VALIDATION STUDY OF A NON-INVASIVE DIAGNOSTIC DEVICE FOR LIPID PROFILE

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VALIDATION STUDY OF A NON-INVASIVE DIAGNOSTIC DEVICE FOR LIPID PROFILE

ABSTRACT

To design and develop a new medical device, a manufacturer must conduct clinical testing on the human subject to test the effectiveness and safety aspect of their newly developed device. In addition, to enable the device to be produced in large mass in the respective country, the manufacturer as well as local representative (if overseas made) must register their device to the authority. Thus, as a part of the registration procedure, a validation study needs to carry out in order to confirm the effectiveness of the device in performing the intended function. Therefore, this study is carried out to validate a new medical device that based on bioimpedance analysis (BIA) principle in estimating lipid profile parameter in diseases through a non-invasive procedure. The objective of the study is to find an association of the new medical device parameter and the lipid profile in subject attending primary care setting. A random group of adult patients was chosen based on the lipid profile form. The 48 subjects were recruited on the test day. Anthropometry measurement, the BIA-based medical device and lipid test measurement were taken on the same day. The subjects were then classified according to lipid profile parameter accordingly. The independent t-test and multiple logistic regression were used for data analysis. Based on the statistical analysis the result showed that the impedance ($5,100,200\ kHz$), phase angle, resistance, capacitance, TBW, ICF can estimate the HDL-C parameter.

Keywords: bioimpedance analysis, lipid profile, validation study, hypercholesterolemia

KAJIAN PENGESAHAN BAGI PERANTIK DIAGNOSTIK BUKAN INVASIF UNTUK PROFIL LIPID

ABSTRAK

Bagi tujuan mencipta dan membangunkan peranti perubatan baru, pengeluar mesti menjalankan ujian klinikal ke atas subjek manusia untuk menguji keberkesanan dan aspek keselamatan peranti tersebut. Di samping itu, untuk membolehkan peranti dihasilkan dalam jisim yang besar di negara masing-masing, pengeluar serta wakil tempatan (jika dibuat di luar negara) mesti mendaftarkan peranti mereka kepada pihak berkuasa. Sebahagian daripada prosedur pendaftaran, kajian pengesahan perlu dijalankan bagi mengesahkan keberkesanan peranti dalam melaksanakan fungsi yang dimaksudkan. Oleh itu, kajian ini dijalankan untuk mengesahkan peranti perubatan baru yang berteraskan prinsip bioimpedan (BIA) dalam menganggar parameter profil lipid di kalangan pesakit melalui prosedur bukan invasif. Tujuan kajian ini adalah untuk mencari persamaan antara parameter peranti perubatan baru dan profil lipid dalam pesakit yang mendapatkan rawatan di klinik penjagaan primer. Pesakit dewasa telah dipilih secara rawak berdasarkan borang profil lipid. 48 subjek telah direkrut pada hari ujian. Pengukuran anthropometri, peranti perubatan berasaskan BIA serta pengukuran ujian lipid telah diambil pada hari yang sama. Subjek kemudiannya telah dikelaskan mengikut parameter profil lipid. Ujian t bebas dan analisis regressi logistik berganda digunakan untuk analisis data. Berdasarkan analisis, keputusan menunjukkan bahawa impedans ($5,100,200\ kHz$) , sudut fasa, rintangan, kapasitansi, jumlah air dalam tubuh dan cecair intrasel boleh menganggar parameter HDL-C.

Kata kunci: analisis bioimpedan, profil lipid, kajian pengesahan, hypercholesterolemia

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF SYMBOLS AND ABBREVIATIONS

TC	:	Total Cholesterol
TG	:	Triglyceride
LDL-C	:	Low-density Lipoprotein Cholesterol
HDL-C	:	High-density Lipoprotein Cholesterol
BIA	:	Bioimpedance Analysis

CHAPTER 1: INTRODUCTION

1.1 Problem statement

1.1.1 Hypercholesterolemia

Development of atherosclerotic plaque begins in the early stage whereby substance known as cholesterol started to deposit at the wall of the blood vessel. Lack of physical activity, smoking and improper diets contribute to the formation of this plaque, thus lead to a condition known as hyperlipidemia which is high blood cholesterol level. According to Ministry of Health Malaysia statistics in 2017, Malaysian suffered heart disease at the early age of fifty-eight years old compared to their counterpart in Thailand(sixty-five years old) and mainland China (sixty-three years old) (Bernama,2018).

A recent study that was conducted based on National Health and Morbidity Malaysia (NHMS) 2015, identify the prevalence of hypercholesterolemia in the country is the highest which is contributed to forty-seven per cent and only a quarter of those percentage are fully aware that they are having the conditions (Mat Rifin et al., 2018).

