Figure 3.6a is the main view of the WithCare++ box, the user will see this view once the authentication is finished. On the top left corner, the cloud shaped icon is displayed to indicate the current internet status. The home icon indicates the mode this box has been configured in. This box supports two role based modes, a patient mode and clinic mode. A home icon indicates it is in patient mode. The five stars in the centre of the screen indicate how the user is engaging with their diabetes care, the criteria is made based on DAFNEplus. On the bottom of this view, a quick feedback system is implemented. Three emotional buttons (positive, neutral, and negative) allow the user to feedback the experience of using the WithCare++ box. If the user pressed the negative button, a system log is sent to the back-end server. This log will help the developers to identify the problem with usability.

The configuration view in Figure 3.6b allows the user to configure their Internet connection. It also allows the user to send the system log to the back-end server for engineers to diagnose the system if they have any problems using it. Wipe data function allows the user to wipe their data on the device at the end of the trial. And the "Set Pin" function allows the user to set a four digits password on their device to protect their privacy.

A review tab provides (Figure 3.7) a summary view of their uploaded records. Users first need to choose the length of the duration they want to review as shown in Figure 3.7a. Available options are '7 days', '2 weeks', '1 month' and '3 months'. After the length of duration has been chosen, the user chooses the type of the charts they want to review. There are 3 types of charts at the moment:

- Glucose value pie chart

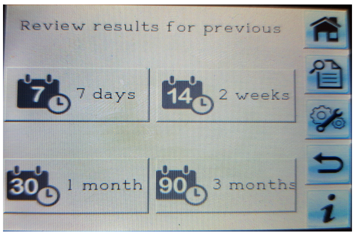
  The Figure 3.7c shows a summary of patient's glucose value within the selected period. This is a generalised summary of how good the patient is managing their diabetes. The goal of a good diabetes is reducing the size of the hypo and hyper area on this chart and get as much as in normal readings as possible.

- Reading vs next reading chart

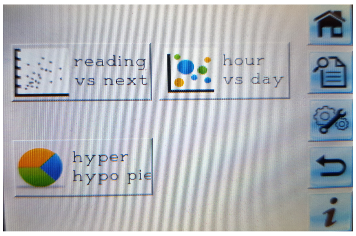
The Reading vs Next Reading Chart (Figure 3.7d) shows user's current reading's value (x-axis) against user's immediate next reading's value (y-axis). This chart will reflect how well the user is managing their insulin injection, hypo and hyper treatments. For example, if a user has a lot of data points on the top right corner of the chart, this means this user is not good at treating hyperglycemia. If a user has a lot of data points on the bottom right corner of the chart, this means this user usually over corrects their hyperglycemia. They were in hyperglycemia then the over correction caused their next reading to be in hypoglycemia range.

- Weekday hourly average chart

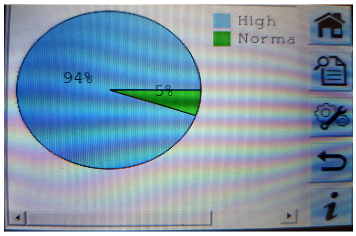
The weekday hourly average chart in Figure 3.7e shows a pattern of patient's average glucose value on each hour of a day in a daily basis. There are seven rows from top to bottom of the chart, indicating the date from Monday to Sunday. The columns in the chart represent the hours in a day. The colour-coded circles in the chart represent an average glucose readings. Blue represents hyperglycemia; Green represents in range glucose value; and red represents hypoglycemia. The size of the circles indicates how many readings are in this time slot. Because most people usually follow a regular daily routine, this chart can help the healthcare professionals and patients to identify patterns of bad diabetes management. For example, in Figure 3.7e a red circle is shown at 2pm of Monday. This shows the user has hypoglycemia at 2pm Mondays repeatedly. The doctors could focus on finding the reasons for the repeated hypoglycemia on that time slot.



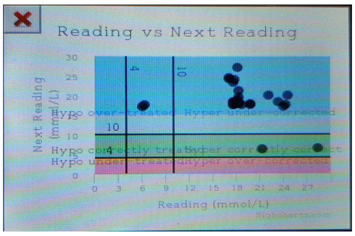
(a) Select time period



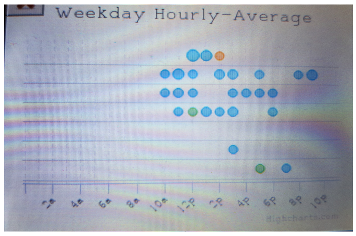
(b) Select chart type



(c) Hypo and Hyper Pie Chart



(d) Reading vs Next Reading



(e) Hourly summary Chart

Fig. 3.7 Interfaces for patients to review their diabetes data

### Connectivity

The first challenge in using the system is how to connect to the home internet network. Most of the tele-healthcare systems discussed in the literature review rely on participant's computer or mobile phone. Unlike those systems,WithCare++ system needs to be integrated into not only users' home network but also enterprise network such as NHS network. There are several mature solutions to this problem based on the hardware design.

- Hardware with limited input and output

  This hardware design are commonly seen in smart home applications or internet of things (IoT). To reduce the cost of those devices, manufactures usually do not put a display on the device. The input method of those devices are also limited, typically only few buttons. The common solution for this is using a Wi-Fi chip that support access point (AP) mode. A companion smartphone application is needed for this solution. This smartphone application first connects to the device's access point and allows the user to configure the Wi-Fi settings. The iOS 11 and Android allows the application to perform those actions automatically without user's interaction, while other operating systems require the user to configure the settings manually. This method greatly reduces the cost of the device because no display is required. But it also has few disadvantages. First, extra smartphone applications needed for different operations systems. Second, before successfully connecting to the device's access point, user cannot know the status of the device because there is no proper display on those devices.

- Hardware with display only

  Some devices have a proper display however without a proper input method. Those devices usually utilize the WPS (Wi-Fi Protected Setup) feature of the wireless router. There are four types of WPS: Pin, Push button, Near-field communication, and USB. Among those, push button is the most appropriate method for hardware without a proper keypad. The user first initialises a connection by selecting their wireless router's SSID on the device, then presses the WPS button on their router to finish the connection process. This method requires minimal user interaction. No password or configuration is required. The disadvantage of this method is due to security reasons, the WPS feature are now disabled by default by most routers.

- Hardware with display and input method

This kind of devices provide better user experiences when compared with the devices that do not have inputs method. The WithCare++ system falls into this category. A touchscreen is used by WithCare++ System allowing users to select their Wi-Fi network and enter their password. An Ethernet port is also available for wired connection. WPS function was included in the earlier version of WithCare++ system. After the first trial, feedback showed that the user did not use the WPS feature in their routers, or even did not realize whether their routers had WPS capabilities. Since then, the WPS function was replaced by a proper user interface that allows user to connect to their router and enter their password. This also shows that although technologies such as WPS exist, users may not know this. Using this technique may affect the overall availability of the system.

When designing the WithCare++ Box hardware, we balanced between the cost and usability. In the end, we chose the solution with higher cost but better user interface to ensure a smooth launch. We optimised the cost or user experience based on the feedback from the pilot test.

**Security**

Security is an important aspect of the tele-healthcare system. WithCare++ box has several authentications and security mechanisms implemented to ensure the security.
All communications between WithCare++ and back-end Server are protected by HTTPS. HTTPS is known as HTTP (Hypertext Transfer Protocol) over SSL (Secure Sockets Layer) or Hypertext Transfer Protocol over TLS (Transport Layer Security). Access to the back-end server is limited to users who have registered. The correct username and password must be

presented when login into the server via a web browser. Nigrin et al.[69] emphasized on the security aspect of tele-healthcare system. In addition to SSL (Secure Socket Layer) which has been commonly used in other tele-healthcare system [50, 52, 53, 54, 56, 57, 60], they suggest using patients' glucose meter as a hardware token which adds an addition layer to the authentication process. Users must connect their registered meter and use their username and password to gain access to their data. The author states that by doing this the system can ensure that users possess:

1. Something they know. i.e. username and password.

2. Something they hold. i.e. a glucose meter.

This way of authentication is similar to a two-factor authentication. It is a authentication utilizing a combination of two different factors. However, it should be noticed that using a glucose meter as a hardware token is somehow flawed. Firstly, they use the serial number of glucose meter as a secret key to perform the authentication. This means the attacker can trick their system by making a hardware device which can response to the system with a matched serial number. The serial number of a meter is usually printed on the back of a meter, which makes using this knowledge as a proof of knowledge less secure. Secondly, if a meter's serial number is compromised, they have no choice but to change their meter, because the serial number of a meter cannot be changed. This drawbacks often seen in a biometric based security systems; because once the user's biometric information has been compromised, the user cannot change it. It is recommended to use a two-factor authentication system, such as Google two factor authentication service where strong dynamic password is used.

Username and password with two-factor authentication is strong enough to access our website with web browser. However, there is a challenge for the WithCare++ box to implement this mechanism. In order to reduce the overall cost of the device, the touchscreen used by the WithCare++ box is only 320 * 420 pixels. Asking the user to input their password and username on this small screen every time when they want to use the device is impractical. On the other hand, store the username and password on the device is not secure and should be avoided if possible. To solve this problem, a cryptographic nonce mechanism and certificate-based authentication are implemented. To activate a WithCare++ box, the user needs to log in the back-end server with their username and password. Once successfully logged in, the user can require a nonce authentication code. This code is a random generated 6-digit code which will only be valid for 10 minutes. Then the user enters this code into their WithCare++ box to finish the activation process. Once the code is entered, the box will query the back-end server with the nonce code. If the code matches the record in the database, a self-signed certificate which is signed by the server will be downloaded to the box. All the communication after this between the box and the server is authenticated by this certificate. This digital certificate is signed by the server with its private key and device's MAC address. This certificate will be valid for one year and becomes invalid if a new certificate is requested by the user. Comparing to Nigrin et al's method [69], this digital certificate is more secure because it is much more difficult to forge a certificate than a meter serial number.

### Data acquisition

Data acquisition is the core part of the WithCare++ box. The requirement of this tele-healthcare system is making uploading as easy as possible. The idea of the design is that after the user did the initial configuration and activation, no extra effort should be made to upload their readings. To encourage the user to use this system, uploading of the data is fully automated. Once connected to the user's home network and registered, the device goes to standby mode.

A thread–running in the background– keeps scanning for USB devices. All the user needs to do is connecting their glucose meter to the WithCare++ box. The background thread will automatically recognise the user's glucose meter via meter's Product ID (PID) and Vendor ID (VID).

For IR based meters, another thread in background sends an Exchange Station Information (XID) discovery frame and waits for an XID response frame via the infrared channel. The user can upload their readings by placing their glucose meter in front of the IR transceiver on the WithCare++ box.

Those threads are running in turn to avoid the racing condition. Once a supported meter is detected, WithCare++ box starts to download the readings, then uploads the readings to the back-end server. A copy of the data is saved in the MySQL database locally. This copy will be deleted if the upload was successful. If any internet error occurs, the WithCare++ device will re-attempt to upload the readings in the database without any user's intervention.

### Data storage

A MySQL database is running on the WithCare++ box. The diagram of the database schematic is shown in Figure 3.8. The WithCare++ box program utilises the QSqlDatabase class from Qt framework to access the local database. Because the MySQL database is not an object-oriented database, an ORM (Object-relational mapping) system was implemented to handle the database related actions. ORM is a technique that converts simple values to an object when retrieves data from the database and converts it back when storing data in the database. To ensure the database integrity, the WithCare++ box will check the database schematic and create tables if the expected tables are missing. A database manager was created following a singleton pattern to coordinate all database actions across the system. This database manager provides basic CRUD (Create, Read, Update and Delete) interfaces to the rest of the program.

There are 7 tables in the database.

- Patients table

  Patients table stores the user information, including their forename and the time for the last upload.

- Certs table

  Certs table records the credential-related information such as the location of the stored certificates, the password to access the certificate, the role of the user and the time the certificate was signed. There is a one-to-many relationship between patients table and certs table (a patient can have many certificates).

- Meters table

  Meters table stores the formation about user's meters, such as meter's serial number, the time of the latest record, and a flag that indicates whether this meter has been synchronised with the back-end server. These information are used to synchronise the local database with the back-end server, so the user can view up-to-date records on both the WithCare++ box and website.

- Readings table and Advisor table

  These two tables store all the readings that was downloaded from user's table. The reading table stores the timestamp, the value, and the type of the readings. The type of a reading could be a glucose, carbohydrate, insulin, or CGM reading. It also stores useful tags that entered by the user such as meals, activities, and hormone cycles. The WithCare++ box uses those stored records to display a summary of user's recent diabetes management.

- PendingReadings table and PendingAdvisor table

  PendingReadings table and PendingAdvisor table are used to store the unsynchronized readings and bolus advisor settings. It ensures that the system can work in an offline mode if the internet service is disturbed and retains the readings in the case of synchronisation failure for the automatic reattempt.

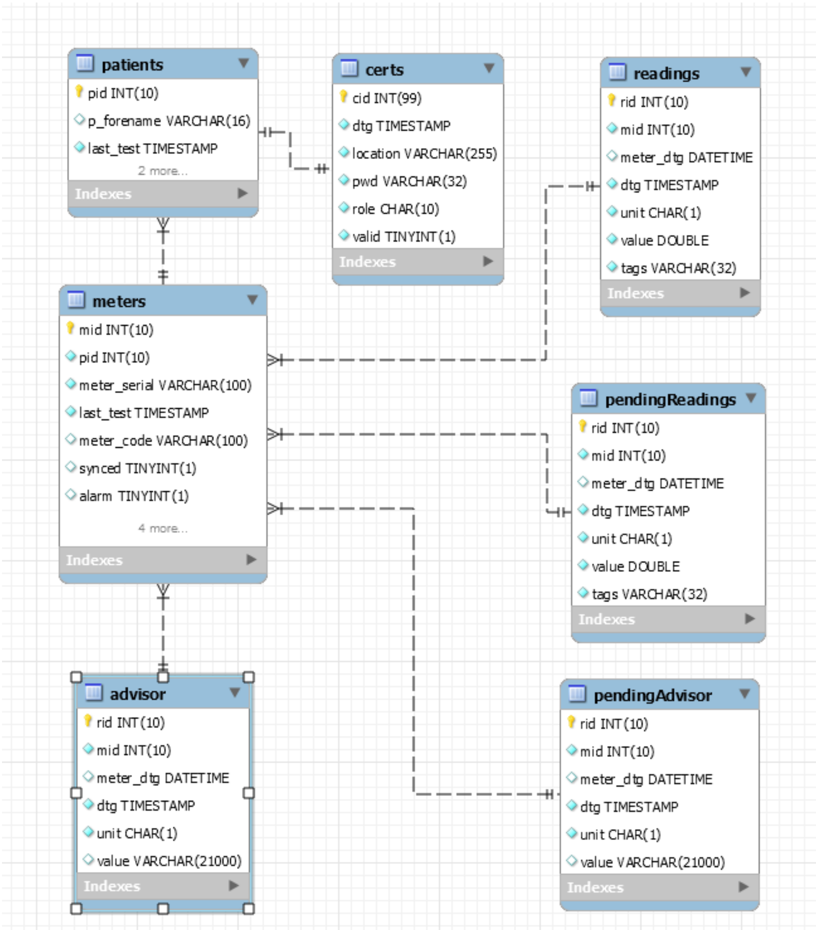



Fig. 3.8 WithCare++ database diagram

### Device remote update and diagnose

Remote update and diagnose is another important feature of the WithCare++ box. Many tele-healthcare studies have been published in the last decades, but only a few reports the detail of technical problems. Farmer et al. report that 153 technical problems have occurred during their trial which involves 94 participants [54]. Malik reports that 5 out of 6 participants have faced technical problems during their pilot trial in his PhD thesis [70]. Since software bugs and technical issues are very common in all kinds of information technology project, it is very unlikely that those studies did not meet any technical issues at all. The technical stability of the tele-healthcare system has been over sighted by most of the studies.

Remote update are implemented for two main reasons: feature update and bug fixing. Since WithCare++ box adopt the agile design approach, the ability of adding new features is one of the requirements. The healthcare professionals and users are constantly providing new feature request and bug report during the trial. Debugging logs are automatically uploaded if any error happened such as failed to upload readings from the meter. Those logs can help the engineers to identify the problem and push bug fixing updates to the remote devices. Since the first version of WithCare++ box, 13 updates have been published during the pilot trial including new features and bug fixes. This also proves that remote update feature should be included in any kind of tele-healthcare project. Without remote update capability, tele-healthcare trial's success could be compromised.

The mechanics of WithCare++ box updating feature is as follows:

- Download the latest list of files and their corresponding MD5 (message-digest 5) hash from the back-end server
- Compare the MD5 hash between the local file and remote file and put files which have different MD5 hashes to a pending list
- Download the file in the pending list from the sever to a temporary folder
- Check the MD5 hashes of the downloaded files against the remote server, re-download if the MD5 hashes do not match
- Copy all the files from temporary folder to the designated location

- If there is a root level update script, check the script's signature with the server certificate then run the script.
- Restart the device when the update is done

Users can also request a remote diagnose if they need further assistants with the WithCare box. The box will open a secured tunnel to the remote control centre which allows the engineers to run the remote diagnose. This feature is very common among the state of the art commercial internet connected products, such as smartphones, tablets and smart home devices. The lack of remote maintenance ability can potentially affect the outcome of a medical research, especially in chronic disease such as diabetes, because the volunteers are required to use the devices on a daily or weekly basis.

## 3.6 Usability pilot study

A usability study was carried out to test the usability of the WithCare++ tele-healthcare system. This study has been reviewed and approved by the Research Ethics Committee at the School of Health and Related Research (ScHARR) at the University of Sheffield. The objective of this study is to prove that the WithCare++ tele-healthcare system is able to reliably acquire data from volunteers operating in a real-life environment.

### Study design

An invitation was sent out to the University of Sheffield "Volunteers" list. Twenty volunteers' initial responses were received. (Minor 1) These were parsed against the following inclusion and exclusion criteria:

- Participants inclusion criteria:
  - A diagnosis of T1D
  - Adults (>18 years)
  - Employee or student of University of Sheffield
- Subject exclusion criteria:
  - Unable to provide informed consent
  - Unable to communicate in written & verbal English
  - Do not have a compatible device

The following Table 3.3 summaries the recruitment in terms of numbers and whether they dropped out at the first stage or were excluded. One volunteer was excluded because they are not a student or staff member of the University of Sheffield and not covered by the ethical approval of this study. Among all the eleven participants, there are 6 females (55%) and 5 males (45%). However, due to the limited sample size and source of recruitment, the participant population does not represent the age distribution of diabetes in the UK very well. University students and staff are more likely to be in the 20—50 age group and have a better IT knowledge than the overall diabetes population.

Table 3.3 WithCare++ usability study recruitment summary

| Response | Number of people | Percentage |
|---|---|---|
| Accepted | 11 | 55% |
| Did Not Attend | 2 | 10% |
| Excluded | 1 | 5% |
| No response | 6 | 30% |

This study is a two-week-long usability test. Each participant attended an enrolment session before the start of the study. During the session, participants were briefed with the purpose of the study. The researchers also demonstrated how to use the WithCare++ box and Glucollector website during the enrolment session. There were 6 WithCare++ boxes available, so some participants were asked if they would prefer a delayed start (for box availability) or use the PC application immediately for uploading data. The PC application is compiled for Windows from the same source code that used in the WithCare++ box. This is one advantage of using Qt, a cross platform framework, it takes less effort to port the application from one platform to another. The PC application has the same user interface as the WithCare++ box. The user uploads the readings by start the PC application first then connect their glucose meter via the USB port on the PC. Supported glucose meters and their test strips are provided to the participants if their current meter was not supported. At the end of the study, participants were asked to fill a questionnaire. This questionnaire is a system usability scale (SUS) questionnaire [12].

**Result**

As shown in Table 3.4, among 11 participants, 10 participants finished the study and finished the questionnaire. One participant attended the enrolment session but did not upload any readings using the WithCare++ box or reply to the research group. This participant was offered the Windows application due to unavailability of the WithCare++ box. Four users were provided with the PC application in total. This study was designed to be running for two weeks for each participant. Three participants did meet the requirement of 2 weeks of usage. Among those three participants, one did not engage with the system at which it is counted as a withdrawal. A second participant (may19v) appears to have cut short their involvement after 11 days so is being counted as discontinuing. Another participant (may7v) cut short their trial period, however on closer inspection this was because they made an unintended late start which went undetected and their WithCare++ box return was requested based on the recorded start date. Two participants used this system for 14 days as requested. The rest of participant used this system for more than the intended 14 days until they are requested to return the device and questionnaire.

As shown in Table 3.5, 1 out of 10 participant said that they would not use this system frequently and this system is cumbersome to use. None of them think this system is unnecessarily complex. Nine out of the 10 users think this system is easy to use. None of them agrees that they need the support of a technical person to be able to use the system. The median usability score is 83.75 and the mean usability score is 81.75 which means the overall system has a good usability.