Lipid profile is a blood test performed in the primary care clinic as a routine to diagnose hyperlipidemia. Hyperlipidemia is defined as high total cholesterol (TC) and low level of high-density lipoprotein- cholesterol (HDL-C) (Expert Panel on Detection, 2001). The panel of expert has recommended that at the age of 30 years old, Malaysians are encouraged to undergo screening for cholesterol (Ministry of Health Malaysia, 2017).

The SMARTMF is a multi-frequency BIA that estimate the lipid profile parameter and it is currently under development process. As part of the design control procedure, a validation study needs to be carried out based on the purpose of producing the

SMARTMF. Based on the function of estimating the lipid profile, the validation study must be conducted with the reference method. lipid profile test.

Few studies that were conducted in the past have shown the correlation between the bioimpedance and lipid profile in university population in Kuala Lumpur (M.S Mohktar et al., 2013), Japanese (Junji Kobayashi et al., 2006), hemodialysis patient(Masahiro Noguchi et al., 2015) and prediabetic (Nayak et al., 2018). However, there is none study that was conducted in the past that utilized SMARTMF in their validation works. Therefore, this study been carried out as part of the design control process.

Even though there is already an established home kit cholesterol monitoring in the market, the functionality is still the same with the laboratory test as it requires a small amount of blood as a sample(Avometer Vantage, 2017; Michael Hoffler et al., 2015). A blood test creates minor complication that not fatal such as the formation of the hematoma and pain (Buowari, 2013).

1.1.2 Lipid Profile

Currently, a well-established method in the clinical setting is known as a lipid profile test. This test is a diagnostic test for measuring cholesterol level in the body thus predicting the risk of having heart or vascular disease such as atherosclerosis. There are four parameters in the lipid profile which is total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL-C) cholesterol and triglycerides (TG). According to Mayo Clinic, an adult who at risk of developing coronary heart diseases are recommended to undergoes this test. In addition, for those who have a positive family history of high cholesterol, overweight, is diagnosed with diabetes and those who smoke are advised to check for their cholesterol level (Mayo Clinic,2019).

1.1.3 SMARTMF

SMARTMF is a multifrequency bioimpedance analysis that produced ($<1mA$) current to the human body and will measure the body composition at multiple frequencies range which is within 5-200 kHz. The body composition data that the device gathered is then sent to a smartphone to be processed and analyzed. This is an application that used to assist individual to have a better lifestyle as it comes with modules comprises of body composition measurement, cholesterol level and biophysical activity (Salat). An individual who wants to monitor these three components in their activity is able to retrieve the data wherever they were as the information will be stored in the cloud system (Sajaratulnisah Othman, 2018).

Based on the problem statement, there is a need for the SMARTMF to be validated to overcome the limitation. Thus, the aim of the study is to validate the SMARTMF as a non-invasive diagnostic tool for lipid profile and the objective of the study is to find an association between the lipid profile parameter and the SMARTMF.

This thesis will be divided into five chapters which began with chapter one, the problems statement. In chapter two will be explaining about the medical device in general, the design and development of the medical device, regulation in Malaysia, an overview of bioimpedance analysis (BIA), clinical validation study and SMARTMF. In chapter three will be discussing the ethical approval, the subject recruitment and the methodology of statistical analysis. Further in chapter four will be elaborating the results and discussion of each of the lipid profile parameter using statistical data, finally in chapter five will be discussing on the conclusion, limitation and future work

CHAPTER2: LITERATURE REVIEW

2.1 The medical device in general

2.1.1 Definition of medical device

Medical devices have been a tool in delivering healthcare service to the community. The definition of medical devices is diverse, and it varied from organization to another. According to the World Health Organization (WHO) defined the medical device as an instrument, apparatus, machine, implant or any related material that is produced by the manufacturer whether to be used in single or incorporate with other medical devices to achieve the objective in treating a patient (Global Harmonization Task Force, 2012).

In Malaysia, the model that been used by the government for making regulation regarding the medical device are based on the GHTF and WHO (Medical Device Regulatory Framework Malaysia, 2014). The Global Harmonization Task Force (GHTF) was founded in the year 1993, by the representatives from developed countries such as Japan, United States of America, European Union and Australia to support developing countries to form policies related to the medical device. This organization also encourage more new ideas and business trade among developing countries by providing standard documentation for guidance(WHO).

And in Malaysia according to Medical Device Act 2012, the definition of the medical device is equipment, graft, in vitro reagent or computer program made by the manufacturer in order to investigate, heal, avoid or monitor disease in human(Definition-Medical Device Authority, 2012).