Table 3.4 WithCare++ usability study usage summary

| Participant Number | Box issued | days of usage | % of days with readings | average readings per day | successful uploads |
|---|---|---|---|---|---|
| May1V | yes | 14 | 100% | 7.7 | Yes |
| May2V | yes | 18 | 100% | 3.1 | Yes |
| May10V | yes | 19 | 100% | 2.9 | Yes |
| May19V | yes | 11 | 100% | 14.1 | Yes |
| May5V | no | 14 | 74% | 2.6 | Yes |
| May13V | no | 0 | — | — | No |
| May7V | yes | 7 | 100% | 4.0 | Yes |
| May4V | no | 63 | 100% | 5.6 | Yes |
| May3V | no | 34 | 94% | 2.0 | Yes |
| May8V | yes | 24 | 100% | 5.1 | Yes |
| May6V | yes | 24 | 100% | 3.4 | Yes |

Table 3.5 WithCare++ usability study questionnaire summary

| Question /Participant Number | may 1v | may 2v | may 4v | may 8v | may 10v | may 19v | may 7v | may 13v | may 5v | may 6v |
|---|---|---|---|---|---|---|---|---|---|---|
| I think that I would like to use this system frequently | 5 | 4 | 5 | 5 | 5 | 5 | 2 | 5 | 5 | 4 |
| I found the system unnecessarily complex | 1 | 3 | 1 | 1 | 1 | 2 | 3 | 2 | 2 | 1 |
| I thought the system was easy to use | 5 | 4 | 5 | 5 | 5 | 4 | 3 | 4 | 4 | 5 |
| I think that I would need the support of a technical person to be able to use the system | 1 | 2 | 1 | 2 | 1 | 2 | 2 | 2 | 1 | 2 |
| I found the various functions in this system were well integrated | 5 | 3 | 5 | 4 | 4 | 4 | 4 | 5 | 4 | 4 |
| I thought there was too much inconsistency in this system | 1 | 3 | 1 | 2 | 1 | 2 | 2 | 2 | 2 | 1 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| I would image that most people would learn to use this system very quickly | 5 | 4 | 5 | 4 | 5 | 4 | 4 | 1 | 2 | 1 |
| I found the system very cumbersome to use | 1 | 3 | 1 | 2 | 1 | 3 | 4 | 1 | 2 | 1 |
| I felt very confident using the system | 5 | 4 | 5 | 4 | 5 | 4 | 4 | 4 | 4 | 5 |
| I need to learn a lot of things before I could get going with the system | 1 | 3 | 1 | 1 | 1 | 1 | 4 | 2 | 2 | 2 |
| Usability Score (SUS-A) as Percentage | 100 | 62.5 | 100 | 85 | 97.5 | 77.5 | 45 | 82.5 | 80 | 87.5 |

Strongly Disagree 1, Disagree 2, Neutral 3, Agree 4 , Strongly Agree 5

**User feedback**

Some feedback from the participant was in favour of the system.

- “Downloading my meter to the box was incredibly easy. I normally don’t keep a diary so normally only download my meter every 4-6 months at clinic, so it’s good to be able to see it at home.” — May19V
- “The WithCare++ box for downloading data is brilliant, and really makes it incredibly easy to get data out of a meter. In the past l’ve found this to be a very frustrating and badly implemented process by the meter manufacturers” — May1V
- “I would very much like to continue using the system as it’s far more convenient than logging my own stats.” — May4V

These feedback show that most of the users are pleased with the system. Some users request to continue using the system after the pre-agreed two week period. An amended ethics approval was issued by the Research Ethics Committee.

There were also some negative feedback which helped the author of this thesis to improve the system. Here is a list of problems that commonly raised by our participants and the solutions.

- "I noticed that the software took a long time to download the data from the meter, and I was wondering whether it was reading everything each time rather than just the recent data."

  This issue is caused by the design of the user's meter. An optimised algorithm is implemented to speed up the downloading process from that meter. This issue also reflects that users care about the uploading time, although it will only take 2 to 3 minutes to download the readings. To improve the user's engagement, the system should upload the data as fast as possible.

- "It would be good to be able to connect the box to WiFi using a password rather than the WPS button for time you may not have access to the button but do have WiFi eg hotels, B&B, etc."

  The first version of WithCare++ box only support WPS for Wi-Fi connection. In the later versions, connecting by password support was added to the system. In tele-healthcare design, something works in the laboratory environment does not necessarily means it will work in real life situation. This kind of feedback emphasise the importance of usability test for a tele-healthcare system before it is used in any kind of trial.

- "Information on the white box is not too useful; would be nice to include table data as in website."

  To improve on this, new charts were implemented on the device via remote update. This reflects the importance of remote updating. The opinions of patients are very important to the development of the system. Patients usually have a better understanding of diabetes than engineers and can provide valuable information to improve the system. WithCare++ tele-healtcare system uses agile design approach to make these remote improvements possible.

- "Where it (the system) lags behind is in its restriction to only a select number of meters in terms of reading the BG data. Where the Diasend platform is superior is that it can upload data from a wide variety of meters, including CGM"

  This is a request for more meter support. The hardware design of the WithCare++ is capable to support more meters. However, it takes time to reverse engineer the protocols of a meter. The latest WithCare++ box supports 9 meters in total. The main barrier that stops the system from supporting more meters is the meter manufacturers do not have a standard protocol in transmitting the diabetes generated data. This problem was also mentioned in Martínez-Sarriegui's paper [58].

- "A smartphone app could also be useful, so you can analyse your data on the go."

> This is a request for a smartphone version. A widget has been developed to support uploading data via smartphone.

This usability study shows that the system achieved an average of 81.75 score in SUS questionnaire, hence it proves that the system has a good usability. All participants managed to upload their readings using the system, except one who withdrew from the study without any engagement with the system. Valuable feedback were collected from the study and improvements were made based on those. With those valuable experiences, this system was used in DAFNEplus pilot trial.

## 3.7 DAFNE graduate single-centre pilot study

With a score of 81.75 in SUS from the usability pilot study, we decided to integrate the WithCare++ tele-healthcare to the DAFNEplus study.

### 3.7.1 Study design

The DAFNE graduate pilot study with a single-centre pilot study to prove that we can combine the DAFNE course with the system we developed and improve patients management of their conditions. The study took place at Sheffield Teaching Hospital, Sheffield, United Kingdom. Ethical approvals to undertake the study have been obtained from NREC of South West - Exeter Research Ethics Committee.

The study participants will be sought by inviting type-1 diabetes patients who have been treated at Sheffield Teaching Hospital NHS Foundation Trust and had finished DAFNE course.

A member of the research team would then contact the participants who have shown interest in the study to arrange an initial meeting. At this meeting, participants would be introduced to the WithCare++ system and given a WithCare++ box to bring it home. Participants will be informed that they have the right to withdraw from the study at any point.

The DAFNEplus pilot trial recruited 12 patients and 5 clinicians from Sheffield Teaching Hospital. All the patients volunteers are recruited with the following criteria:

- Participants inclusion criteria:
  - A diagnosis of T1D
  - Managing own insulin doses for > 1 year
  - Adult (Aged 18+ years)
  - Have attended and finished DAFNE course
- Subject exclusion criteria:
  - Unable to provide informed consent
  - Unable to communicate in written & verbal English

The patients recruited for this study were DAFNE graduates who have completed DAFNE and experienced in diabetes self-management. At the end of the study, they and the participated clinicians would be invited to a focus group to give their feedback on the system. During the study, both the patients and clinicians were given access to a feedback form online. The research team closely monitor the feedbacks and hold regular meeting to discuss and act upon the feedbacks. HbA1c were measured every three months to evaluate the clinic outcome.

### 3.7.2 Data collection

Medical data were collected by using WithCare++ box. All the 12 patients were given a WithCare++ box at an initial meeting after they gave their consent and successfully set up the system in their home and uploaded their data regular. Feedback were collected using an online form during the study and all the feedback were stored secured in a server hosted by the University of Sheffield. At the end of the study, all participate were invited to a focus group and audio of that meeting were recorded and transcribed with their consent.

### 3.7.3 Outcome

The outcome of the study was measured by the usage of the system and the HbA1c improvement. All 12 patients were successfully uploaded from home. The study was started from October 2016 and was designed to run for 12 months. All 12 patients continued using the system after the intended study period. The first patient who stopped upload was on 07/03/2018. Majority of patients uploaded their readings on a weekly basis, while few of them uploaded on daily basis. Patients who did not upload readings for more than weeks were sent a reminding email and then continued to upload.In terms of clinic outcome, the HbA1c data measured before the start of the study are compared with the data measured 12 months after the beginning of the study, the DAFNE graduates on average improved by 0.41 mmol/mol per month($p<0.05$).

## 3.8 DAFNEplus multicentre pilot study

### 3.8.1 Study design

With the success of the usability pilot study, we decided to integrate the WithCare++ tele-healthcare to the DAFNEplus study. The DAFNEplus pilot trial is a multicentre clinical pilot trial which recruited 66 patients and 10 clinicians across three centres (Sheffield Teaching Hospital in Sheffield, King's College London in London, and Norwich and Norfolk Hospital in Norwich). This study is covered by NREC ethics approval from South West - Exeter Research Ethics Committee. All the volunteers are recruited with the following criteria: [64]

- Participants inclusion criteria:
  - Adults ($\geq$18 years)
  - Diagnosis of type 1 diabetes for at least 6 months, or post-honeymoon
  - Prepared to undertake multiple daily injection (MDI) therapy and frequent self-monitoring of blood glucose
  - Confirms availability to attend all sessions as part of the intervention
  - Investigator has confidence that the patient is capable of adhering to all the trial protocol requirements
- Subject exclusion criteria:
  - Unable to provide informed consent
  - Unable to communicate in written & verbal English

- Previous participation in standard DAFNE course less than 5 years before proposed study enrolment date
- HbA1c > 12%/108 mmol/mol or has Serious diabetic complications

(Minor 3.8) The DAFNE course is a educational course for adults with T1D. It provides the skills for T1D patients to achieve better glucose control. DAFNE is 5 day course and has been confirmed that patients who have completed it have better quality of life, better glucose levels (in the short-term) and are admitted to hospital less often for diabetes emergencies. However, patients find it difficult to maintain the skills and get support from healthcare professionals after they finished the course. [48] The DAFNEplus is a re-developed version of DAFNE which is aiming at providing a lifelong package for type-1 diabets. In addtion to the current DAFNE program, the DAFNEplus program allows the patients revising the course, having structured follow-up with health professionals after the course, and using technology. [64] The DAFNEplus course consists of 5 sessions regarding different aspects of diabetes management. The volunteers attended one session every week. At the end of the DAFNEplus course, volunteers attended a follow-up session. After the recruitment stage, the WithCare++ tele-healthcare system were introduced to the volunteers during their first session of the DAFNEplus course by the healthcare professionals. All the healthcare professionals were trained to use the WithCare++ system before the study to ensure that the system can be adopted by both the patients and healthcare professionals without any intervention from the engineering team. The experience learnt from this process can be helpful when the system is adopted by a larger clinic trial due to the small engineering team could not provide support for every training session. In the first training session, each volunteer were given a WithCare++ Box and registered an account on the Glucollector website. After the first session, the volunteers take the WithCare++ Box home and setup the system by themselves. Should they encounter any problem, they can contact the engineering team via the feedback form on the website or contact their healthcare professional. All the reported problems were recorded by the system and discussed in the next agile design meeting.

### 3.8.2 Study result analysis

The DAFNEplus consists of three centres across the UK. Each volunteer will use the system for 6 months and attend the semi-structured interviews at the end of their 6 month usage. The clinical outcome of this study is measured by the improvement in HbA1c levels. The usability of the system in this study is measured by the statistics of the usage and feedback provided in the semi-structured interviews.

#### Usage analysis

In DAFNEplus pilot study, we recruited 66 volunteers (31 males and 35 females) aged between 20 and 80, the detail is shown in Table 3.6. This distribution ensures that our research covers all age groups and is better representative of the general population than our first usability pilot study, which recruited only from the university.

During the pilot study we collected 414664 glucose, carbohydrate, basal insulin and bolus insulin readings from 85 glucose meters used by the 65 volunteers. One volunteer withdraw from the study due to their move to another city. All the volunteers were asked to use an Accu-Chek Expert meter to measure their blood glucose level and record their carbohydrate

Table 3.6 WithCare++ distribution of age of the volunteers

| Age range | Number of people | Percentage |
|---|---|---|
| 20-29 | 9 | 14% |
| 30-39 | 11 | 17% |
| 40-49 | 19 | 29% |
| 50-59 | 16 | 24% |
| 60-69 | 10 | 15% |
| 70-79 | 1 | 1% |

consumption and insulin injection. However, volunteers are allowed to use additional meters if they wish. Among the 65 volunteers, 8 volunteers have used Freestyle libre CGM meter, 4 volunteers have used Accu-Chek freestyle optium meter, 2 volunteers have used Accu-Chek Mobile meter and 2 volunteers have used Contour USB Next glucose meter alone with their provided meters.

The Retention of the system is 90%. Among the 66 volunteers, there are 3 volunteers only uploaded once in the first session and did not use the system from home, another 2 volunteers only used the system for one month. The rest of them have been using the system since they were enrolled, even though the pilot study finished and the follow-up sessions have been carried out. There are 5 of the volunteers have been using our system for more than 2 years, 26 volunteer users have been using the system for more than 1 year. At the time of writing this thesis, 27 volunteers continue using the system.

In terms of the frequency of uploading, the average frequency of uploading is 3 uploads every week. However, the HbA1c does not show any correlation with the frequency of uploading. The meter used in this study can record four types of data: glucose level, carbohydrate, basal insulin and bolus insulin. There are three volunteers only recorded glucose readings in the system and two volunteers only recorded glucose readings and carbohydrate. The rest of the volunteers recorded glucose, carbohydrate and bolus insulin. In addition, there are 7 volunteers recorded their basal insulin. The lack of carbohydrate and insulin intake recording could imply the volunteer has a low engagement with their diabetes management. However, no conclusion can be made regarding the correlation between HbA1c and the type of the readings has been recorded due to the low number of volunteers.

#### Technical feedback

Another important aspect of this pilot study is to test the usability and the stability of the system. To ensure a smooth launch of a randomised clinical trial, the reliability of the WithCare++ system is important. All the volunteers managed to set up the WithCare++ Box in their home, except for the 3 volunteers who left the pilot study after first session. There was one volunteer reported that the box would not upload from one of their glucose meter. This problem was caused by a bug in our reverse engineered meter driver and fixed with a remote update. Another volunteer reported that the WithCare++ Box could not connect to our server. After further inspection, this is due to the software on the WithCare++ Box is outdated. The volunteer was advised to reboot the box to trigger the auto update script and the problem was resolved. We added more checking points for checking updates in the software to avoid such a problem in the future. Another volunteer reported that the WithCare++ Box could not connect to their router via WiFi. The user was advised to use the Ethernet connection. None of the volunteers have reported any problem that would require a home visit. All the update and remote diagnose mechanisms were working as intended.

During the two-year pilot study, we pushed 32 updates to the WithCare++ Box remotely including bug fixing, new meter support, and user interface improvement.

The overall usage of the WithCare++ Box met the expectations of the healthcare professionals. None of the volunteers left the study due to technical difficulties. Problems were more likely to be encountered when the volunteers tried to set up the WithCare++ Box in their home for the first time. Using the combination of email communication and remote diagnose mechanism, all the problems were resolved remotely.

**Clinical outcome**

We also studied the clinical outcomes by comparing the HbA1c measurements at the beginning and end of the study. Volunteers who had HbA1c less than 58 mmol/mol at the baseline were excluded from the analysis, as HbA1c changes within this target range do not represent how good the patient is managing their diabetes (They are already at the national target). From the 55 qualified volunteers, 17 participants did not improve their HbA1c. The rest of the volunteers have improved their HbA1c during the study. Figure 3.9 shows the HbA1c comparison of the individual volunteers.

Overall, the volunteers in DAFNEplus pilot study achieved an average HbA1c improvement of 0.45 mmol/mol per month which is 5.5 mmol/mol for a year.

**User Feedback**

(Minor 3.9.c)A semi-structured interviews was carried out by Dr Stephanie Stanton-Fay at University College London at the end of the pilot study. The volunteers expressed their high

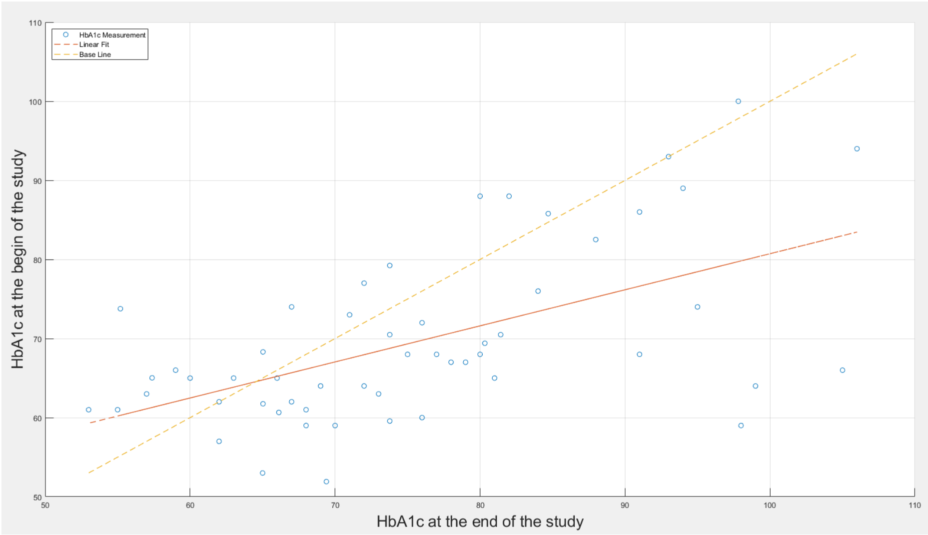



Fig. 3.9 HbA1c comparison for individual volunteers at the beginning and the end of the study

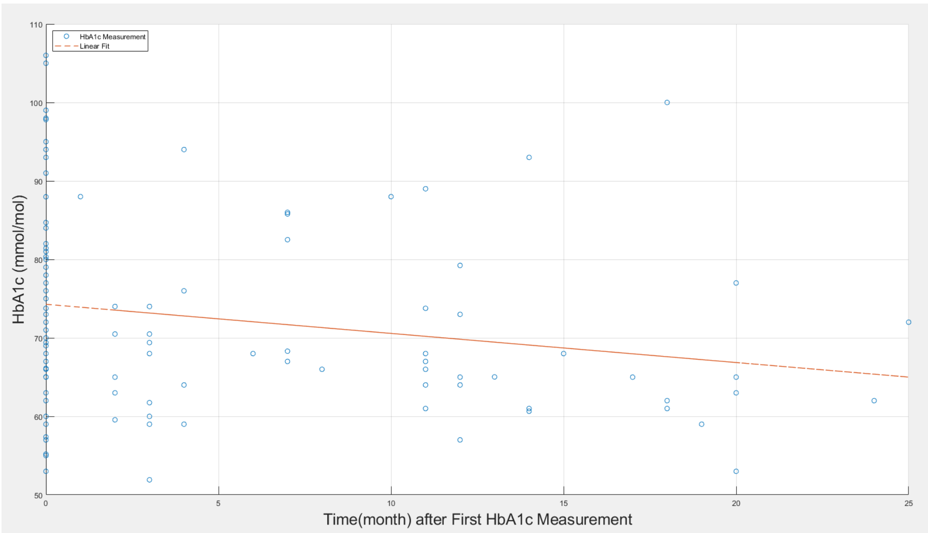



Fig. 3.10 HbA1c measurements over time

acceptance of the tele-healthcare system : "Yes, of course, I'll definitely use it. I think in terms of diabetes, there's always a lot of questions as someone with diabetes that you can explore and you can find out." Feedback from users are mainly focused on the usage of the website as it is the presentation layer of the system and the part they spent the most time with. Feedback such as "So, being able to see the trends. . . .the pie charts and stuff, having green for when you're in range and when [you've] got a percentage in range, when you're on target, it's positive, you know, it's a bit of a positive reinforcement.... this is a really good way to get constant reinforcement that what you're doing is the right thing." and "This is the most I've gone with active testing all the time. ...I think it's because I get a direct benefit from it, and I can see the data straight away, as soon as I upload it. " implies the volunteers from DANFEplus study utilised and enjoyed the improved data visualisation.

Volunteers also expressed that they like that they can upload it from home. "I love that system, you know, we've got now. Like now, we've been on that DAFNE course. Like being able to download it myself at home and then look at it, that's... It's... brilliant, it's really good."

The frequency of uploading, the large amount of data we collected and continued usage of the system after the intended study period proves that the WithCare++ Box served its purpose as a data acquisition device. There were criticisms about the small touchscreen on the WithCare++ Box which is unpractical to use in terms of reviewing diabetes data. We simplified the content on the screen to only show useful feedback such as the "5 star" feedback system which was introduced by the psychology team. In addition, we decided to design a new branch of the system that utilises user's smartphones to achieve a mobile user experience.

## 3.9 Conclusion

This chapter presented the design, implementation and evaluation of the WithCare++ tele-healthcare system. We utilised agile design pattern and minimum viable product pattern to develop a user-centred tele-healthcare system for type-1 diabetes management and diabetes data acquisition platform for data-driven diabetes research.

In the development process, we utilised the agile design and minimum viable product design approach. In the initial design stage, we worked closely with the healthcare professionals to deliver a minimum viable product that would satisfy the patients. There are few reasons that patients were not involved in our initial agile design. Firstly, it is difficult to find patients that are willing to spend their time in a prototype design. Secondly, it is difficult to establish an efficient communication mechanism that works among healthcare professionals, patients and engineers. Thirdly, flaws of a prototype design could have a negative impact on the engagement of the volunteers. When both the healthcare professional team and engineering team were pleased with the minimum viable product, we started the second agile design phase which carried out a usability study and included the patients' feedback into our agile design process. In the end of the initial design phase, we prototyped a minimum viable product and built an efficient feedback system to collect user's feedback.

In the second development phase, we carried out two pilot studies. The system achieved a 83.75 score in SUS questionnaire during its first usability pilot study. In the DAFNEplus multi-centre clinical pilot trial study, we recruited 66 volunteers age from 20 to 80 years old. The wide population coverage proves that the system can be adopted by the people with different IT literacy. Overall the volunteers in our study achieved a significant improvement of HbA1c ( 0.45 mmol/mol per month). We released multiple fixes, improvements and new features to our system by the utilised agile design process. The system was well accepted by our volunteers. We had to amend our ethics approvals so the system can be used by our volunteers past the intended study length.

The expendable and flexible design of the hardware can ensure the system stays relevant with the rapid development of the consumer electronics after its use in the clinical trial which usually lasts for 5.5 years [71]. Systems used in other researches are limited in terms of the types of data that can be collected automatically. Most systems are designed for a specific meter and the data can be collected are limited by the meter used in that research. The table 3.7 shows the types of data collected by different systems. Due to the lack of expandability, very few systems are reused in different trials. To the best of the author's knowledge, only DIABTel are used in different trials, and they redesigned the data acquisition device to be able to work with the new meter they used. Comparing to the system used by other researches, the WithCare++ system supports extra data such as ketone, activity, and heart rate. The design of the WithCare++ Box enabled us to improve the system according to the requirements from the healthcare professionals and patients. For example, we can add extra sensors to monitor data such as sleep pattern if the healthcare professionals or patients require them in the future. The ability of adding extra types of data also helps our system to be used as a data-driven research platform [72]. In addition, developing a tele-healthcare can be very time and resource consuming. Using an expendable system can save the researchers significant time in system development.

Table 3.7 WithCare++ types of data collected by tele-healthcare studies

| System | Glucose | Carb | Insulin | Ketone | CGM | Activity | Heart Rate |
|---|---|---|---|---|---|---|---|
| Chase et al.[50] | A | N/A | N/A | N/A | N/A | N/A | N/A |
| Roudsari et al.[52] | A | N/A | N/A | N/A | N/A | N/A | N/A |
| McMahon et al.[53] | A | N/A | N/A | N/A | N/A | N/A | N/A |
| Farmer et al. [54] | A | M | N/A | N/A | N/A | N/A | N/A |
| DIABTel.[56, 57] | A | N/A | N/A | N/A | N/A | N/A | N/A |
| DIABTel.*[58] | A | A | A | A | A | N/A | N/A |
| Mackillop et al. | A | A | A | A | A | N/A | N/A |
| Rigla, et al [60] | A | A | A | A | N/A | N/A | N/A |
| Proposed System | A | A | A | A | A | A** | A** |

A :Automatic M: Manually.* DIABTel used in [58] used a redesigned hardware. ** Device support is developed but not used by volunteers due to trial schedules

In conclusion, the WithCare++ system is well accepted by the pilot study volunteers and meets the criteria in the checkpoint report to the National Institute for Health Research (NIHR). The user-friendly interface and high usability design encouraged the patients to upload their readings from their home and improved their diabetes engagement. By utilising the agile design approach, we met the requirements from both healthcare professionals and the patients. This system is adopted by the DAFNEplus RCT (RP-PG-0514-20013). It is important to note that the system was not specifically designed for the DAFNEplus RCT. The flexible design of the system allows us to alter the system for a specific clinic trial which means this system can be used as a diabetes research platform for any data driven healthcare research projects. With such a research platform, healthcare professionals can focus on their research without the worries about the engineering aspects. Although this system is designed for type 1 diabetes, it can also be used for other chronic disease management which requires remote healthcare data acquisition.

# Chapter 4

# WithCare++ Mobile

## 4.1 Introduction

In the previous chapter, we demonstrated the WithCare++ tele-healthcare system , a system for remote diabetes management and data driven diabetes research. With the rapid development of consumer electronics technologies, there is an increased research interest in supporting diabetes management on the smartphone based platforms. Expanding the WithCare++ tele-healthcare system to the mobile platform not only adds the mobility in the system, but also reduces the cost of the system which is essential for a large scale research. Mobile healthcare apps are widely accepted by the healthcare givers [73]. They are expected to become even more widely adopted in clinical practice [74]. Self-monitoring of blood glucose is the basic functionality of a smartphone diabetes management application. In addition, other functions such as data analytics, education, and reminders are commonly included in a diabetes management smartphone application [75].

This chapter presents the design of the WithCare++ Mobile, a smartphone based system for WithCare++ tele-healthcare system with low-cost and small form factor design.

## 4.2 Literature review of smart phone based solutions

Rossi et al.[76] designed a mobile phone application which incorporates carbohydrate counting and a bolus advisor . The application sends patients' diabetes data to physicians by SMS (Short Message Service). They carried out a randomised clinical trials using their DID (Diabetes Interactive Diary) mobile phone application [77]. This trial did not show statistically significant improvement on HbA1c, but it showed a statistically significant improvement in terms of treatment satisfaction in the intervention group. They used the same mobile phone application in another trial in 2013 to compare the effect of their carbohydrate counting function in their mobile application with traditional carbohydrate counting education. However, their results did not show a better HbA1c reduction when compared to the traditional carbohydrate counting education [78]. Quinn et al.[79] recruited patients ageing from 45 to 64 years old and carried out a randomised clinical trial using a mobile diabetes management software application (MDMA). The MDMA allows patients to enter diabetes data on a mobile phone and receive educational messages based on their data. Their study showed a statistically significant decline in HbA1c of the intervention group. All the smartphone phone based diabetes management application mentioned above incorporate various kinds of functionality to help improve the diabetes management, but all of them require manual data input which increases the burden of diabetes on patients. Adu et al.[75] reviewed 11 smartphone based diabetes management applications, only 3 of the 11 applications supported automatic data upload.

Downloading data from user's glucose meter with a smartphone has been a challenge for telehealthcare system in both commercial and academic sectors because the meter manufacturers use different protocols and interfaces for data uploading. Compared to the fast-advancing smartphone technologies, the technologies used in blood glucose meters are still lagging behind. The last generations of smartphones use proximity communication technologies such as NFC and Bluetooth as the primary technology for communicating with peripheral devices. However, glucose meter manufacturers tend to use technologies such as USB, UART and Infrared as their primary communication technology. Arsand et al.[80] designed diabetes management system which included a smartphone, a Bluetooth adapter (Polymap Wireless, LLC, Tucson, AZ) and a step counter for type 2 diabetes management. This system works on most phones with Windows Mobile operating system and reads the readings from OneTouch Ultra 2 blood glucose meter. The system utilises a Bluetooth widget to download data from an off-the-shelf blood glucose meter which only has a UART interface and cannot be accessed by a smartphone directly. Waki et al.[81] designed DialBetics, a smartphone-based diabetes management system. This system used a customised device to synchronise the users' glucose readings, blood pressure, body weight from Bluetooth or NFC enabled medical devices. After the synchronisation, the user could review their diabetes data on their smartphones. This system was proven to be an effective tool for improving type 2 patients' HbA1c. However, this study also has certain weaknesses, such as its limited size and duration. It also has a relatively high drop out rate (9.3%) which indicates this system has issues in terms of usability and could face difficulty when widely adopted.

Milak et al.[70] designed a Bluetooth 2.0 based widget which utilises the radio frequency communication (RFCOMM) layer to transfer readings from the widget to smartphones. The RFCOMM protocol works as an emulated RS-232 serial ports. Their design only works with glucose meters using UART port and does not include functionalities other than data acquisition.

The state-of-the-art solution for glucose meter data acquisition has its weaknesses. Due to the limitation of the interfaces on the smartphones, most researchers chose to use a customised device as a bridge to read from different glucose meters. However, this kind of customised device usually only supports single kind of interface. Other researchers chose to use Bluetooth and NFC enabled glucose meters. Those kinds of meter only occupy a very small portion of the market. To the best of the author's knowledge, none of the smartphone based tele-healthcare research project for diabetes support USB based glucose meters which is the most commonly used interface among the popular glucose meters in recent years. Although this kind of design which only uses one meter in the system can reduce the overall development time, but reduces the reusability of a system. From the literature review in chapter 3 and this chapter, only the DIABTel system being used in multiple diabetes trials [56, 57, 58]. And front end system of the DIABTel has to be redesigned to cooperate with the new meters used in later trials. In commercial sector, Tidepool supports multiple meters with their system, however it is only compatible with the USB glucose meters.

Many attempts have been made by researchers and commercial companies [54, 70, 59, 82, 80] to overcome the problems caused by the lack of a universal standard for glucose data transmission. Some of them choose to use meters with standard protocols such as Bluetooth. However, patients have to enter their readings manually if their meter does not support Bluetooth [82]. Others designed a specific hardware to support meters which do not have Bluetooth interface. Farmer et.al.[54] uses a proprietary cable to download readings from a specific model of meter in 2005. While others [70, 59] started to design a Bluetooth based widget as a bridge between smartphone and UART based meters, those solutions have few disadvantages. Firstly, UART based meters do not occupy a big share of the market. The most commonly used interface in recent years is USB because it can not only be used for data transmission but also for charging. Secondly, their system only supported a specific model of a meter and could not support more type of meters without redesigning the hardware.

The chapter proposes a novel design of a widget that is low cost and supports same meters which are supported by the WithCare++ Box using USB, Infrared and Bluetooth interfaces.

## 4.3 WithCare++ mobile solution architecture

Similar to the WithCare++ Box solution, the WithCare++ mobile solution utilises the Acquisition, Processing and Presentation (application) architecture. The WithCare++ mobile solution replaced the WithCare++ box with a USB memory stick sized customising widget as its acquisition layer without compromised the data acquisition ability. The widget supports the same interfaces as WithCare++ box with much lower cost. In addition , the WithCare++ mobile solution enhanced the presentation layer by providing an Android application that allows the user to review their diabetes related data on their phone or tablet. The WithCare++ mobile shares the same processing layer as the WithCare++ box. All the data are synchronised with the cloud sever, WithCare++ Box and WithCare++ Mobile.

## 4.4 Communication protocols used by glucose meters

The main task of WithCare++ widget is working as a bridge between different communication protocols, i.e. Bluetooth to USB, and Bluetooth to Infrared. To achieve this, it is important to understand the difference between those communication protocols such as differences in throughput, data format and timing requirements. In this section, the details of each communication interface, and the differences between them is discussed.

### 4.4.1 Bluetooth low energy

BLE (Bluetooth Low Energy) is a wireless communication technology designed and marketed by the Bluetooth Special Interest Group (Bluetooth SIG). It is also known as Bluetooth 4.0 or Bluetooth smart. Compared to its predecessor classic Bluetooth (Bluetooth 3.0), BLE is intended to work with reduced power consumption and cost [83]. BLE is widespread in today's market. Major mobile platforms such as iOS, Android, Windows Phone natively support BLE. Desktop operating systems such as macOS, Linux, and Windows also support BLE if the computer has a BLE chip built in. Its low energy characteristic and wide compatibility make it an excellent technology for a great variety of applications, including e-health applications, automotive applications, smart home, internet of things, etc... The BLE protocol consists of 10 layers. These layers are grouped into three main blocks: application, host and controller as shown in Figure 4.1

- Application layers

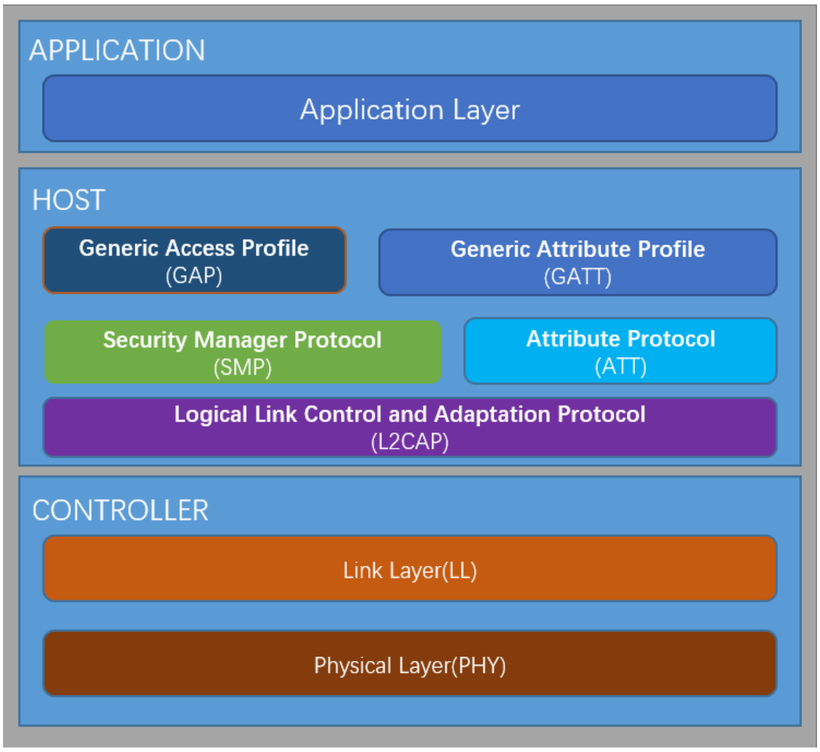



Fig. 4.1 Bluetooth stack

In these three blocks, the application layer is the highest layer of the stack, and it directly interacts with the user code. In the application layer, the user can interact with customised profiles or various different pre-define profiles provided by Bluetooth SIG, including Continuous Glucose Monitoring profile and Glucose profile which are specifically designed to transfer diabetes related data.

- Host layers

The host layers consist of 5 sublayers: Generic Access Profile, Generic Attribute Profile, attribute protocol, security manager protocol, and Logical Link Control and Adaptation Protocol(L2CAP). The host layer is a standard protocol that sits in the middle of the BLE stack. It handles the communication between the controller and the user application layer. It defines a set of protocols and events to translate between raw data and data packets. The L2CAP is responsible for protocol multiplexing i.e. multiplex between BLE and Classic Bluetooth, segmentation and reassembly operation i.e. handling the data from lower layers (Link layer) and reassemble them into the standard Bluetooth packet format and vice versa. The Security Manager Protocol consists of several security algorithms for data packets encryption and decryption [84]. Based on the role of the device, it defines two different procedures during the establishment of a connection. It handles pairing, bonding and encryption of the devices based on their configuration. BLE supports four different pairing methods for devices which has no input/output, display only, display yes/no, keyboard Only, and keyboard & display [85]. Generic Access Profile (GAP) sits on the top of the host layers. It defines the role, mode of the device and manages the connections between the devices. The generic access profile also stores all the information and settings of a device. The user can specify the role of a device using generic access profile depending on the state of the device. In the broadcasting state which the device is not connected, a device can be configured either as a broadcaster or an observer. Once the connection is established, Generic Access Profile (GAP) also handles the connection related parameters such as connection interval, connection supervision timeout, connection slave latency, MTU (maximum transmission unit) etc. User needs to tune these parameters to reach the optimised settings. The ATT (Attribute Protocol) is a low level mechanism that defines how to transfer a unit of data (an attribute). Attributes are defined in the attribute protocol. An attribute contains three elements: a

16-bit handle which uniquely identifies an attribute on a server referenced by a client during communications, a UUID (Universally Unique Identifier) which identifies the type of every attribute, a set of permissions which define some rules on how a client should interact with a specific attribute, and a value which is an array of bytes.The GATT encapsulates the ATT layer, and it defines how all profiles' information and data are exchanged in a BLE link. Profiles are pre-defined rules that outline to BLE devices how to communicate with each other. Profile is a hierarchical structure composed of services. Similarly, service is a hierarchical structure composed of characteristics. As mentioned, the ATT protocol defines two roles in a BLE connection, client and server. The profile is stored in the server side of a BLE connection, and the client communicates with the server by reading and writing the characteristics in the master device. The Bluetooth SIG has pre-defined some standard services and characteristics for different applications. For example, in diabetes applications, the Bluetooth SIG defines Glucose Profile for devices to connect and interact with a glucose sensor. During the connection establishment, the client will query the server for its services. A BLE server device can contain one or more than one service. A service is a container that contains a set of characteristics. Each service can contain one or more characteristics. Each characteristic has its properties, a descriptor and the data value.

These properties define which operations are allowed to be performed on the characteristic. Common properties are listed in Table 4.1. The descriptor defines the human readable name of the characteristic and the short description of the characteristic. And the value is the data stored in this characteristic.

Table 4.1 BLE characteristic properties

| Properties | Description |
|---|---|
| Broadcast | Permits broadcast of this characteristic value |
| Read | Permits read of the characteristic value |
| Write without response | Permits write of the characteristic value without response |
| Write | Permits write of the characteristic value with response |
| Notify | Permits notification of the characteristic value without acknowledgement |
| Indicate | Permits indication s of the characteristic value with acknowledgement |
| Authenticated Signed Writes | Permits signed writes to the characteristic value |

This hierarchical structure is defined in the server device and transmitted to the client device after the connection is established.

- Controller layers

The controller layers consists of physical layer (PHY) and linker layer (LL). The controller layers are the lowest layers in the BLE stack which is normally implemented in hardware. It is responsible for controlling the radio of BLE. The BLE radio works on a frequency band which is ranging from 2.4000 GHz to 2.4835 GHz and divided into 40 channels. The controller layers also controls the limits for the radio transmit power which is important for BLE devices to optimise the power consumption and increasing the range of the signal. Some computationally expensive functionalities in the controller layers are usually implemented in hardware to avoid wasting the resources of a microcontroller.

In conclusion, the BLE works in a master and slave structure. Both master and slave can initiate a data transmission using characteristic read/write or notification. The default length of a packet is 20 bytes although it is extended to 255 bytes in BLE 4.2 and later. The theoretical throughput of BLE is 1 Mbit/s. However, it is not achievable in real life application.

### 4.4.2 Universal serial bus

The Universal Serial Bus which often referred as USB is one of the most popular interface used in modern computer world. It is commonly used by different peripherals such as mouse, keyboard, printer, smartphone,etc. It is often found in glucose meters as an interface for data uploading and battery charging. The earliest version of USB (USB 1.1) was released in 1996. It specified data rates of 1.5 Mbit/s (Low Speed) and 12 Mbit/s (Full Speed) [86]. In 2000, USB 2.0 was released. The new USB specification improved the throughput by supporting the data rate of 480 Mbit/s. In addition, USB 2.0 added On-The-Go Supplement which allows a USB device become a host or a client based on the application. The latest USB specification (3.0) was released 2008 which hugely improved the throughput by supporting SuperSpeed (5.0 Gbit/s) [87]. Based on the meters supported by WithCare++ project, the most commonly USB specification used by glucose meters is USB 1.1.

Similar to BLE, the USB also uses a master-slave structure. However, unlike the BLE which both master and slave can initiate a transmission, the USB only allows the master to initiate a transmission. The USB uses device class to identify the type of the slave device which is similar to a Bluetooth profile. However, the device class does not have a strict standard which defines how a class should work. The driver and protocol is defined by the device manufacturer. From our experience, most glucose meter manufacturers do not follow the standards and design their own protocols.

While Bluetooth uses characteristics as its basic transmission channel, the USB uses endpoints as transmission channels. Two USB devices communicate with each other by writing on different endpoints. USB endpoint has four modes of transfer that are designed for different purposes hence has various data structure and throughput. The WithCare++ widget needs to work with those differences and translate them into a format that is compatible with BLE protocol.

- Control transfer

  Command and status operations are usually carried out using control transfers. Each USB device will have at least one control endpoint for handling control transfers. Control transfers are essential to configure a USB device and sent commands to it. Control transfer are usually random and has the highest priority in USB communications. The minutes transmit unit is called packet. A control transfer consists 2 or 3 stages based on whether data is presented. Those stages are setup stage, data stage (optional) and status stage. Each stage consists 3 packets. The size of a control transfer packet can be 8, 32 or 64 bytes depends on the USB specifications. The are three types of packet in a stage, token packet, data packet and handshake packet. User has to fill the data of token packet and data packet while handshake packet is mostly handled by the USB controller.

- Interrupt transfer

  Interrupt transfer is non-periodic, small size communication. Unlike a traditional interrupt used in a microcontroller, an interrupt transfer is polled by the host device. A host device start a transfer by sending a setup token packet. This setup token packet indicates the direction of an interrupt transfer. There are two types of an interrupt transfer : in and out. When the host sends an in setup packet, the client will response with a data packet, then a handshake packet will be sent by the host to terminate the transfer. The out interrupt transfer works similar to the in interrupt transfer, the differences are the data packet is sent by the host and the handshake packet is sent by the client. According to different USB specifications, the maximum packet size of a low-speed device is 8 bytes, the full-speed device is 64 bytes, and the high-speed device is 1024 bytes.

- Bulk transfer

  Bulk transfer is similar to the interrupt transfer. It can be used for large bursty data. Bulk transfers are usually used for time insensitive communications, because there is no guarantee of throughput. Only full and high speed devices implements Bulk transfers. The transfer structure is identical to the interrupt transfer which consists of three packets. The size of a data packet in bulk transfer can range from 8 to 512 bytes.

- Isochronous transfer

Isochronous transfer occurs continuously and periodically. It is commonly used for time sensitive data such as audio and video stream. Unlike the other three transfers, isochronous transfer does not have a handshake packet which means it does not have a mechanism for retry if error happens. This kind of transfer does not usually found in a glucose meter.

In conclusion, there are four types of USB transfer. However, in a glucose meter, control transfer, bulk transfer and interrupt transfer are most commonly used. There are three types of USB devices, low-speed, full-speed and high-speed. However, from our experience, glucose meters mostly use the full-speed interface. Full-speed USB device supports 64 bytes long data packets which are ideal for transferring glucose data.

### 4.4.3 Infrared

Infrared communication is a common, inexpensive, wireless communication technology. It is commonly found in all kinds of remote controllers, such as TV controller, AC controller, etc. Infrared device uses infrared light-emitting diodes to emit infrared beams to send data and uses silicon photodiode to convert the infrared beam to digital signal. Unlike USB and Bluetooth, infrared does not have a protocol on its own. IrDA is an industry-driven interest group which builds specifications for wireless infrared communications based on infrared hardware. IrDA was popular from the late 1990s through the early 2000s. However, it is slowly becoming obsolete due to the rising of other radio based wireless communication protocols such as Bluetooth. Accu-Chek glucose meters which made by Roche uses infrared communication to transfer glucose readings and are complied with IrDA standard.