2.1.2. Classification of a medical device

Based on the Medical Device Act 2012, it is a responsibility of the manufacturer to classify their medical device based on the risk the medical device have on human and the objective of its production (Medical Device Authority., 2012). This is needed as every medical device produced is associated with a certain level of harm to the patient. The risk associated with the medical device will determine the classification of the device itself based on a set of rules. Generally, there are four class of medical device which is class A, B, C and D (Classification-Medical Device Authority, 2014).

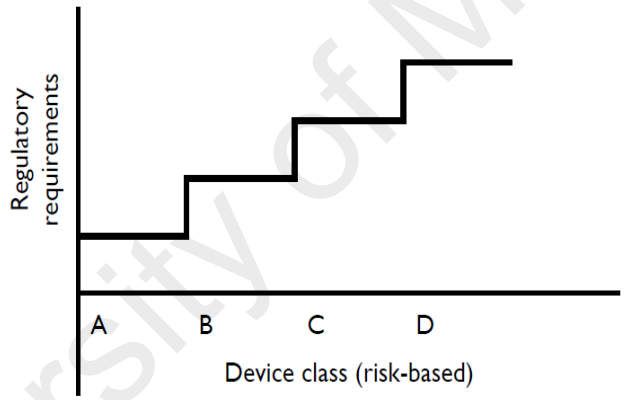

Figure 2.1: Classification according to risk (Medical Device Regulatory Framework,2014)

Based on figure 2.1, the classification of the medical device increases as the risk associated with the usage of the device increases. For example, if the device is only to be placed outside the human body then the device is classified as low-risk which falls under class A. And as the risk increases such as an implant into the human body then it considered as high-risk which is class D classification (Medical Device Regulatory Framework-Medical Device Authority., 2014).

In this section, the author will elaborate extensively regarding the rules to classify the medical device in each of the four-class based on the Principles of Medical Devices Classification. For a medical device to be classified under class A which is known as low risks , it must fulfil either one of these conditions, which is; (1) non-invasive; (2) can be used to be applied externally to stop bleeding such as simple wound dressing and cotton wool ;(3) used as a container to store body liquid, liquid or gas such as urine collection bottles ; (3) if it is invasive to the body orifices for organs such as ear canal and oral cavity . For the ear to the extent of the eardrum and for the oral cavity to the extent of the pharynx. Both of these organs must be used continuously for less than 60 minutes. Examples such as denture and dressing for nose bleed (Classification-Medical Device Authority, 2014).

Going further to classify class B medical device known as low-moderate risk. The conditions are; (1) to treat wound that has exposed the dermis layer of skin such as non-medicated impregnated gauze dressing ;(2) the device must be connected to another medical device which use electrical energy to function such as anaesthesia breathing circuit ; (3) if the device is invasive, the device must be inside the body orifice continuously for more than 30 days such as orthodontic wire, fixed dental prosthesis; (4) the medical device used for the therapeutic purpose such as hearing aids; (5) active medical device for diagnosis such as ultrasonic diagnosis and diagnostic radiology (Classification- Medical Device Authority., 2014).

The third classification of the medical device according to the risk is class C which is also known as moderate-high risk class. The criteria to classified the medical device under this class are: (1) the device are invasive and used for continuous use for more than 30 days such

as contact lens and urethral stent;(2) the device is made to deliver radiation therapy for treatment of cancer such as brachytherapy; (3) the device is used for patient-administered medication by themselves such as insulin pen; (4) implants for the device to be used in orthopaedic, dental, ophthalmic and cardiovascular field for such as maxilla-facial implants and prosthetic joint replacement (Classification-Medical Device Authority., 2014).

Last in order but not of importance, in the classification of the medical device which is class D known as high risk. The criteria under this classification are; (1) the device must be surgically invasive and it must be used for central nervous system, for example, neurological catheter; (2) the device is used for the cardiovascular-related system such as angioplasty balloon catheter, prosthetic heart valves; (4) active implantable medical device such as pacemakers and implantable defibrillators (Classification- Medical Device Authority.,2014)

2.1.3 The life cycle of a medical device

The life-cycle of the medical device begins with the design and developmental stage by the manufacturer, consequently, accessibility of the device in the market and utilization by the users, and end with disposal after the usage. To describe this, MDA has outline three common stages of the life cycle of a medical device which is pre-market, placement on the market and post-market (Regulatory Framework- Medical Device Authority, 2014).

In the pre-market stage, the manufacturer must perform conformity assessment for their medical device (Conformity-Medical Device Authority., 2014). The conformity assessment is a systematic procedure whereby the conformity assessment body will assess the safety aspect of a medical device. This procedure must be done by the manufacturer to prove that their product is safe and behave according to the objective of the manufacturer producing the medical device. In the conformity assessment, the manufacturer must provide evidence

according to the essential principles of safety and performance requirement (EPSP) (Regulatory Framework-Medical Device Authority, 2014). The EPSP serves as a guideline for the manufacturer to undergoes the conformity assessment process (Medical Device Authority, 2014 -b).