Similar to USB and Bluetooth, the IrDA also uses master and client structure. In order to talk with each other, the master device needs to discover the client device by sending a discovery XID command frame to discover a client device. The client device will response with a discovery XID response frame containing information about itself. Once the discovery processes are complete, the master device may decide that it wishes to connect to the discovered device. Once connected, two devices can start to communicate with each other. According to the IrDA specification, the communication operates in half-duplex mode. The data rate of the communication can range from 9600bps to 4Mbps based on the design of the device. For example, Accu-Chek glucose meters talk on 115200bps. Similar to the Bluetooth and USB protocol which all define a fixed packet size, IrDA also defines a maximum packets size.

## 4.5 WithCare++ widget design

### 4.5.1 WithCare++ widget hardware design

To meet the requirements of the client, the system needs electronic chips which can support communication interfaces including Bluetooth, Infrared and USB. The following components are used to meet these requirements.

- CC2640 (Texas Instruments)

  CC2640 is an ultra-low power wireless microcontroller for BLE. The CC2640 device contains a programmable 32-bit ARM Cortex-M3 processor that runs at 48 MHz. Its main processor has 128KB of ROM and 20KB of Ultra low-Leakage SRAM which holds the user application. This chip has two SPI interfaces which are used to communicate with the Vinculum-II USB host chip and a 4Mb EEPROM in this design. The BLE controller runs partly on an ARM Cortex-M0 processor which is dedicated to Bluetooth and can not be programmed for other purposes [88]. This architecture allows that the Bluetooth dedicated task and application task to run on separate threads and improve overall system performance.

- Vinculum-II (FTDI)

  Vinculum-II (VNC2) is a USB Host / Slave controllers designed and made by FTDI . This chip features a 16-bit MCU, with 256KB ROM and 16KB RAM. The device supports a range of flexible interfaces including UART, SPI, FIFO and PWM. Unlike other microcontrollers which rely on software level USB data handling, this microcontroller has a dedicated hardware USB controller. This allows the USB protocol to process data at hardware level without consuming CPU resources for user developed tasks. There are two SPI interfaces on this devices which are used to communicate with the CC2640 Bluetooth chip and a 4Mb EEPROM. The UART interface is connected to an infrared transceiver which are used to communicate with glucose meters with infrared ports.

- MX25V4006E

  MX25V4006E is a 4Mb electrically erasable and programmable read-only memory. It is used as a shared memory between CC2640 Bluetooth chip and VNC2 USB host chip. It is designed to hold temporary data that downloaded from the glucose meter and device firmware update data. It is configured as a slave device on the SPI bus and controlled by the CC2640 and VNC2.

The CC2640 Bluetooth microcontroller works as the main processor in the proposed widget. It handles the command received from a smartphone via Bluetooth and controls the Vinculum-II (VNC2) to interact with glucose meters. It holds all the driver of glucose meters. VNC2 works as a coprocessor which is responsible for handling USB and infrared communication. (Minor 4.4)The WithCare++ Widget also has an 8Mb off-chip flash memory which stores temporary data and over the air download(OAD) data.

The abstraction of hardware architecture is shown in figure 4.2. The detailed schematic attached in the appendix. A PCB was made for the device and the case is 3D printed .

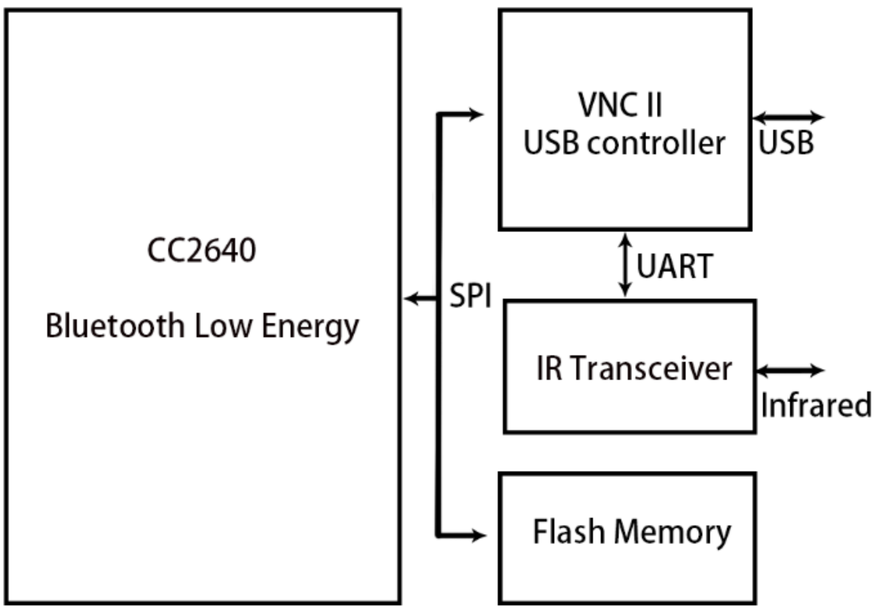



Fig. 4.2 WithCare++ system diagram

Fig. 4.3 WithCare++ Widget

## 4.6 WithCare++ widget software design

The WithCare++ widget works as a bridge between an Android application and glucose meters. It contains a CC2640 as a core processor and a Vinculum-II (VNC2) as a co-processor. The Android application controls the CC2640 via BLE while CC2640 communicates with Vinculum-II (VNC2) via SPI bus.

### 4.6.1 WithCare++ widget BLE profile

(minor 4.3) In BLE, generic attribute profile defines the way that devices communicate with each other. The Bluetooth SIG has defined some profile for various applications. Glucose Profile is the dedicated profile that has been design by Bluetooth SIG to transfer glucose data.The (Figure 4.4) shows the detail of the glucose profile :

The Glucose Profile contains two services : device information service and glucose service. The device information service contains 9 characteristics in total. They are manufacturer name string, model number string, serial number string, hardware revision string, firmware revision string, software revision string, system ID, IEEE 11073-20601 regulatory certification data list, and uPnP ID [89]. All the characteristics are readable only. Those characteristics store all the basic information of the device such as manufacturer name, model number, hardware revision, etc. The glucose service is the most important service in the glucose profile. It has 5 mandatory characteristics (Glucose Measurement, Glucose Measurement - Client Characteristic Configuration descriptor, Glucose Feature, Record Access Control Point and Record Access Control Point - Client Characteristic Configuration descriptor) and 2 optional characteristics (Glucose Measurement Context, Glucose Measurement Context - Client Characteristic Configuration descriptor).

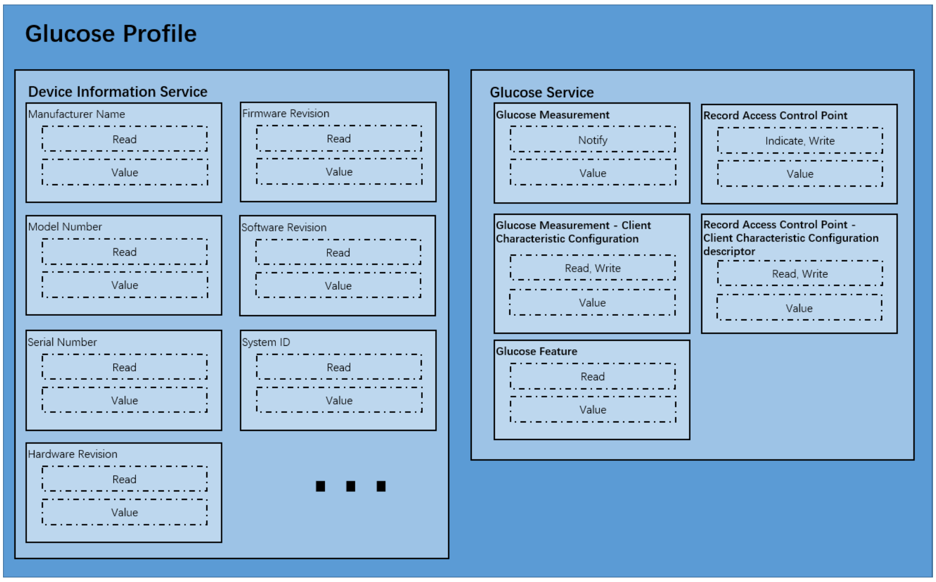



Fig. 4.4 Glucose profile

The client communicates with the server by writing and reading the characteristics. The following uses Glucose Service as an example. In Glucose Service, data are stored in the format of record. A record consists of a mandatory glucose measurement characteristic value and an optional corresponding glucose measurement context characteristic value. The client can query one or more records by writing to the record access control point characteristic.

The data written to the record access control point characteristic consists of an Op Code, an operator and an operand.

For example, the client can write code [0x04, 0x01("all records")] to request number of all records . Then the server will indicate back [0x05,0x00] with an operand containing the number of all records. Then client can write [0x01 (report stored records), 0x01("all records")], the server will notify all records using glucose measurement characteristics. At the end of the transmission the server indicates[0x06 (response code), 0x00 (null)] using record access control point characteristic.

(Minor 4.3)This profile is specifically designed for BLE enabled glucose meters. However,WithCare++ widget requires a custom BLE profile to work with meter without BLE. The custom BLE profile allows the WithCare++ Widget to transfer non-standard data from glucose meter to user's smart phone.

This WithCare++ profile contains three services: glucose service, OAD service and With-care++ service.

- Glucose service

  The glucose service is a pre-defined service for transferring glucose related data. This service has been described in section 4.4.1. WithCare++ profile utilises this service to transfer formatted glucose readings. All the readings read from glucose meters are formatted from its original packet either a USB packet or an inferred packet to a standard BLE packet.

- Over the Air Download Service

Following the same design principle of WithCare++ box, an over the air download service is implemented in the widget. This service allows remote firmware update which is used to push new updates after the widgets are shipped to volunteers.

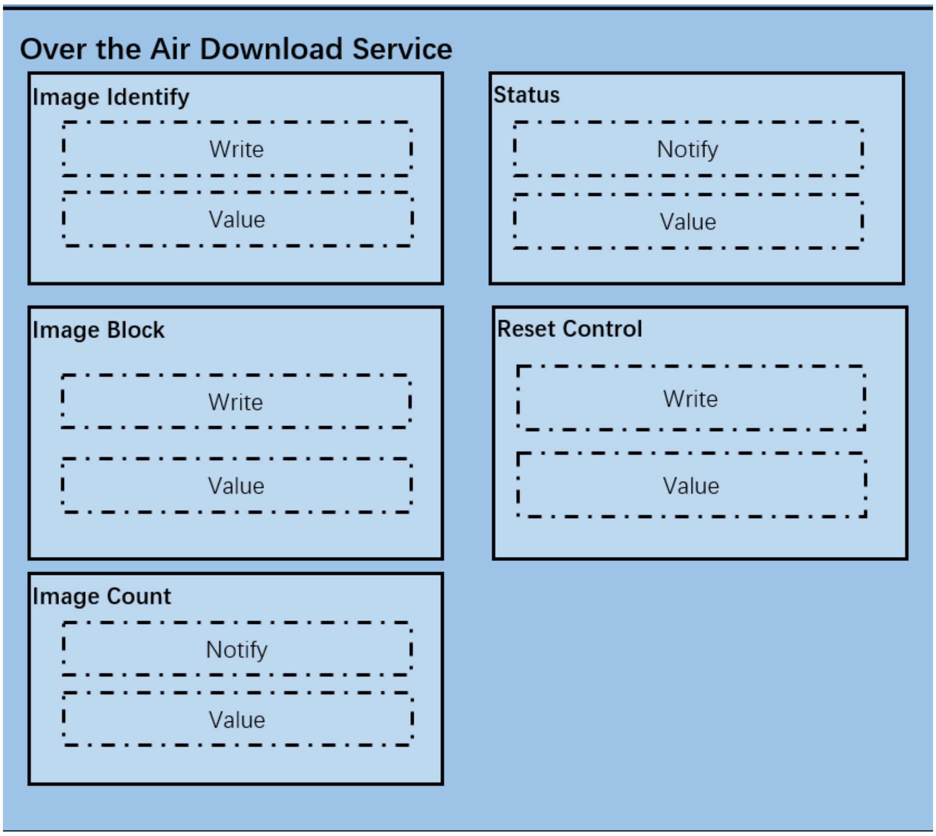



Fig. 4.5 Over the air download service

The OAD service is designed to update the program written in both CC2640 BLE chip and the Vinculum-II (VNC2) USB chip. The OAD service shown in Figure 4.5 contains five characteristics. To write a new image to the device, the client which in this case is an Android phone will write the image header of a new image to the image identify characteristics.

The image header (Figure 4.6) is 16 bytes array which contains the information about the image we want to write. Once the header is sent, the CC2640 will check and store

| Field | Size (in bytes) | Description |
|---|---|---|
| crc_old | 2 | CRC calculated by OAD client before transfer |
| crc_new | 2 | CRC calculated from flash after transfer |
| ver | 2 | Software version number |
| len | 2 | Size of the image |
| uid | 4 | User-defined Image Identification bytes |
| addr | 2 | Address offset in 4-byte blocks |
| imgType | 1 | Define the type of the image, it could be driver, firmware for cc2640 or firmware for VNC-II |
| Status | 1 | This field is not used until after the data is stored. Bootloader uses this field to check if the Image has already been loaded into internal flash. |

Fig. 4.6 Over the air download image header

the information of header and ask the client to send the image using the image count characteristic. The image is divided into 20 bytes long blocks and written into the image block characteristic by the client. On the CC2640 size, the data received by image block characteristic will be written into the off-chip memory. On completion, the CC2640 will read all the content from the off-chip memory and compares the results from cyclic redundancy check (CRC). If the calculated CRC is identical to the one received from the client, the status characteristic will notify the client and start to reprogram the chip. With this mechanism, we can not only fix the bug in the firmware of both chips but also add more meter support in the future.

- WithCare++ Service

The WithCare++ service handles all the commands and data received from the Android application. There are four characteristics in the service as shown in Figure 4.7.

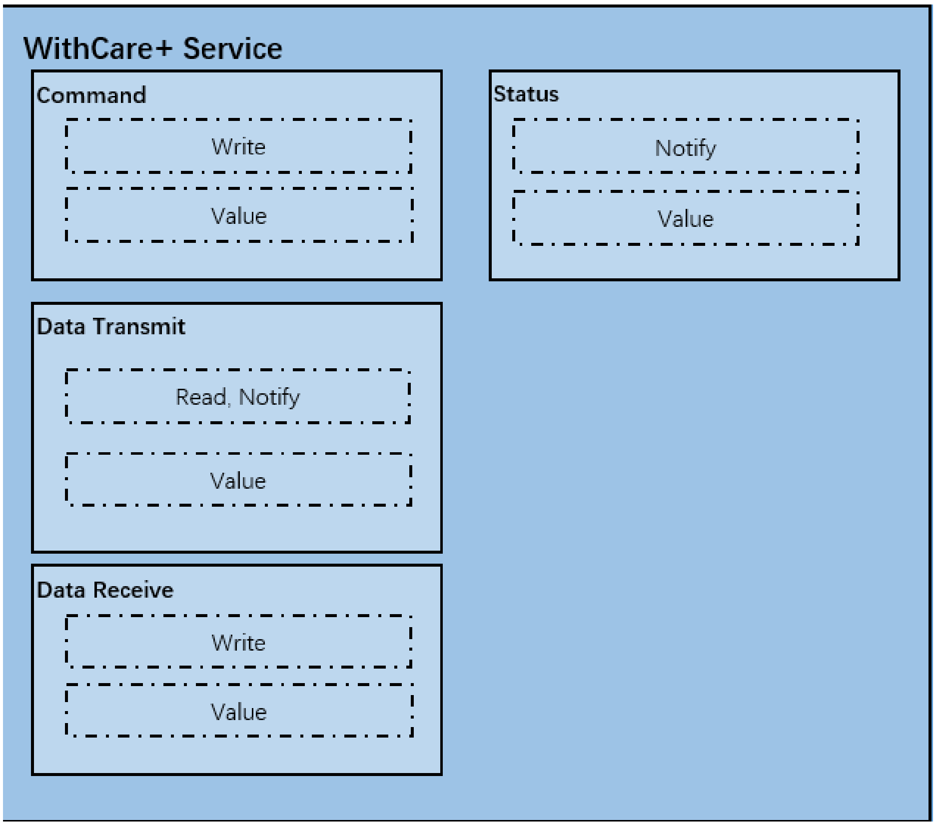



Fig. 4.7 WithCare++ service

- Command characteristic

  The command characteristic is used to send the commands to CC2640 and VNC-II. All the commands are stored in a 20 byte array and sent to this characteristic. As shown in Figure 4.8, the CMD Start is a constant indicates the start of a command. Field CMD Receiver is used to indicate the receiver of this command, it could be either CC2640 or VNC-II. The CMD field indicates the accuracy command need to be carried out. If additional data is needed, the length of the additional data will be written into the next field followed by the additional data.

| CMD Start | CMD Receiver | CMD | Length of addition data | Additional Data |
|---|---|---|---|---|
| 1 byte | 1 byte | 1 byte | 1byte | Up to 16 bytes |

Fig. 4.8 Command characteristic data structure

– Status characteristic

The status characteristic will notify the result of a command after it has been executed which contains a byte indicating whether the execution was a success or failure, along with an error code if it was a failure.

– Data transmit characteristic and data received characteristic

(Minor 4.5.b)Most commands are transmitted using the command characteristic and status characteristic. However, when the amount of data exceeds the default BLE packet 20 bytes size limit. The data transmit characteristic and data received characteristic are designed to transmit large chunks of data.

The data transmit characteristic and data received characteristic (Figure 4.9) and status characteristic contain four fields: transfer id, number of packets, packet number and data.

| Transfer Id | Number of packets | Packet number | Data |
|---|---|---|---|
| 1 byte | 1 byte | 1 byte | 17bytes |

Fig. 4.9 Command characteristic packet structure

(Minor 4.5.b)The transfer id is an autoincrement number to identify individual transfer. Number of packets and packet number are used to assemble all the sub packets. Once the receiver receives all the sub packets, it will acknowledge the sender.

### 4.6.2 Multi-meter support in WithCare++ Widget

One of the challenges in building this widget is synchronising all the timing requirement of all different communication protocols. If the host device does not respond within a certain time, some glucose meters will automatically reset and it will be possible to exceed this time limit if another layer of communication protocol was introduced without caution. In addition, it is important to reduce the overall downloading time to satisfy the expectation from the users. From previous WithCare++ box pilot study, we know that users dislike a slow download.

Comparing to BLE, the throughput of USB and Infrared is fixed and guaranteed by their respective protocols. On the other hand, in terms of throughput and latency, the performance of BLE varies based on the design and configuration of the device. The mandatory over the air data rate is 1 Mbps, but the real application throughput is far less than that. In order to achieve an overall low power consumption, BLE has limited active radio time. The application throughput is affected by several parameters.

To overcome those problems, the following sections describe the parameters that affect the throughput of BLE and few optimisation methods which are implemented for different types of communication interfaces.

### BLE throughput parameters

The throughput theoretical of a BLE device may reach the limit of 230 kbps, but real throughput of actual applications can only achieve up to 100 kbps [84]. There are few parameters that can affect the overall performances of a BLE application.

- Connection Event (connEvent)

  The Connection Event (connEvent) in BLE specification defines the periodical event in which two devices exchange packets. All the BLE communication happens in the periodic connection events and become idle between two connection events. In each connection event, either master or the slave will send a data packet as a sender and then the receiver will send an ack packet to acknowledge the receipt. Certain BLE communication such as write without response and indicate do not require an acknowledgement packet. A pair of data packet and ack packet is called a round trip. The number of round trip connection events are specified by different systems, such as Android operating system allows 6 round trips in a connection event while iOS allows 4 round trips [90]. The number of round trips affect the throughput of the BLE connection.

- Connection Interval (connInterval)

  Connection Interval (connInterval) is the time between the beginning of two connection events. As shown in the Figure 4.10, the connection interval is the sum of time during connection event and radio idle. According to the BLE specifications the minimum connection interval is 7.5 milliseconds and increases in steps of 1.25

milliseconds until 400 milliseconds maximum. The shorter the connection interval is the more energy hungry the device is, so smartphone manufactures usually use customised minimum connection interval. For example, the iOS sets the minimum connection interval to 15 milliseconds instead of 7.5 milliseconds. On Android device, the minimum connection is set by device manufacturer independently. The length of the connection interval also affects the throughput of the BLE connection.

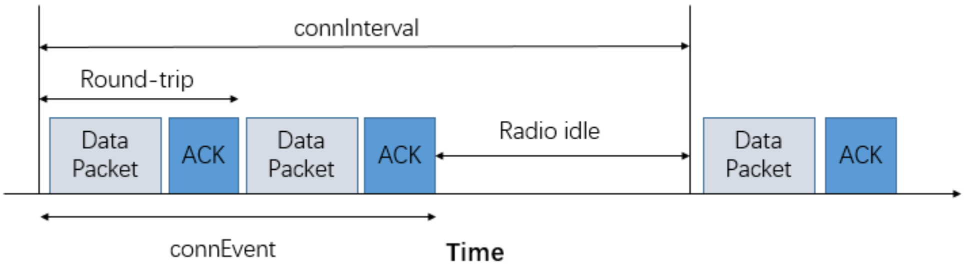



Fig. 4.10 Example of data communication with the transmission of data packets and ack packets

- Data per packet

  Another parameter that will affect the throughput of the BLE connection is data per packet. The default size of a Bluetooth packet is 20 bytes in BLE v4.0 and v4.1. In BLE v4.2, the size limit has been increased to 255 bytes with a data packet length extension. With data packet length extension, one BLE data packet can hold up to 255 bytes data instead of 20 bytes in BLE v4.0 and v4.1. However, this feature is not supported by all operating systems and hardware [91].

All the parameters mentioned above affect the throughput of a BLE connection. The theoretical throughput is calculated as equation 4.1 , where $N_{packets}$ is the number of packets in a connection interval and $N_{bytes}$ is the number of bytes in a packet[84].

$$Throughput = \frac{1000mSecs * N_{packets} * N_{bytes}}{connInterval} \quad (4.1)$$

For example, the theoretical throughput of a BLE connection on an iOS device would be $\frac{1000mSecs*4*20bytes}{30} = 2.67\ kilobytes\ per\ second$. Theoretically, it will take an iOS device about 15 seconds to download 1000 glucose readings from a glucose meter. The theoretical throughput can only be achieved in an ideal situation. Additional software overhead such as fetching data from the memory, parallel process, delay between the link layer and physical layer and radio interference will decrease the overall application throughput.

**Multi-meter support in WithCare++ widget**

In the previous section , we introduce the differences between each communication protocols. The biggest difference between USB and Bluetooth which affects the implementation of the system is throughput. (minor 4.6)Throughput affects the time needed for uploading data from a meter to a smartphone. It is not necessary a problem when working with a BLE enabled meter as those meters are optimised for transmitting glucose data. However, the WithCare++ Widget is designed to work with some popular meters which do not have BLE support. Since the client device is an Android phone or iPhone, the BLE parameters of those devices are defined by the mobile phone manufactures. The minimum connInterval we can achieve is 30 ms while still have the best compatibility. To be compatible with BLE $V4.2$ and before, the data per packet which is also known as MTU (maximum transmission unit) is set to 20 bytes. And the number of packets in connection event is set to 4 which is decided by iOS. In the worst case scenario, the widget can send 4 packets of 20 bytes to the smartphone every 30ms. However, some USB devices require a 10ms pulling rate which means our system needs to send 64 bytes every 10ms. In addition, with Bluetooth added as another layer of communication into the round trip, the latency between the host device and client device becomes even larger. Due to the restriction of some glucose meters, this additional latency will cause a hardware reset in the glucose meters.

To solve the problem, the WithCare++ widget needs to handle the time intensive tasks within itself. The whole or part of the glucose meter driver has to be hosted on the WithCare++ widget instead of the mobile phone to reduce the latency between mobile phone and widget, and meet the timing requirement of the glucose meters. By placing the meter record downloading driver and dedicate the task on the WithCare++ widget, readings can be downloaded from the glucose meters without any time-out issue. However, this solution introduces another problem. Unlike many other research projects, the requirement of this project is to designing a flexible and future proof system that can work with different glucose meters. Due to the lacking of a universal protocol for downloading data from glucose meters, each manufacturer uses protocols designed by themselves. Unlike a smart phone, the memory on a BLE chip is very limited, it is impossible to put all the drivers into a BLE chip. Furthermore, it is required to support meters in the future thus simply placing a driver on WithCare++ widget is not a feasible solution.

To provide multi-meter support, we utilise a modular design approach. Instead of programming the chip with certain drivers, programming overlay and over-the-air download are used to dynamically load the necessary drivers into the chip accordingly. Programming overlay is a technique that allows transferring a block of program code into main memory and replacing the current stored code. It is similar to the abstract function in programming where a function is only declared with its signature and the implementation is written somewhere else. This technique is very useful when the physical memory is limited. The Bluetooth chip used in the WithCare++ widget only has 128KB of in-system programmable flash. With all the software stack and tasks occupying the flash memory, the space left for meter drivers are very limited. According to the Texas Instrument, the available memory space for user application is only around 55Kb. By using programming overlay, we can reprogram parts of the chip to support more meters.

The WithCare++ widget consists of a 8Mb off-chip flash memory. This memory is partitioned into two parts. The first part has 6Mb of memory and it is used to save any temporary data shared between the CC2640 and VNC-II. The 2Mb left is used to store all the drivers for multiple meter support and firmwares updates for CC2640 and VNC-II. The memory partition is shown in figure 4.11.

At the beginning of the download, the widget will query the model of the meter using a universal command specified by the USB specification. With the received model number, the widget will compare the model with the driver that is loaded in the overlay. If the model matches the loaded driver, the widget will download the readings immediately. Otherwise, the widget will query the off-chip flash memory to find the specific driver. The overlay manager will reprogram the overlay region with the driver, if the driver is found on the off-chip memory. If the driver is not found on the off-chip memory either, the widget will inform the App on the phone and downloads the desired driver from the smartphone via Bluetooth. The flowchart of downloading is shown in the figure 4.12. The process of OAD

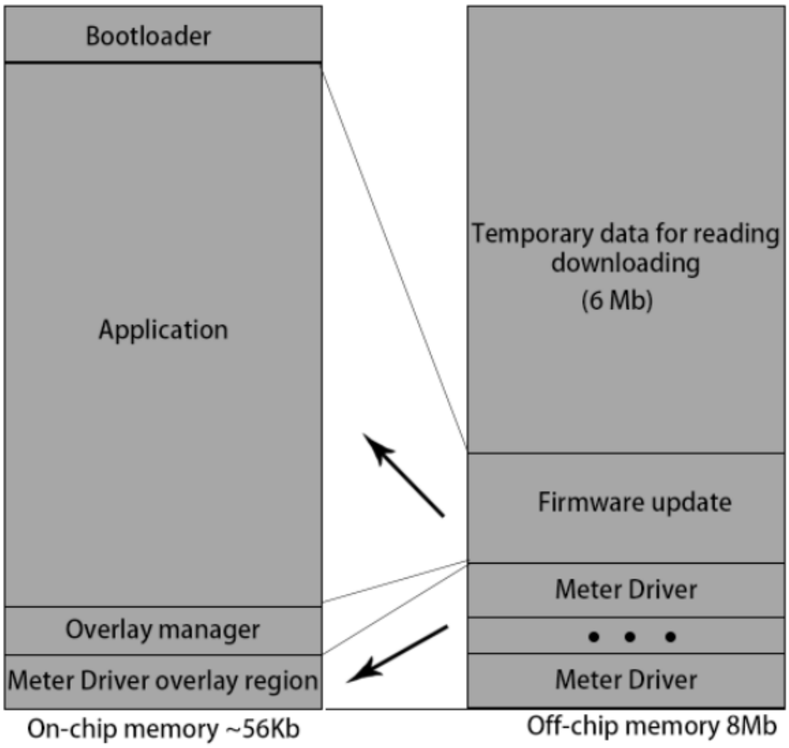



Fig. 4.11 WithCare++ Widget memory partition

and program overlay rewrite will take about 10 milliseconds depending on the size of the meter driver. With this implementation, we can support different models of meters without hardware redesign. New meters can be supported by software update, the engineers only need to focus on the driver development. The users can have the same upload experience as using the WithCare++ Box. This is more likely to be adopted by a large scale trial, because the overall cost of a WithCare++ Widget is about 10% of a WithCare++ Box. (Minor 4.5.a)At the time of writing, the WithCare++ Widget support all 8 meters which are supported by WithCare++ box except the FREESTYLE Libre. New meter drivers are under development to support more glucose meters.

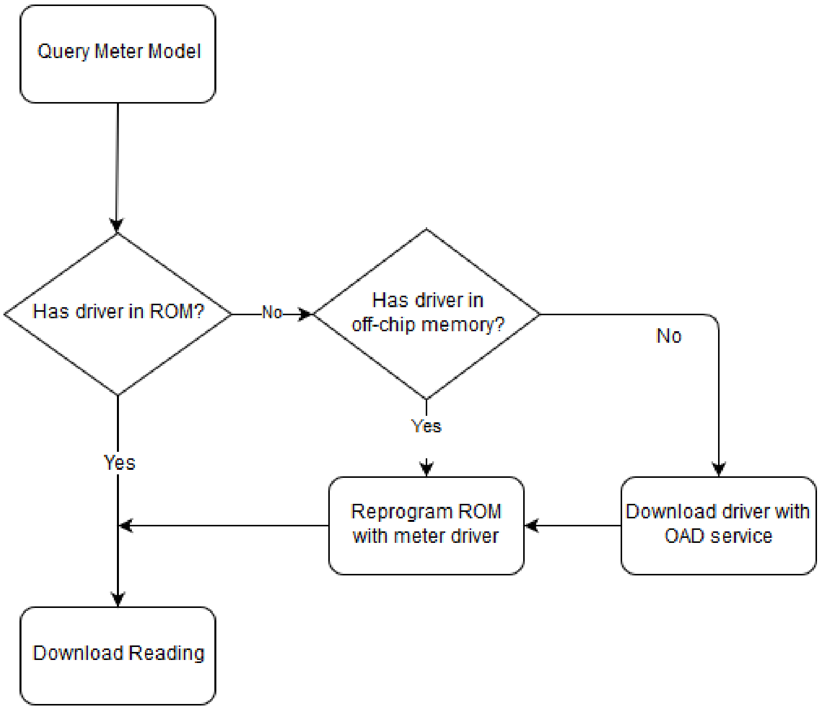



Fig. 4.12 Flowchart of meter downloading

## 4.7 Design of WithCare++ Android application

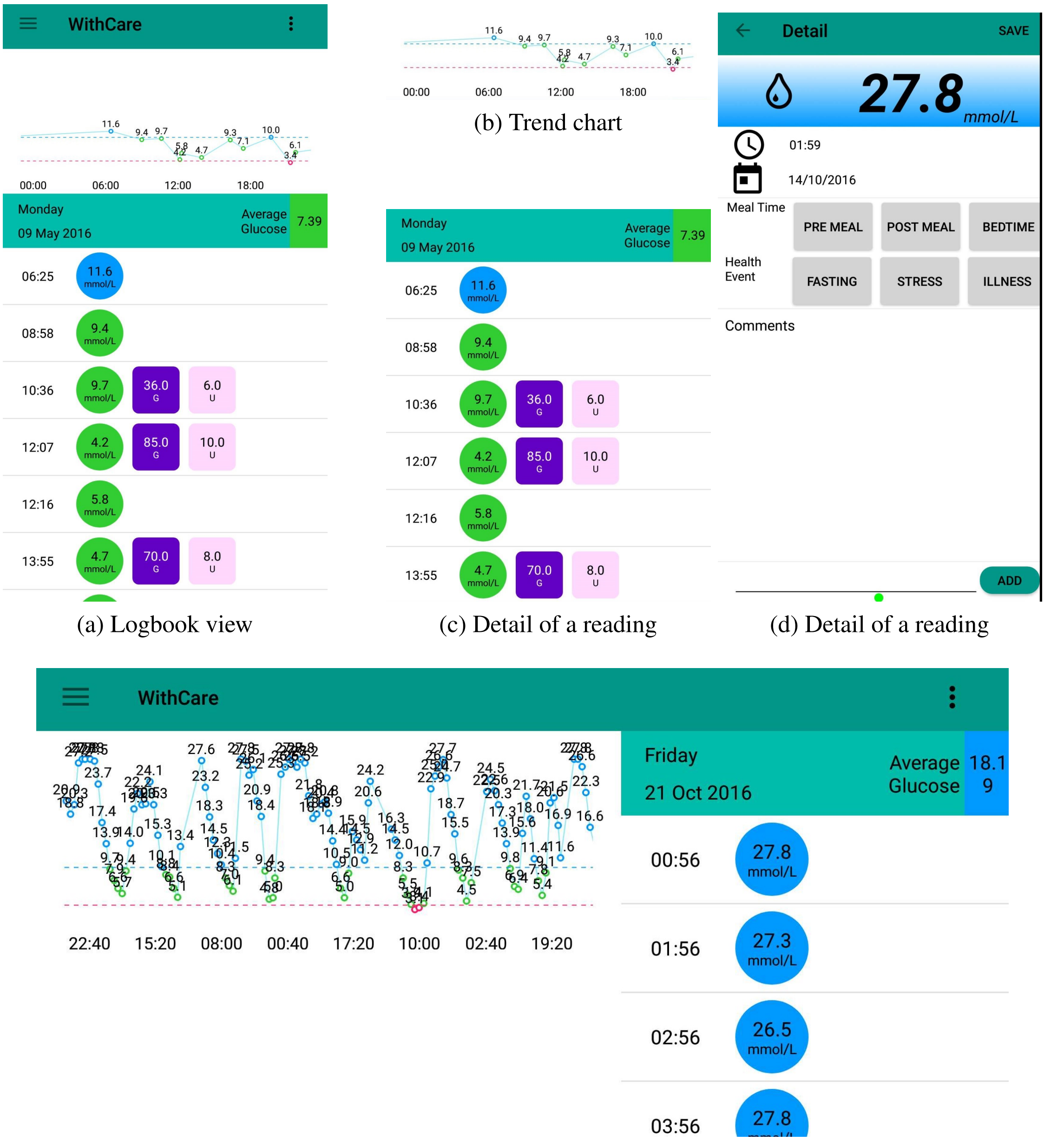
The WithCare++ Android application works as both acquisition and presentation layers in the WithCare++ System. The WithCare++ Android application can download data from user's glucose meters and activity trackers with the help of WithCare++ Widget. It also presents the data that processed by the Glucollector server to the patients and empower them with their diabetes management with the built-in features.

### Log book

The log book view allows the user to view their daily glucose trends. This view supports both data from a SMBG meter (Figure 4.13a) and CGM meter (Figure 4.13e) in both portrait and landscape modes which the former is suitable for phones and the latter is suitable for tablets. The top part (Figure 4.13b) of the screen shows a trend chart of the user's glucose. The user can zoom in or zoom out on the chart to see the full picture of their glucose level or focus on a period that is particularly interesting. The bottom (Figure 4.13c) of the screen shows the individual readings of the day that is being focused on the trend chart above. This allows the user to focus on a certain day and reviews all the glucose, carbohydrate intake and insulin injections on that day. By clicking on an individual reading, the user can view that reading in detail (Figure 4.13d). Users can modify their readings by adding tags and comments on those. This is particularly useful for patients who want to log more information while their meters do not support that. Those comments and tags can also assist the healthcare professionals with their diagnoses.

### 4.7.1 Uploading

The uploading view allows the user to upload their readings using WithCare++ Widget. The user need to pair their phone with the widget for the first time. After the WithCare++ Widget is paired and connected, uploading starts automatically. A dedicated background thread will instruct the WithCare++ Widget to scan for supported meter. If no meter is found after 3 minutes, a help view will pop up and guide the user to upload the readings. Should the user encounter any problem during the uploading, a diagnostic system will upload the corresponding logs to the server automatically for further debugging. During our pilot study, we found that not all users will report their technical problems. With the implemented



(a) Logbook view

(b) Trend chart

(c) Detail of a reading

(d) Detail of a reading

(e) Logbook in landscape mode with CGM data

Fig. 4.13 Logbook Views

diagnose system, we can identify the problem in the WithCare++ Widget and WithCare++ Android application.

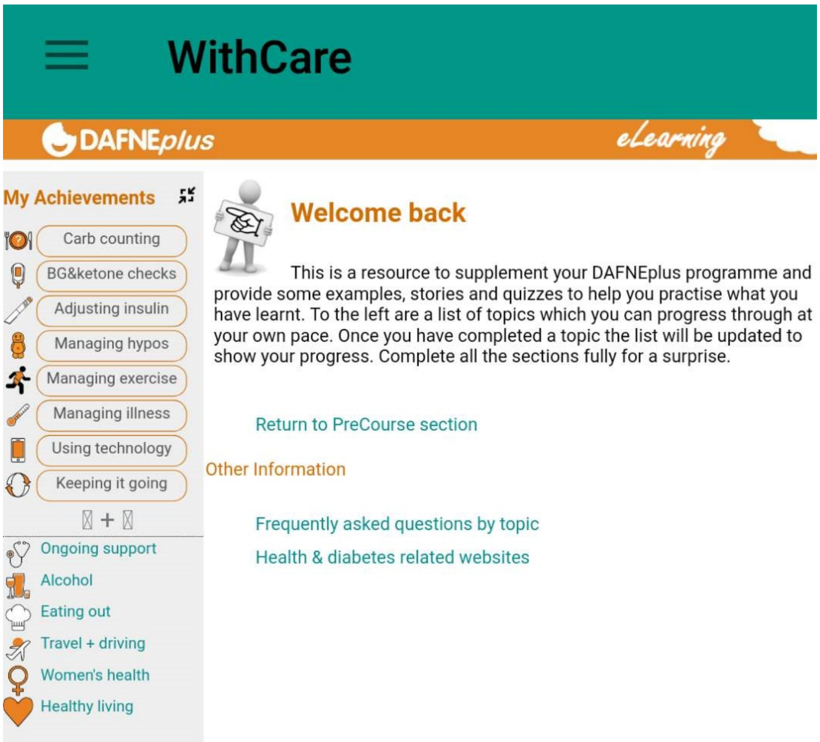



Fig. 4.14 DAFNEplus E-Learning

### 4.7.2 E-learning

We cooperated with DAFNEplus to provide the latest DAFNEplus curriculum to our patients. The DAFNEplus curriculum covers subjects including Carb counting, BG & Ketone checks, insulin adjustment, and management during exercise and illness. Users can also find help in topics of eating out, travelling or driving. Each topic also comes with a quiz that helps the educators to identify the problems that patients encountered during their study. Comparing to the conventional DAFNE course, we can also collect the usage statistics with users' consent and help the educator to improve their education materials with those statistics. As a data driven research platform, it is also possible to cooperate with other diabetes related courses and help the educators to evaluate their courses.


Fig. 4.15 Example of hypo case collection

### 4.7.3 Reviewing system

To make the most use of a tele-healthcare system, a reviewing system is implemented. This system allows the researcher to collect relevant data to develop their algorithms. In real life situation, it is very common that patients forget what they have done before hypo and hyper events especially when those events happened weeks before the clinic visit. With the implemented system, patients will be prompted with the reviewing system if specific event is detected. During our study, we implemented two questionnaires: hypo cases study and bolus cases study. The result of those questionnaires are used by researchers for further analysis. Comparing to the conventional paper based survey, this system allows the researchers to ask more patient specific and customised questions without arranging an interview. Every question and answer can be linked to specific reading or readings while paper based questionnaires can only ask about general questions.

### 4.7.4 Carb centre

Carb counting is one important skill for insulin therapy and one of the main topics in DAFNEplus. The Carb centre in WithCare++ Android App empowers the patients with their carb counting skill by providing carb information of a variety of dishes and images for portion reference. Patients can search their favourite food from more than 800 dishes, and save their favourite dishes and meals for further usage. The meal recorded in the carb centre are automatically linked to the carb readings recorded on the patients' log book. This system is implemented to reduce the burden of record keeping and encourage the patients to record their meal information. Comparing to the conventional glucose meters only, this facility provides the healthcare professionals with more information such as the fat, protein, glycemic index, etc. of the consumed food; which can affect the insulin sensitivity [92].

## 4.8 Usability test

### 4.8.1 Study design

A usability study was carried out the measure the usability and the acceptability for the WithCare++ Widget and the android App. This study was covered by the ethic approval obtained from the University of Sheffield. The methods used in the study is a mixture of quantitative and qualitative methods. The qualitative method involves recruiting volunteers to use the widget for two weeks, analysis their usage from the log, and collect their feedback. The quantitative method is comparing the usability of the WithCare++ Widget to the WithCare++ Box as a baseline which has achieved a score of 83.75 in the SUS. The metrics used in the qualitative methods to compare the two systems is shown as follows. The tasks in the metrics are the day to day tasks a user would normal do while using the system. The data were either collected from usages log or measured by the researcher. This study has been reviewed and approved by the Research Ethics Committee at the School of Health and Related Research (ScHARR) at the University of Sheffield.

Table 4.2 WithCare++ Widget Usability study qualitative metrics

| Measurement | source |
|---|---|
| % of patient upload readings | log |
| Number of attempts required to uploading a reading | log |
| Number of clicks required to upload readings | researcher |
| Number of clicks required to view readings | researcher |
| Number of clicks required to comment on readings | researcher |
| Number of clicks required to send feedback to clinicians | researcher |
| Number of clicks required to using carb centre | researcher |

Participants were recruited from the existing participants in WithCare++ Box pilot studies who has been familiar with the WithCare++ system. An email invitation were sent to the existing registered participants who have already given a formal consent before. In addition ,the participants must fulfil the following eligibility criteria:

- Participants inclusion criteria:
  - Adults ($\geq$18 years)
  - Participated in the WithCare++ Box study
  - Has a compatible device
- Subject exclusion criteria:

– Unable to provide informed consent

– Unable to communicate in written & verbal English

### 4.8.2 Qualitative analysis

Five participants were recruited from existing volunteers of the previous studies. To test the acceptability of the new device, no training session were given as they have already been familiarised with the system. WithCare++ Widget and a user manual was sent via mail. The results are either observed from the system log generated automatically by the WithCare++ Widget or WithCare++ App or from direct communication from the participants i.e. email, bug report. One of the 5 users was using a USB based meter and the others were using Accu-Chek expert meter which is an infrared based meter.

Four of the users managed to upload readings to our server with WithCare++ Widget while only one user is complaining about the WithCare++ Widget won't pair with their phone. After analysing the logs sent from the WithCare++ Widget , it appears that the WithCare++ Widget was paired for once and could not be discovered later. There was one user that was not able to power the WithCare++ Widget at the beginning, a USB on-the-go dongle was provided to solve this problem. In the future, we are considering providing a USB on-the-go dongle to every user, so they can power the widget with their phone. Due to the usb ports on both sides of the WithCare++ Widget , one female port for powering and one male port for downloading from USB meters, one user connected the devices in the wrong order. A user manual with more detailed instruction would be provided in the future. The most common problem encountered by our volunteers is the infrared based meter disconnected from the

WithCare++ Widget due to the loss of the line of sight especially during the first use. The WithCare++ Widget will download all the readings at the first attempt which would normally take about 1 minute. A firmware update was released remotely to the WithCare++ Widget to address this problem.

Among the four participants who successfully uploaded, three of them favour the WithCare++ Box over the WithCare++ Widget . Those three participants uploaded from home where the WithCare++ Box was already be set up. It saves the trouble from setting up the WithCare++ Widget every time. The participant who preferred the WithCare++ Widget uploads reading from workplace and prefer a device that is portable and low profile.

Table 4.3 WithCare++ Widget Usability study qualitative result

| Measurement | WithCare++ Widget | WithCare++ Box |
|---|---|---|
| % of patient upload readings | 80% | 97% |
| Number of attempts required to uploading a reading(average) | 1 | NA |
| Number of clicks required to upload readings | 2 | 0 |
| Number of clicks required to view readings | 0 | 1 |
| Number of clicks required to comment on readings | 1 | 2 |
| Number of clicks required to send feedback to clinicians | 2 | 2 |
| Number of clicks required to using carb centre | 2 | 2 |

### 4.8.3 Quantitative analysis

The quantitative analysis was carried out using the metric from 4.2. The metric consists of two main parts: measurements from the analysis of the log and measurements carried out by the author. The measurements from the analysis of the log measures the overall usage of WithCare++ Widget , while the measurements carried out by the author measures the simplicity of the WithCare++ Widget compared to the WithCare++ Box , i.e. how many clicks are required to perform certain task. The result of the analysis are shown in 4.3. The number of participants who successfully uploaded is calculated based on the number of enrolled participants including the ones who were withdrawn. Only 88% of the participants of WithCare++ Widget users successfully uploaded their readings compared to that 90% of WithCare++ Box users uploaded. This due to two reasons, the limited sample size of WithCare++ Widget study and all the participants of WithCare++ Box study have been attended a training session where they have been demonstrated how to use the device. In terms of the simplicity of the WithCare++ Widget system, it shows a similar result to the WithCare++ Box system. The usability of the WithCare++ Box system has been demonstrated in 3.6,3.7 and 3.8.

## 4.9 Conclusion

This chapter presents a smartphone based solution for WithCare++ tele-healthcare system. WithCare++ Mobile is an alternative for the WithCare++ Box. In chapter 3, we presented WithCare++ Box , a data acquisition device that has been used in two pilot studies by more than 80 patients. As data acquisition device, the WithCare++ Box has been tested for more than 2 years and proved itself as a reliable design for the acquisition layer of our WithCare++ tele-healcare system. However, the cost of the WithCare++ Box is about £90 which could be a problem when widely adopted. The WithCare++ Mobile is designed to be used as a low cost and portable solution for the acquisition layer.

The WithCare++ Mobile consists of the WithCare++ Widget and the WithCare++ Android App. WithCare++ Widget is a low cost data acquisition device that has the identical interfaces as the WithCare++ Box but only cost one tenth of the latter. One challenge faced while developing the WithCare++ Mobile system is the multi-meter support. Multi-meter support with single device is one key aspect of the WithCare++ tele-healthcare system. Systems such as Tidepool which only supports USB meters could limit the patients' options when choosing their glucose meter. Patients are potentially forced to stop using the system if they wanted to use a meter that is not supported. Systems support multiple meters which have different interface but uses different acquisition devices such as Diasend®could be confusing for patients. It is also becoming a challenge for the engineers to maintain multiple acquisition devices at the same time. WithCare++ Mobile can support three different interfaces that are widely used by popular glucose meters.

Comparing to the WithCare++ Box design, WithCare++ Mobile has the following challenges. Firstly, addition time in the round trip while downloading the readings. WithCare++ Box can directly access the glucose meters with its native interface support while the WithCare++ Android App has to use WithCare++ Widget as a bridge. Conventional Bluetooth bridge design host the meter driver on the smartphone [70]. This is sufficient for UART based meter because UART has a lower baud rate than Bluetooth. However, USB is a protocol that is much faster than Bluetooth. During our development, we found meters that will timeout due to the slow download speed. To solve this problem, we implemented the meter drivers on the

WithCare++ Widget to reduce the overall round trip time. By doing this, we were faced with another problem in the design. The WithCare++ Box is built upon a Linux based SOC. It has a 8GB SD card to host its programs and has internet connectivity to download the latest meter drivers where WithCare++ Widget is an ARM M3 based micro-controller which only has 128Kb memory and no internet connectivity. In order to support the same meters as the WithCare++ Box, we implement the OAD and program overlay that allows us to reprogram the WithCare++ Widget when needed.

In terms of the cost, the WithCare++ Widget only cost a fraction of the WithCare++ Box . The table 4.4 shows a comparison between the individual components used in these two devices. Arguably, the cost of WithCare++ Box can be reduced by further development. However, it is very unlikely the cost of WithCare++ Box will come close to anywhere near the cost of WithCare++ Widget .

Table 4.4 Cost of the WithCare++ Widget and WithCare++ Box

| WithCare++ Box | | WithCare++ Widget | |
|---|---|---|---|
| Raspberry Pi 3 Model B | £34.5 | SaBLE-x BLE Module | £8.78 |
| Adafruit PiTFT - 320x240 | £32.5 | Vinculum-II (VNC2) | £2.39 |
| Case | £10 | Flash memory | £0.267 |
| SD card | £6 | 3D printed case & PCB | < £3 |
| Power supply | £8 | | |
| Sum | £91 | | < £15 |

Patients from our pilots study mentioned that they would like to use a mobile phone app for further convenience. The WithCare++ Android App provides improved interfaces compared to the WithCare++ Box. It also adds another dimension of data to our acquisition layer by incorporating the activity trackers.

# Chapter 5

# Bolus Advisor Reviewing Tool

## 5.1 Introduction

Intense insulin therapy is recommended for Type 1 diabetes (T1D) management. Patients who have T1D cannot produce enough insulin due to the destruction of the beta cells. Intensive diabetes management can prevent or delay the development of comorbidities in T1D [93]. To control their blood glucose level, multiple daily injections (MDI) of insulin or subcutaneous insulin infusion (CSII) are required [94]. Patients who perform MDI in their daily management need to match their insulin injections with their carbohydrate (CHO) consumption and activities. Numeracy skill , good carb counting and activities estimation skills are essential to calculate the correct amount of an insulin dose [95]. Due to the complexity of the process, many patients do not follow and optimise their insulin regimens [96, 97]. To help patients with their insulin calculations, some manufacturers provide glucose meters and pumps with bolus calculation feature. Bolus calculators or bolus advisors assist patient with their calculation by automatically calculating the amount of insulin based on current glucose level, target glucose level and carbohydrate consumption.

Advanced bolus advisor also takes the activities, mental status and insulin-on-board (IOB) into account. Bolus advisor eases the process of bolus calculation which is both complex and time-consuming. A large randomised clinical trial has shown that the usage of bolus advisor can help patients achieve > 0.5% HbA1c reductions [98]. The correct use of a bolus advisor is also important. Bolus advisor relies on its setting such as insulin sensitivity factor (ISF), insulin-to-carbohydrate (ICR) ratio, etc.. to give correct recommendations. Healthcare professionals need to check the appropriateness of the settings on the bolus advisors and discuss with the patients how often they accept the bolus advice or override it.

The chapter presents a novel tool that helps healthcare professionals to examine the patients' adherence and their understanding for the reasons to override the bolus advisors' recommendations.

## 5.2 Literature review

Calculation of correct amount of insulin injection can be complex and time-consuming. Using an automatic bolus advisor can help patients reduce the burden of the intense insulin therapy. However, automatic bolus advisor cannot achieve optimal glycaemic control without carefully optimising the settings on the bolus advisor. Healthcare professionals need to work together with individual patients to figure out the optimised settings [98]. Bolus advisor can help patients to calculate the amount of bolus insulin. Bolus insulin, also known as quick acting (QA) insulin, lasts for 2-5 hours. Patients usually inject bolus insulin before a meal or when they are experiencing a hyperglycaemia. The bolus insulin consists of two parts : meal insulin and correction insulin [26].

$$Bolus\ insulin = Meal\ insulin + Correction\ insulin \tag{5.1}$$

where

$$\begin{aligned} Meal\ insulin &= \frac{CHO}{ICR} \\ Correction\ insulin &= \frac{Current\ BG - Target\ BG}{CF} \end{aligned} \tag{5.2}$$

Before each meal, patients need to match their meal insulin with their CHO using carbohydrate counting. Patients count their CHO in grams or as carbohydrate portions (CP). One CP usually equals to 10 grams. It is important that patients set the correct unit in their automatic bolus advisors. ICR represents how many CHO is needed when one unit of QA insulin is injected. Patients and healthcare professionals need to carefully optimise the ICR as it varies between individuals. Patients also need to practice their carbohydrate counting skill to ensure the correct amount of CHO is given to the bolus advisor.

It is also recommended that patients measure their blood glucose level before each meal. If a blood glucose is measured and is out of the target glucose level, patients need to correct their blood glucose level as well. If the patient's current blood glucose level is higher than their target blood glucose level, they need to inject additional insulin to correct their blood glucose level. If their blood glucose level is lower than their target , they need to reduce the amount of their meal insulin or intake extra CHO. Correction factor (CF) sometimes called insulin sensitivity factor (ISF) represents how much glucose level will drop when one unit insulin is injected. Similar to the ICR, patients and healthcare professional need to carefully adjust their CF value.

The above formula works for a single bolus injection. In real life, patients inject bolus insulin before each meal. As mentioned, bolus insulin can last for 2-5 hours. If patients try to perform a bolus correction while their last insulin injection is still active, they need to take IOB into consideration. IOB is the amount of active insulin remaining in patients' system since the previous injection. IOB is estimated by patients' specific duration of insulin action (DIA) and insulin kinetics [99]. There is a potential of insulin stacking if IOB is not included in the equation and insulin stacking can lead to a hypoglycemia. There isn't a standard equation to calculate IOB decay, both linear and non-linear decay are adopted by different bolus advisors. Companies choose their equation by IP considerations and competitive marketing [100]. Besides, the insulin decay model differs from bolus advisors to bolus advisors . By introducing IOB now the equation become :

$$Bolus\ insulin = Meal\ insulin + Correction\ insulin - IOB \tag{5.3}$$

Roche's method does not subtract the IOB if the patient has not measured their blood glucose prior to their injection. This can avoid insufficient insulin injection , however this can cause confusion to users if they are familiar with the IOB concept.

The insulin sensitivity can also be affected by patients' physiologic state (PS) which makes the calculation more complex. Events like physical activities can increase patients' insulin sensitivity while things such as illness will decrease patients' insulin sensitivity. With increased insulin sensitivity, patients usually reduce their total insulin by a PS factor (< 1) and vice versa. (minor 5.3)However, there is no research quantifying the PS, patients need to find a suitable value through trial-and-error. In [26], the equation which incorporates the PS is :

$$Bolus\ insulin = \frac{CHO}{ICR} + \frac{Current\ BG - Target\ BG}{CF} * PS - IOB \tag{5.4}$$

To make things even more complex, ICR and CF also vary during the day. Patients need to change their bolus advisor settings accordingly to achieve optimised results. Healthcare professionals and patients need to work together to revise their ICR, CF and PS settings regularly. Without using a fairly accurate settings, bolus advisor fails to work as intended, even sometimes giving false results.

Palerm et al.[101] proposed a run-to-run algorithm to determine the optimised ICR for the patients. This algorithm modifies current day's ICR based on previous day's ICR using the following equation.

$$v_{k+1} = v_k + K(\psi^r - \psi_k) \tag{5.5}$$

where $v_{k+1}$ is the ICR at day k+1, $v_k$ is the ICR at day k and $\psi^r$ is performance measure corresponding to the ideal postprandial response. The K is a gain determined using linear regression to best match the decision made by the healthcare professionals. In this algorithm, ICR is modified based on previous day's ICR. However, in real life situation, modification is usually made based on multiple days' result.

Herrero et al.[102] proposed an algorithm that combines the run-to-run algorithm and case based reasoning . They used case based reasoning to retrieve similar cases from previous days based on the time of the day, glucose level, CHO, activity and IOB. Every case has the ICR and CF used in the standard bolus advisor equation. Once the cases are retrieved, the distance between previous cases and the current case is calculated using a weighted average distance function. The case with minimal distance is used for current inquiry.

Stawiski et al.[103] utilised artificial neural network to estimate insulin sensitivity of children . This artificial neural network uses 13 inputs including BMI SDS, HbA1C, insulin, sex, age. This model achieved a median error of 0.6% and an $R^2$ = 0.66. Although this is not a direct implementation of a bolus advisor, it relatively solves the problem of finding the optimised insulin sensitivity which was determined by trial-and-error. However, this method does not address the issue that insulin sensitivity varies during the day.

Herrero et al.[104] proposed a run-to-run based algorithm to determine the optimised ICR that incorporates the intra-day variability. Comparing to Palerm's method where each "run" is one day, Herrero et al divided a day into three meals. Each meal has its corresponding ICR where in Palerm's method, one ICR is used throughout the day.

Torrent-Fontbona et al.[105] also utilises case based reasoning to find the optimised ICR . Comparing to Herrero et al.'s method, they use hour of the day, CHO, past and future physical activity to retrieve similar cases. The hour of the day is adjusted using a rounded value and the CHO is categorised into three levels (low, medium, high) based on the meal size. Instead of using the ICR from the most similar case, they use a weighted average of ICR of all similar cases. Their algorithm outperformed other state-of-the-art algorithms in in-silico test. All the proposed case based reasoning algorithms [102, 104, 105] require the usage of CGM to revise their new cases.

## 5.3 Bolus advisor in Roche Accu-Chek Aviva Expert

The outcome of using a bolus advisor depends on the manner in which it is used [26]. In DAFNEplus, the Roche Accu-Chek Expert is used as a primary meter. The design of a bolus advisor is often driven by IP considerations and competitive marketing [100]. It is important that both healthcare professionals and patients understand how the bolus is calculated in their devices. Same setting can yield different results in different bolus advisors.

### 5.3.1 Bolus advisor equation

The standard equation of bolus advisor is equation 5.1. However, in Accu-Chek Expert, the equation is written as [106]:

$$Bolus\ insulin = \begin{cases} Meal\ insulin + Correction\ insulin, & \text{if } Blood\ glucose\ is\ measured \\ Meal\ insulin, & \text{otherwise} \end{cases} \tag{5.6}$$

where

$$Correction\ Insulin = \frac{Current\ bG - Currently\ Allowed\ bG}{CF} \tag{5.7}$$

The bolus advisor in Accu-Chek Expert will ignore the correction insulin if glucose level is not presented even if IOB exists.

Furthermore, Roche's bolus advisor also utilises PS , however, their equation is different compared to equation 5.4

$$Bolus\ insulin = (\frac{CHO}{ICR} + \frac{Current\ bG - Currently\ Allowed\ bG}{CF}) * PS \tag{5.8}$$

There is no study showing which equation is better. It is important for healthcare professionals and patients understand how the PS modifier is applied to avoid over modifying.

Roche's bolus advisor incorporates the intra-day insulin sensitivity variability using time blocks. Time blocks allow the patients use different CF and ICR during the day based on the timestamp.

### 5.3.2 Insulin on board and covered blood glucose

The definition of insulin-on-board in Roche's bolus advisor is also different from the conventional definition. In conventional bolus advisor, the IOB is defined as the sum of correction insulin and meal insulin, while in Roche's bolus advisor , only correction insulin is considered as insulin on board. For example, if a patient who has 1:1 ICR consumes 6 grams of carbohydrate and injects 8 units of insulin, only the 2 extra units of insulin are considered as IOB.

Roche's bolus advisor uses the concept of covered blood glucose (coveredBg) instead of IOB. The coveredBg is calculated by the following rule. If the previous reading has glucose reading and the user followed the bolus advisor:

$$coveredBg = glucose\ reading - target\ value \tag{5.9}$$

If the previous reading does not have glucose reading or the user did not follow the bolus advisor:

$$coveredBg = (insulin\ injected - meal\ insulin) * CF \tag{5.10}$$

coveredBg is always equal or larger than 0.

In terms of currently allowed Bg decay, Roche's bolus advisor uses a linear decay mode with an offset. It introduces two variables in its settings: offset time and acting time. The offset time defines the duration before the currently allowed Bg starts to decay and the acting time defines the time that IOB will decay from 100% to 0%. Healthcare professionals and patients can determine those values with the help of devices such as CGM. If an insulin is injected before the previous insulin expires, the currently allowed Bg will stack (figure 5.1).

The most noticeable difference between Roche's bolus advisor and conventional bolus advisor is Roche's bolus advisor uses the covered blood glucose instead of IOB. All the IOB is converted to covered blood glucose in their bolus advisor. This makes no difference when the IOB does not cross time blocks because the conversion between IOB and covered blood glucose uses same CF. However, when the IOB lasts more than one time block, it works differently from conventional bolus advisor. The following is an example of how coveredBg and IOB changes overtime. In this setup, a virtual user injected 10 units of insulin at $T_0$. For the first 60 minutes the user has a CF of 4. After 60 minutes, the user is in another time block

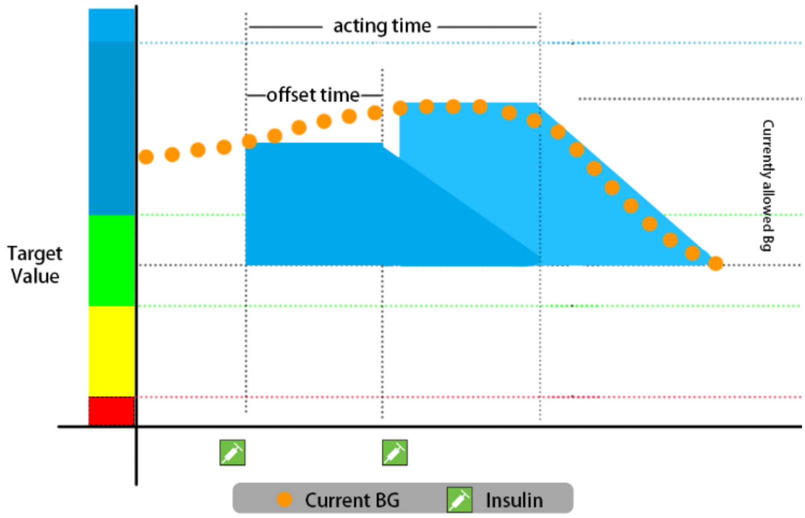



Fig. 5.1 Insulin Stacking

which has a CF of 2. We can see that the IOB of after 60 minutes is larger than the total amount the user has injected.

This behaviour is quite confusing for patients who use conventional bolus advisor. To our best knowledge, no research has been made to compare this model with conventional IOB model.

### 5.3.3 Meal rise and snack size

Roche's bolus advisor also introduces the concept of meal rise. Meal rise defines the allowed blood glucose level rise after the patient has intake of carbohydrate. The meal rise is a fixed variable which is not affected by the portion of the meal or the time of the meal. It should also be noticed that, Roche's bolus advisor uses meal rise regardless of the injected insulin for the meal which could lead to an insufficient insulin injection. Meal rise is also treated as a source of coveredBg, however, unlike coveredBg, it will not be stacked (figure5.3). If

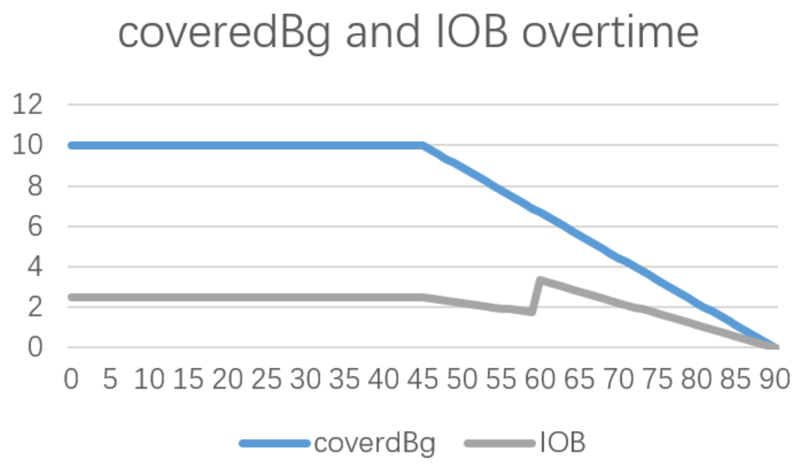



Fig. 5.2 IOB and coverd bg decay over time

patients have a new meal, the meal rise is restarted. In addition, it also introduces the concept of snack size. If the CHO is less than the snake size, the meal insulin is omitted.

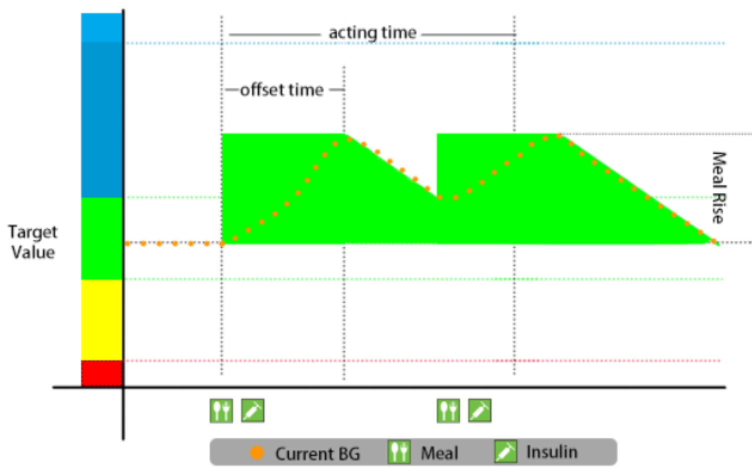



Fig. 5.3 Stacked meal rise

### 5.3.4 Currently allowed blood glucose

The Roche's bolus advisor uses currently allowed blood glucose value instead of IOB. The Currently Allowed Blood Glucose Value consists of three parts: mean target glucose value, meal rise and covered blood glucose [106].

$$\begin{aligned} Currently\ Allowed\ Blood\ Glucose\ Value = {} & Mean\ Target\ Glucose\ Value \\ & + Meal\ Rise \\ & + \sum Covered\ Blood\ Glucose \end{aligned} \tag{5.11}$$

Once the currently allowed blood glucose value is calculated, the final advised bolus is calculated with the following additional rules.

- if current bg is more than currently allowed bg, the correction bolus is $\frac{current\ bG - currently\ allowedbg}{CF}$
- if current bg is more than hypo warning limit and less than target range lower limit, the correction bolus is $\frac{current\ bG - target\ range\ average\ value}{CF}$ .
- if current bg is more than the target range upper limit and less than currently allowed bg, the correction bolus is 0.

## 5.4 Bolus advisor checker and reviewing tool

The standard bolus calculation is complex and time-consuming [107, 108]. However, automatic bolus advisors also require carefully optimised settings [26]. There are 14 different settings in Roche's bolus advisor , and there is not a standard regarding how those settings should be altered. Patients and healthcare professionals need to adjust the settings through trial-and-error approach. In Accu-Chek Aviva Expert meter, only the final recommendation of the bolus advisor is stored, the intermediate values such as meal insulin, correction insulin, covered bg and meal rise are discarded. This makes the review more difficult for patients and healthcare professionals to figure out which settings are inappropriate. Patients and healthcare professionals have to perform the same calculations as the bolus advisor which is unpractical and time-consuming in a real life consulting session. Both [26] and [98] emphasis the importance of an appropriate setting, however, there is not a tool that allows patients and healthcare professionals to review their settings. In addition, as outlined in [98] healthcare professionals need to understand when and why patients reject the recommendations from a bolus advisor.

DAFNEplus pilot and randomised controlled trial adopt Roche Accu-Chek Aviva Expert as their primary glucose meter. Hence, WithCare++ tele-healthcare implemented a bolus advisor checker to help both healthcare professionals and patients to review their bolus advisor settings more efficiently.

### 5.4.1 Implementation

We utilised the review system in section 4.7.3 to implement a bolus advisor reviewing system. We implemented the bolus advisor used in Roche Accu-Chek Aviva Expert according to their advanced user manual [106]. Once the data is uploaded via the WithCare++ front end devices, a background service on the Glucollector server will process all the readings automatically. (Minr 5.9)The record of insulin inject in patients uploaded data will trigger

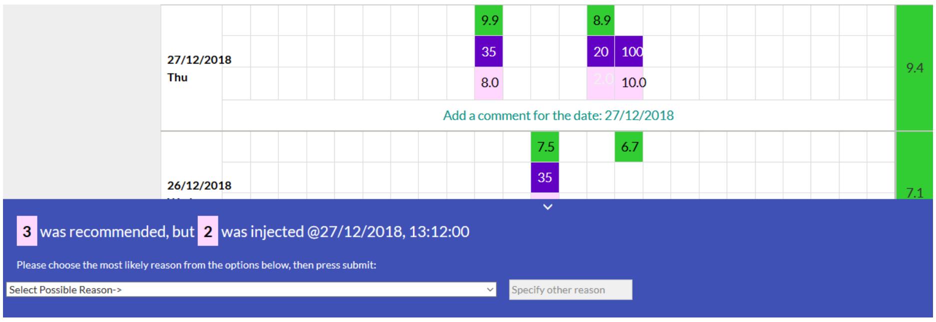



Fig. 5.4 Bolus advisor review system

the calculator to generate a corresponding insulin recommendation. If there is a discrepancy between our insulin recommendation and patients' insulin record, the reviewing system shown in figure 5.4 will prompt the patient to review their insulin injection decision and ask them about the reason for overriding the advice from the meter.

If the user injects insulin more than the recommended value, the reasons cloud be:

- I followed the bolus advisor
- Decreased physical activity
- High fat meal
- Meter keeps advising too little quick acting insulin, but unsure how to change the settings
- Other(specify)

On the other hand, if the user injects insulin more than the recommended value, the reasons cloud be :

- I followed the bolus advisor

- Increased physical activity (and did not use exercise setting)
- Drinking alcohol
- Recent hypo so being cautious
- Meter keeps advising too much quick acting insulin causing hypos, but unsure how to change the settings
- Other(specify)

Patients can select their reasons for overriding the recommendation. Those reasons are stored in the Glucollector database and healthcare professionals can use these information to help patients to improve their understanding of insulin calculation, optimise the settings in their bolus advisors and improve their confidence in using bolus advisors. In addition, all the intermediate values are displayed (figure 5.5) in our system. Healthcare professionals and patients can review the detail of each bolus recommendation, identify which part of their setting is inappropriate and adjust their settings based on those details. All those details are not stored in the meter, our system shows those important information and save the healthcare professionals and patients' time to perform the complex calculations.

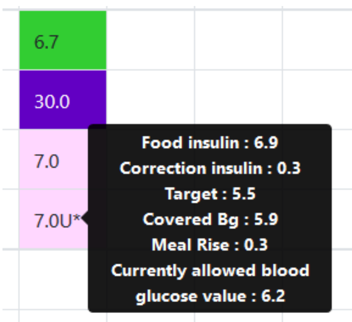



Fig. 5.5 Bolus advisor result detail

### 5.4.2 Verification

Our implementation of the Roche's bolus advisor is based on the document provided by Roche. It is important for us to verify our implementation because there could be a discrepancy between our implementation and the implementation in Roche's glucose meters. Even Roche had a recall of their bolus advisor due to software bug [109, 110]. This also implies the lack of a rigorous method to validate a bolus advisor. Faulty bolus advisors that contain software bugs could be released to the market even under FDA's supervision.

In order to verify our implementation, we use the Roche's bolus advisor with control solution to create different scenarios such as: normal use, stacking insulin, stacking meal, overriding recommendation in previous injections. Once all our results matched the results from the Roche's bolus advisor , we released the bolus advisor review system to the patients. The patient can select the "I followed the bolus advisor" option when they followed the advisor but our system recognised otherwise. During our verification, we found two major issues caused by our misinterpretation of Roche's document.

- IOB and currently allowed blood glucose value

  In the Accu-Chek Aviva Expert's bolus advisor, the IOB is displayed. However, the IOB is never used in their algorithm. All the IOBs are converted into currently allowed blood glucose values (section 5.3.4) and used during the calculation. This was misleading at the beginning of our implementation and confusing to the patients. There won't be a discrepancy if two tests are done in the time blocks using same CF and ICR, which makes spotting the bug difficult.

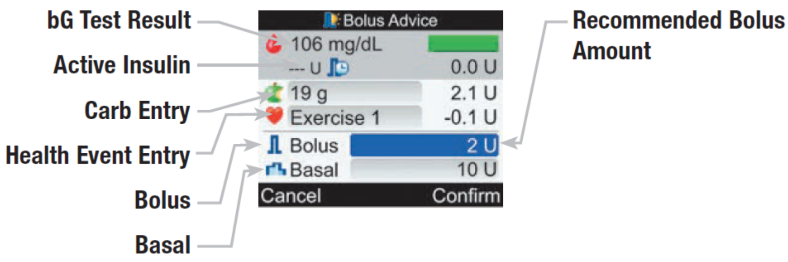



Fig. 5.6 Bolus advisor showing active insulin instead of currently allowed blood glucose value

- Meal Rise

  According to[106], meal rise is defined as "During or after meals, an increase in blood glucose levels is considered normal, or "allowed," within a certain range, even though a meal bolus has been delivered. A meal rise is in effect for a specified time period." We assumed the meal rise is only added after an insulin is injected for the meal. However, in Roche's bolus advisor the meal rise is added regardless whether an insulin has been administered for this meal. This is confusing to the patients, sometime they will find the bolus advisor suggest less amount of insulin even though them haven't inject any insulin within the past 5 hours.

There isn't a detailed guide of how to optimise all the settings. Healthcare professionals and patients who do not have a deep understanding of how Roche's bolus advisor works could make poor decision on those settings.

### 5.4.3 Study design

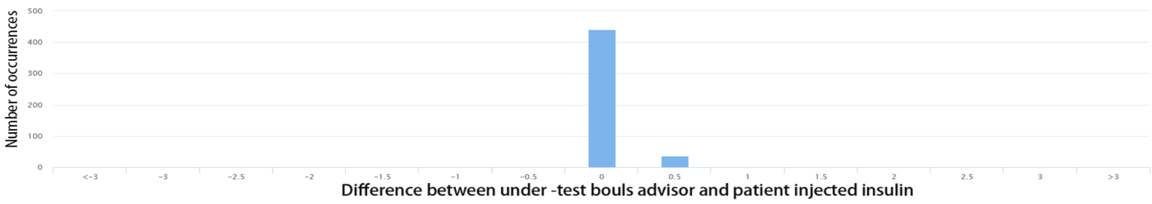
Participants from pilot study (section 3.6) and DAFNE graduate study (section 3.7) were emailed the details of the bolus advisor checking tool. The use of the tool are voluntary.

The bolus advisor checker was running in the background and the results were visible to the patients who have given the formal consent from studies in section 3.6 and 3.7 only. This study has been covered by ethical approval granted by the Research Ethics Committee at the School of Health and Related Research (ScHARR) at the University of Sheffield. All the responses are stored in the glucollector server securely.

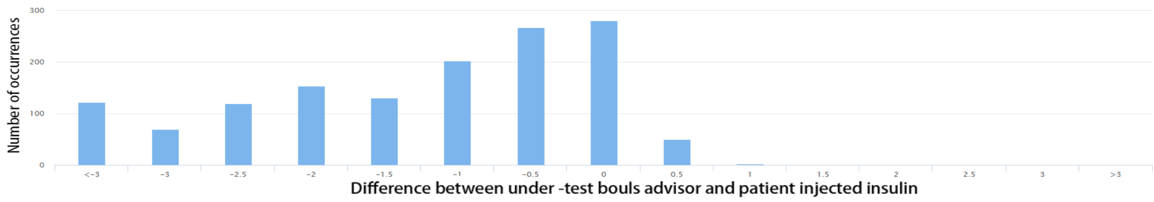
### 5.4.4 Results

We analysed the data collected by our WithCare++ tele-healthcare system. The 63 patients in our system use Accu-Chek Aviva Expert meter with 370 different bolus advisor settings. There are 5 patients who never changed their bolus advisor settings. Only 18 patients update their bolus advisor settings every 3 months. Most of the modifications are made to ICR and CF as well as the time blocks. Only very few patients made modification on their exercise settings. None of our patients have modified the snack size.

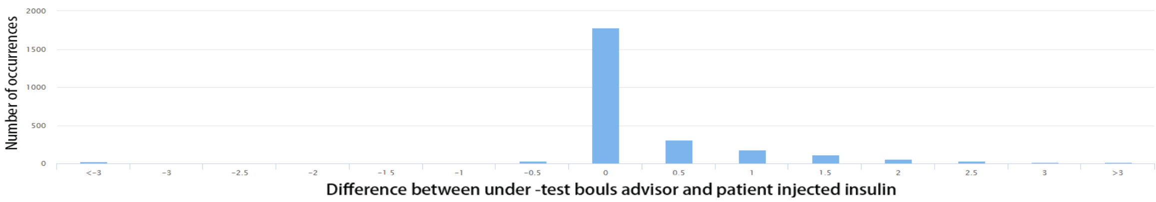
In total, 24439 insulin administration made by the patients. In which, there are 1404 cases where users rejected the recommendation from bolus advisor. With further inspection, we found one patient has rejected the recommendation 658 times, this user is excluded from our checker as clearly they do not use the bolus advisor on the device. This also exposes a problem that the bolus advisor on Accu-Chek Aviva Expert does not record whether a recommendation is accepted or not. It is difficult to check patients' adherences with the features provided by the meters. Another problem we encountered is the bolus advisor only stores the latest settings. If the patient do not upload their current setting before modifying it, we can no longer retrieve the settings they used. We recommended to our volunteers to upload their settings before and after they make a modification to their bolus advisor settings. With the implemented bolus advisor checker, histograms are generated for individual patient. Healthcare professionals can customise the duration of the data to show the histogram of a specific period. The following histograms (figure 5.7) contain three different examples of patients' adherence. The x-axis is the difference between the patient injected insulin amount and the amount that is recommanded by the bolus advisor. The y-axis the number of occurrences of those discrepancies happened. The middle bar of the histogram is the value zero which the patients followed the advise from the bolus advisor. To the left of the middle bar is where the patient injects more than recommanded value and versa vice. The figure 5.7a is an example of good adherence where most of the insulin injections are identical to the recommended value. On the other hand, the figure 5.7b shows that this patient tended to inject more insulin than the recommended value. Healthcare professionals need to review this patient's readings to check if this patient has frequent hypoglycemia. The figure 5.7c shows a patient who follows most of the recommendations, but overrides them from time to time by injecting smaller dose than the recommendations. The patients could made this kind of decision due to the fear of hypo or the exercise settings are not suitable for them. After the bolus advisor reviewing tool was released, our patients used this tool voluntarily. We collected 172 cases from 11 patients since the tool was released. There 111 cases where user selected the pre-define answers, the rest are answered with free text. The most common reason for overwriting a bolus advisor recommendation is activities related including either increased of decreased activities. The Roche's bolus advisor provides




(a) Good adherence




(b) Poor adherence




(c) Good adherence with few adjustments

Fig. 5.7 Interfaces for patients to review their diabetes data

two settings for different level of exercises. It allows the user to set a modifier from -50% to 50%. But it requires at least 6 clicks so that a user can alter the value for the modifier. Patients tend to directly override the insulin recommendation instead of changing the settings. Activities work similar to carbohydrate, patients also need to estimate their activities. Unlike carbohydrate which has dedicated course for carb counting such as DAFNEplus, there aren't many courses that teach patients how to 'count' their activities. A system that incorporates activity tracker could help patients to estimate their activities more accurately.

There are 9% of the cases related to meals such as high fat meal and alcohol. The Roche's bolus advisor does not incorporate meal information. According to the DAFNEplus course, both fat and alcohol will affect the insulin sensitivity. Patients also reject the bolus advisor recommendation due to recent hypos to avoid repetitive hypos. The Roche's bolus advisor does not consider this and always uses the mean target value to adjust insulin dose. It would be helpful if the bolus advisor allows the patients to choose which target is used to adjust the insulin dose.

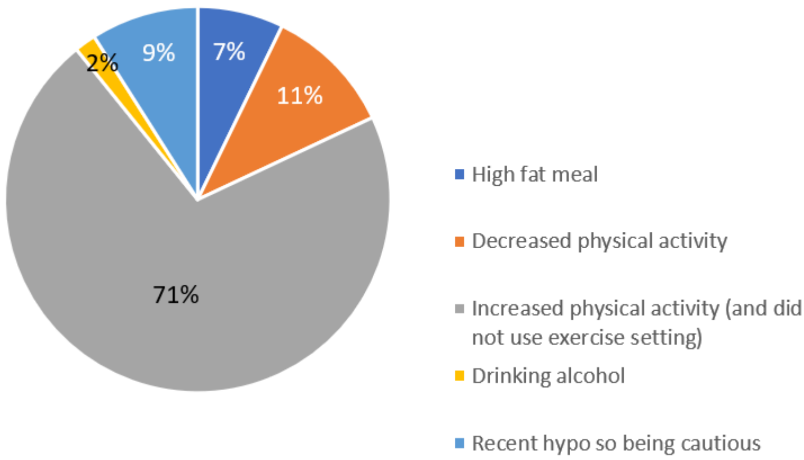



Fig. 5.8 Reasons for bolus advisor recommendation overwrite

Our review system also allows patients to enter free text reasons. One common reason they put was "I cannot remember". It is very common that patients forget the reason they made certain decision. Our system can prompt them to record their decision and providing the healthcare professionals more information during patients' next visit. Patients also mentioned had "Only a snack but meter thought it was in the evening meal time frame". Roche's bolus advisor uses time blocks to determine the ICR for the meal. However, patients usually found their time block setting was not always fit for their living pattern. Especially Roche's bolus advisor only have one setting, it would be more helpful if patients can set different settings for weekdays and weekends. It shows that Roche's bolus advisor cannot cooperate with snack that greater than snack size, patients want to use different ICR setting for snack and meal. The limit on the modifier is also a reason that patients reject the recommendation. The Roche's bolus advisor only allows a maximum of 50% reduction on insulin while some heavy activities requires more than that.

## 5.5 Conclusion

Bolus advisor has proven useful for diabetes management. To make the best use of a bolus advisor, it is recommanded that patients and healthcare professionals regularly review the settings on the bolus advisor [98]. Currently, the reviewing and optimisation of the bolus advisor settings is inefficient, time-consuming and cumbersome. Researchers utilise CGM and design case based reasoning algorithm to determine an optimised ICR for the conventional bolus advisors [102, 104, 105]. Comparing to conventional bolus advisor, Roche's bolus advisor has more variables in its settings and more complex rules are required. In addition to ICR, parameters such as PS, IOB, offset time, acting time, and snack size are used in commercial bolus advisors. WithCare++ , data-driven tele-healthcare and a research system, integrated the Bolus advisor reviewing tool for Accu-Chek Aviva Expert meter's bolus advisor.

A study has shown that hypoglycemia unawareness is associated with reduced adherence [97]. A patient usually makes three to four insulin injections per day. It is very time-consuming for healthcare professionals to analyse patients' adherence without an aiding tool. With the help of WithCare++ tele-healthcare system, we developed a bolus advisor checker for the healthcare professionals to examine patients' adherence.

It is recommended by [98] and [26] that healthcare professionals monitor patient's therapy persistently and discuss with patients how often they override a bolus advice. We implemented a bolus advisor reviewing tool that prompts patients with a quick questionnaire when they override a bolus advice. This tool helps our data-driven system collect essential features for future modelling.

Accu-Chek Aviva Expert meter is the primary glucose meter used in DAFNEplus randomised clinic trial. However, the usage of its bolus advisor lacks a structured analysis. WithCare++ tele-healthcare can help the healthcare professional to collect the usage of bolus advisor by collecting bolus advisor settings with WithCare++ tele-healthcare front end devices. To the best of our knowledge , no research has collected this information to analyse the usage of bolus advisor. Accu-Chek Aviva Expert meter's bolus advisor uses 13 different settings in their system. Without carefully studying their implementation, it is difficult to interpret the recommendation of the bolus advisor and make adjustment accordingly. Due to the limitation of bolus advisor, important intermediate values such as meal insulin, correction insulin, and IOB are discarded after calculation. We implemented the bolus advisor used in the Accu-Chek Aviva Expert meter to recover those values to be used as a reference by the patients and healthcare professionals when reviewing their bolus advisor settings.

# Chapter 6

# Conclusions and Future Work

## 6.1 Summary and conclusion

This thesis presented a novel tele-healthcare and data-driven system for Type 1 diabetes. To design and develop a tele-healthcare system which will be adopted by clinical trial, we combined of the agile design approach and the minimum viable product design approach was used to enable fast product design iterations. Formal questionnaire and focus group with semi-structured interview were used to improve the usability of the system that can cover different types of population. To design a scalable and maintainable system, The development process was divided into two phases, where only the healthcare professionals were involved in the first phase dealing with the initial design process and in the second phase patients' feedback was sought after the minimum viable product was prototyped. By doing this, responses were collected from both healthcare professionals and patients while avoiding disappointment among patients with technical problems in the early prototypes. The agile design approach is widely used in the software development. In this thesis, we applied the same approach in front-end device development. Remote update and diagnosis features are embedded in the front-end devices allowing the agile design approach to be applied. This system has been used by two pilot studies and will be used in the DAFNEplus large randomised clinical trial in 2019. To cope with the trial, 300 devices were assembled in the University of Sheffield for the intervention group. The front-end devices have been used by patients for more than two years without encountering any technical problems which requires a home visit or replacement. During the two years usage, more than 20 updates have been released remotely. This system has proved to be user-friendly and reliable .

With the recent advances in consumer electronics, smartphones have shown potential to be useful for type-1 diabetes management. Based on the success of the pilot trial of the WithCare++ box, we expanded our front-end devices with a mobile phone based solution. In the previous researches and commercial products, mobile phone based solutions tended to only support one type of glucose meter or one interface only. We utilised program overlay and OAD in our design to allow the WithCare++ Widget to work with three different interfaces and multiple meters. The WithCare++ widget has the same functionality as the WithCare++ Box with only fraction of the cost.

WithCare++ tele-healthcare system is a data-driven research platform. In our system, common features such as glucose, insulin and carbohydrate are collected. In addition, we also collected features which have not been seen in other systems such as activities and bolus advisor (BA) settings. With the additional collected data, this thesis presents a set of tools that enables the analysis of bolus advisor usage. A bolus advisor checker was developed to help healthcare professionals check patients' adherence and collect reasons of why patients reject the advice.This tool was designed to help both patients and healthcare professionals understand the result of bolus advisor better and provide knowledge to develop next generation bolus advisor.

## 6.2 Recommendations for future work

Future work could focus on the following aspects:

The WithCare++ box has been tested by more than 80 patients for more than 2 years in three different centres in the UK. This system was supported by three engineers and one help desk during the pilot study. In 2019, the system will be used in a large randomised clinical trial. This trial will recruit more than 600 patients from 14 centres. Detailed analysis could be made on the performance of the system under heavy load. In addition, the current WithCare++ Box costs around £90. Further development could be made to reduce the cost of the device without compromising its functions.

The WithCare++ widget has been tested by few users. In the future, the Android app could be ported to iOS platform and tested by more users. In our early tests, some volunteers were confused by the instruction. A detailed instruction could be made to help patients use the device. Additional drivers need to be developed for multi-meters support.

WithCare++ tele-healthcare system has provided a platform for optimising patient's bolus advisor. With the addition data we gathered such as heart rate and activities, future works could focus on developing an automated data-driven algorithm for optimising Roche's bolus advisor settings which is used in the DAFNEplus randomised clinical trial.

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# Appendix A

# WithCare++ Box User Manual

DAFNE plus

Dose Adjustment For Normal Eating

WithCare+

## Instructions for use

Version 1.0 May 2016
(Initial user testing)

If you are having any problems with your device initially contact Gemma who will kindly book a call-back from one of the team.

**g.hackney@sheffield.ac.uk Tel: 0114 222 4320**

Department of Electrical & Electronic Engineering
The University of Sheffield
Mappin Street
S1 3JD

# Installation


Connect the WithCare+ unit using the power supply provided. It requires 5V @ 2A. Wait about 60 seconds for the device to start up

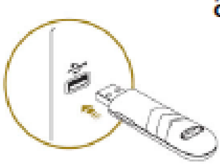
Press the “cog” icon or “configure internet” and choose your connection type:

**WiFi Connection (most users):** Press on the WiFi icon, a list of compatible routers will be displayed. Locate your router and press to select it. This box connects using “WPS”, if your router supports this there will be a button on it (symbols below). Press it within approx. 30 secs. The screen shows status.

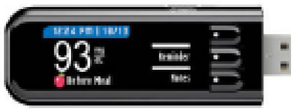

**Ethernet connector (alternative):** This connector allows direct connection to your home router (“broadband”) using an “RJ45” Ethernet cable. Connect with the ‘ethernet’ cable supplied – press on the Ethernet icon. The screen will report on success or failure.

# Connecting Your Meter

Simply plug any of the following meters into any USB connection on the WithCare box.



**Freestyle Optium Neo**



**Contour Next USB or Link**

**AccuChek Mobile**

For the following **AccuChek Aviva** meters please connect the **SmartPix** interface to WithCare first and place behind meter..

**Expert**

**Nano**

**Combo**

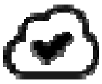
If the meter doesn't immediately detect a computer connection you should follow the manufacturer's instructions for sending data to a computer. Typically this is pressing the on-button and occasionally selecting 'send data' from the menu.

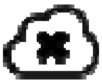
The process of transferring data is automatic, the box may ask you to press on your name to confirm it has the correct person associated with the meter.

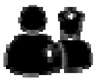
The screen will indicate success or failure.

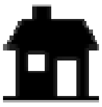
# Synchronising Data

There are a number of icons on the top of the home screen to aid diagnosing any connection issues:

 In contact with our server all is well

 Not connected

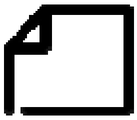
 The box is in clinic mode (for multiple users)

 The box is in home mode (just for you!)

The box keeps a local copy of your data so if it doesn't immediately connect don't worry you can even power it off and next time it connects to the server it will automatically send the data.

The process is automatic and a message will be displayed indicating successful or failed transfer.

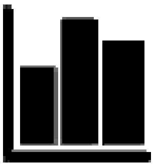
If you have a persistent problem or are concerned please contact us so we can help



# Reviewing Results

The WithCare box provides a limited display of the recent results: Click on the history icon (above to access)

Trend graph showing latest week / fortnight / month / quarterly results.



Bar graph showing number readings categorised as hypo-, normal or hyper-glycaemic.


Much more detailed analysis and visualisation of the results is available on the supporting secure website

**https://red.shef.ac.uk/**

If you don't have login details please see the registration section of this guide.

# Appendix B

# WithCare++ Widget User Manual

DAFNE plus

WithCare+ Widget

Instructions for use

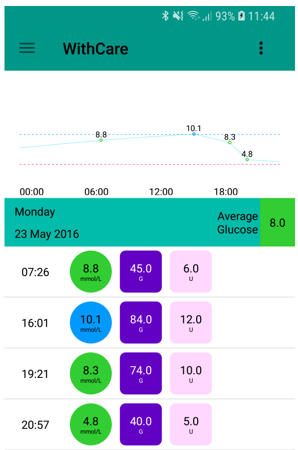
Version 1 May 2018

https://red.shef.ac.uk/

### Installing the App


We have written an app for Android smartphones, this is in the google App store but is limited to only registered users. To be able to download the app you'll need to let us know your google email, so we can send you an invitation. This invite will let you download and install the app from the google App store (its free). Once the app is installed you'll be asked to login, you need to use your registered glucollector login details (those for red.shef.ac.uk). If you have difficulty logging in please contact our Helpdesk (details at end of these instructions). After several seconds the app should sign you in to our server so you can access your data.

### Logbook view



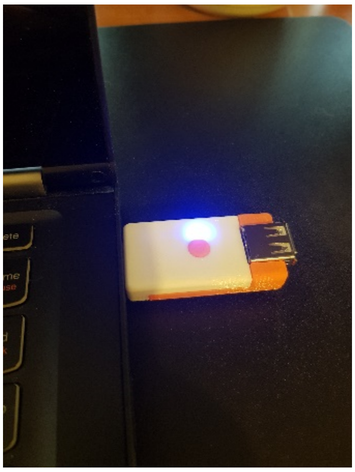

Once the app has synchronized your data with our server it displays both a tabular and graphical view of your readings. This response to finger swipes and pinches to scroll and zoom to change the view to view different days and periods.

The logbook view uses the same colour coding as on the glucollector and is intended as a quick and convenient reference and electronic log book for your data.

If you tap on a reading you can add in your own comment to aid later review.

**Power your widget**

The widget is used to transfer data from a supported glucose meter to your phone. It uses secure wireless transmission to the phone. Only a few glucose meters are supported at present. Some of these use infra-red communication and others need to be connected to the USB port on the widget. The widget needs to be connected to a power source in order to work. It uses a standard "USB" connector for powering itself. It may be connected to any standard USB charger or USB port on a device in order to work.



(a) Desktop or laptop computer

(b) Phone with USB on-the-go (OTG) adaptor

(c) A phone / tablet charger

After connect to a power source, the indicator on the widget will glow BLUE. If the indicator is RED then there is a problem with the device, please contact the Helpdesk to let us know, so we can help.

### Connecting your meter

If you are using a USB meter, connect the meter to the USB port on the widget using the cable supplied by the manufacturer (typically a micro-USB cable) and that is this step completed. The remainder of this section describes how to connect an infra-red communicating meter such as the AccuChek Aviva Expert.

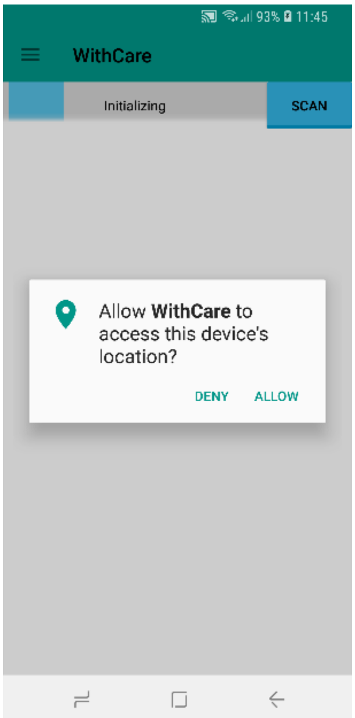
The first step is to align the meter's IR sensor (at the top above the Accu-Chek writing) with the widget's IR sensor next to the (unused) usb connector. The devices should be spaced a few centimetres apart.

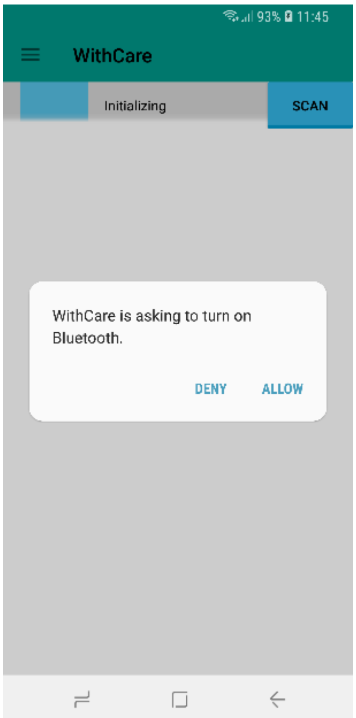
Press the power button on the Expert meter and then select "MyData" on the menu followed by "Data Transfer" the meter display should then indicate transferring data.

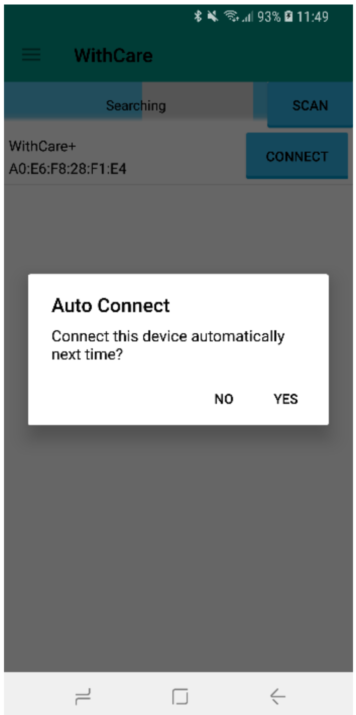
The next step is to request that the App starts downloading data and this needs to be started within 30 seconds or so otherwise the meter will automatically power off.

### Connect your phone to the widget

If the Withcare app is not already running then start it and login after which you will reach the logbook view. Click the menu icon ≡ located at the top left corner of the screen. A menu will appear from which you need to select "Upload". The operating system may prompt you to give "location permission" this is needed to allow us to turn on Bluetooth; We don't use or store your location, it is to get the country which is need as part of the permission to enable Bluetooth. You may also be prompted to turn on Bluetooth again please answer yes.



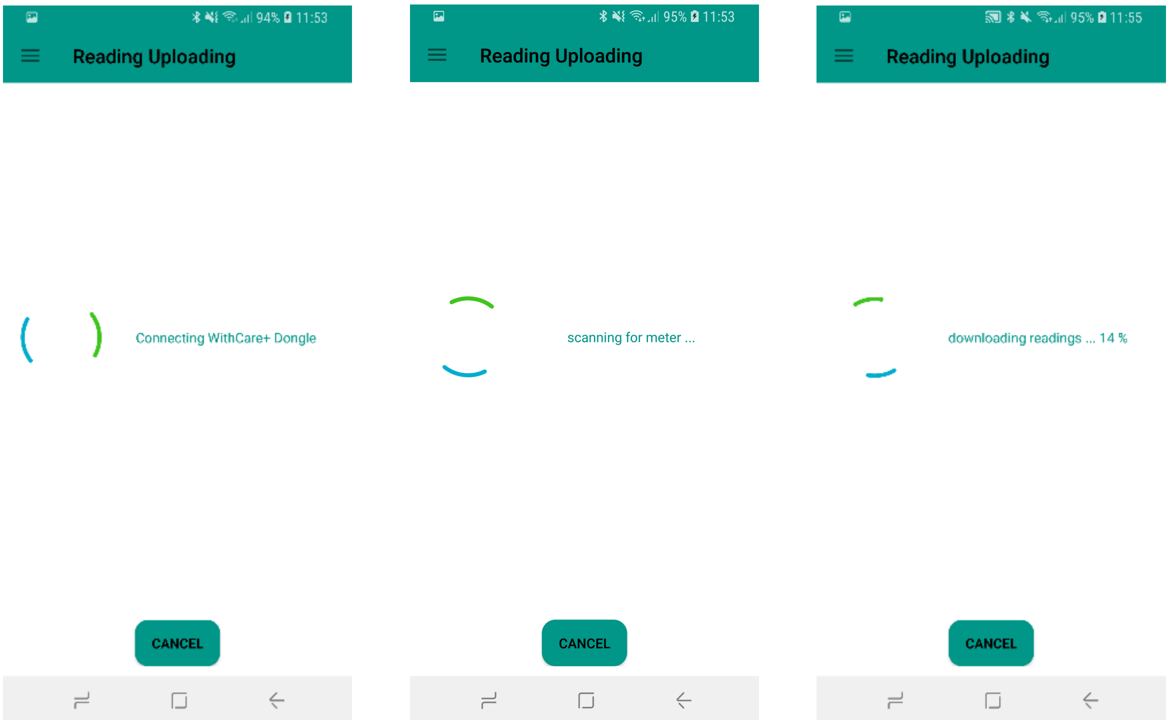




After several seconds of scanning the phone should detect the widget and display "Withcare+" and its ID. Please click on CONNECT and all being well the phone will connect to the widget then prompt if you wish Auto Connect in the future, the answer to this is yes so you won't be bothered with this step in the future. If it didn't connect try disconnecting and reconnecting the power to the widget. If the problem persists please contact the Helpdesk.

### Start uploading

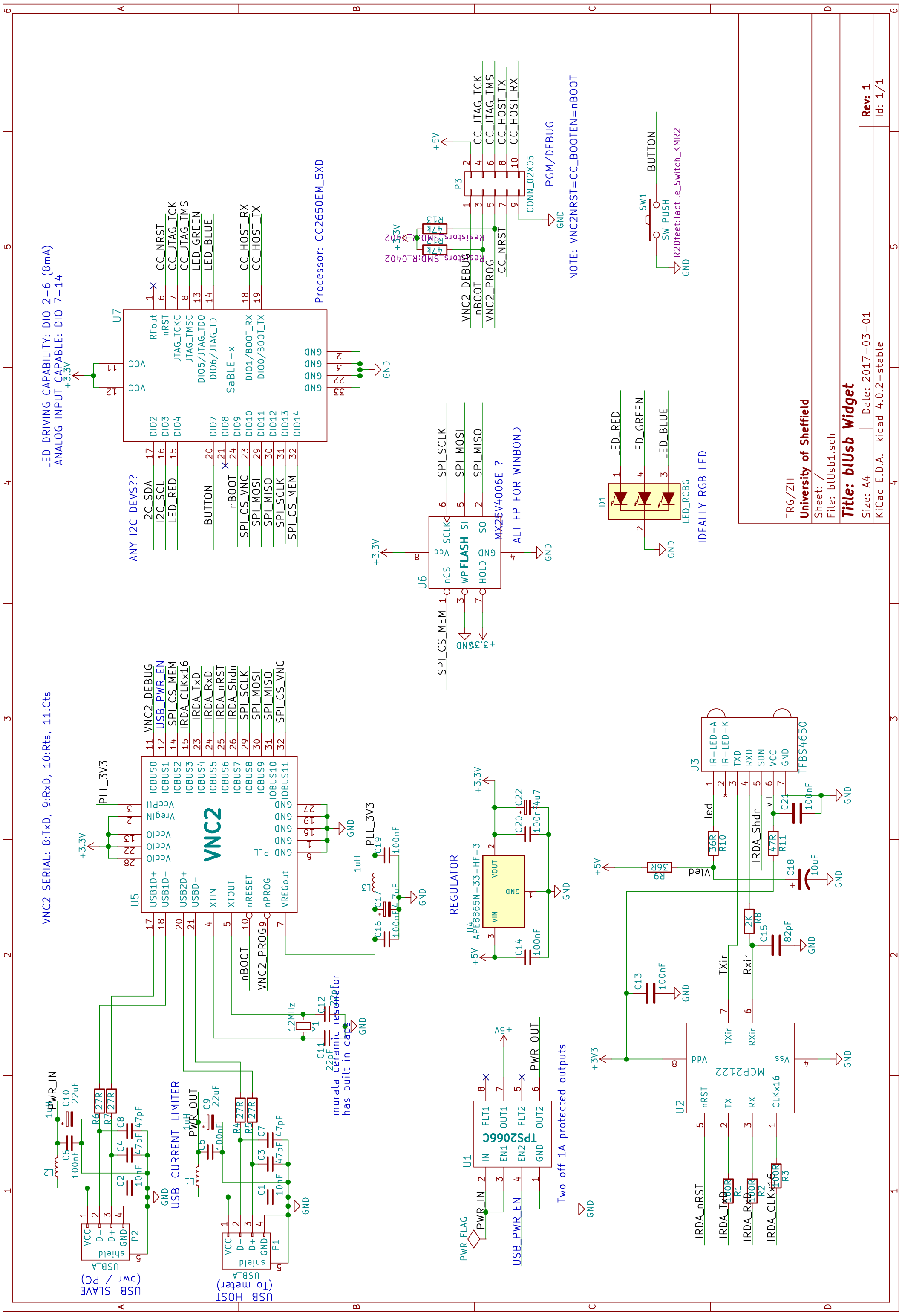
With the meter connected to the widget and the widget connected to your phone you can now start uploading. This is done from the ≡ icon by selecting "Upload" from the drop-down menu. Make sure you have your meter by your side. Click the 'connect' button to start upload. The phone will try to connect to the widget, if it failed at the stage, or stuck at this stage for more than 20 seconds, click cancel and power cycle the widget. The indicator on the widget will turn GREEN when connected.




Now the App will read and upload the readings from your meter to our server. Do not move/disconnect your meter during this process. It will take 1—2 minutes and will take less time after the first uploading if you regularly upload.

# Appendix C

# WithCare++ Widget Hardware Diagram


TRG/ZH
University of Sheffield
Sheet: /
File: blUsb1.sch
Title: blUsb Widget
Size: A4
Date: 2017-03-01
KiCad E.D.A. kicad 4.0.2-stable
Rev: 1
Id: 1/1

# Appendix D

# Home Internet Access Questionnaire

# Home Internet Access Questionnaire

Which type of diabetes do you have

- ○ Type 1 Diabetes
- ○ Type 2 Diabetes
- ○ Other
- ○ Not known

Have you attended a structured education course

- ☐ DAFNE
- ☐ DESMOND
- ☐ OTHER
- ☐ NONE

Do you have a desktop computer at home?

- ☐ Windows PC
- ☐ Apple MAC
- ☐ Other
- ☐ NO

Do you have a tablet computer at home?

- ☐ Apple iPAD
- ☐ Android Tablet
- ☐ Other
- ☐ No

Do you have a smart phone?

- ☐ Apple iPhone
- ☐ Android Phone
- ☐ Other
- ☐ No

Do you have access to the internet at home?

- ☐ Wired Broadband(router+phoneline)
- ☐ Mobile Data(3G/4G)
- ☐ Wireless WiFi
- ☐ Not Known
- ☐ No Access

If it was simple to do, secure,(and free) would you be willing to send blood glucose data from home to your healthcare professional so that they could review it?

- ○ Yes Definitly
- ○ Possibly
- ○ Not sure
- ○ Unlikely
- ○ Definitely Not

Do you have a desktop computer at home?

- ☐ Windows PC
- ☐ Apple MAC
- ☐ Other
- ☐ No

Make

Model

Do you have a tablet computer at home

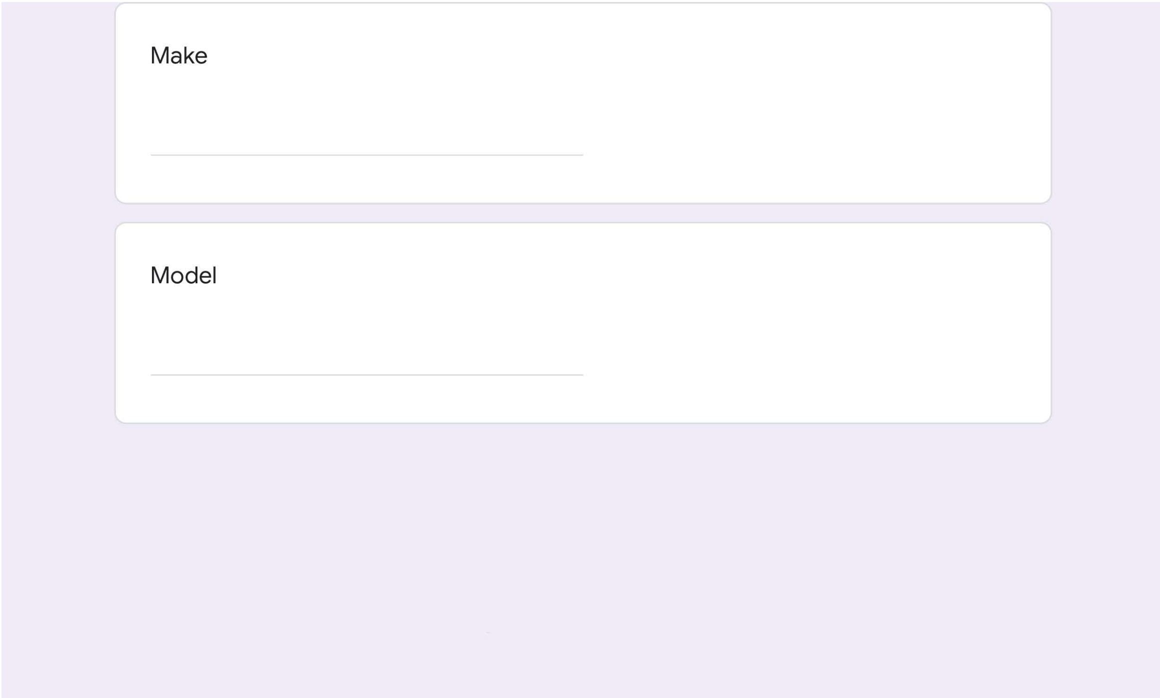
- [ ] Apple iPAD
- [ ] Android
- [ ] Other
- [ ] No

Make

Model

Do you have a smart phone

- ◯ Apple iPhone
- ◯ Android
- ◯ Other
- ◯ No



Make

Model