For the product to be placed on the market, the manufacturer and distributor are required to register themselves to the authority. If the device is overseas made, the local distributor has to maintain good contact with the manufacturer. This is crucial to ensure that any accident related to the medical device shall be known by the manufacturer. In addition, the manufacturer and the distributor should not mislead their users with an advertisement by claiming their device beyond the ability (Regulatory Framework-Medical Device Authority, 2014). At the post-market stage, the manufacturer and the local distributor are still bound to the authority and they are required to conduct post-market surveillance. This means any accident related to the usage of the device must be recorded and further action such product recall must be taken (Regulatory Framework-Medical Device Authority., 2014). According to the Malaysian of Domestic Trade and Consumer Affair (MDTCA), a product recall is a withdrawal of a product from the market if the device is found to be faulty or not comply with the law (Malaysian of Domestic Trade and Consumer Affair, 2014).

2.1 Design and Development of Medical Device

2.2.1 Design control

In developing a new medical device there is a need to have a system that ensures that device that is produced is high in quality and safe to the users, this process is known as design control (Gilman et al., 2009; M.B. Teixeira., 2013). Design controls is a process to ensure that the design of the medical device meets the end-user needs and the purpose of its production.

The main objective that the design control is needed because to ensure that the device is safe to the users. Statistically based on a publication by Stanley Liu, forty-four per cent of product recall being done on the device control process itself from the year 1983 to 1989. Meanwhile, ninety per cent of software were recalled due to an error related to the design from the year 1983 to 1989 (Liu.S.,2014). This shows that through the design control process, the faulty medical device can be discarded at the early stage of designing itself. Therefore, having this knowledge of producing a medical device will ease and assured the consumer about the safety aspect of the product who already made available in the market.

2.2.1 Stages of design control

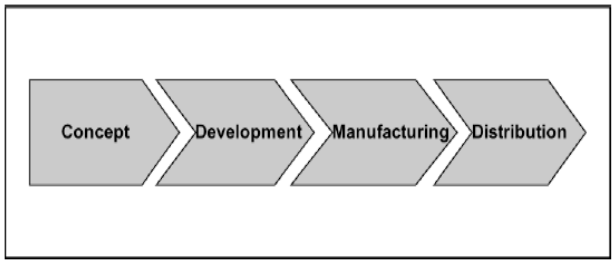

Figure 2.2: The process of making a medical device(Gilman et al., 2009)

According to the Food Drug and Administration (FDA), there are seven requirements for the design control process (Liu. S., 2014). However, authors L. Gilman et al in the publication entitled Medical Device Design Process, provide an overview of the process of developing in the medical device. For simple medical device here are four stages of design control which is concept, development, manufacturing and distribution as shown in figure 2 (Gilman et al., 2009). Meanwhile, Marie B. Teixieria has extensively elaborated the process of design control into five phases which is definition and documentation, developing design output, verify and validate, transfer and improvement and optimization in her publication (M.B. Teixeira, 2013).

L. Gilman et al., cited SurVivaLink, an automated external defibrillator (AED) as an example of the design process. The first step that been done by the company in order to initiate the process is to conduct a literature review. In the review, the company realized there is a need for a simple and portable defibrillator. The company need to determine the needs of the customer and must be documented(Gilman et al., 2009). In addition to that, Marie B. Teixeira, the document also known as design input needs to be comprehensive, realistic and must be inlined with the customer requirement(M.B. Teixeira, 2013). She added, it also needs to be reviewed and approved by appointed individual and in case any issue may arise, it needs to be clarified (M.B. Teixeira., 2013).

For the case SurVivaLink, the document had been reviewed by an emergency related personnel such as physician, paramedics and nurses as well technician. They added by talking to the right expert is the fundamental key in the first stage of developing the medical device (Gilman et al., 2009). The author mentioned that the first document that needs to be produced is known as Customer Requirement Specification (CRS). Like the design input, this CRS is based on the interview from the expert and the patient who is dealing with the problem that the manufacturer tries to overcome through producing a medical device (Gilman et al., 2009).

The author had summarized three stages of the design control process by FDA which is the design output, design review and design verification into one step known as development stage (Gilman et al., 2009; Liu. S,2014). In the developmental stage, the document from the design input will be used to make a prototype of the medical device to be used for clinical testing (Gilman et al., 2009). In this stage, another document needs to be provided by the engineer known as the product requirement specification. This document needs to be amended as the prototype is consistently undergoing improvement through clinical testing (Gilman et al., 2009). From the author understanding, the development stage is also included validation study.

Design validation is a question that needs to be answered by the manufacturer whether they made the right product or not and this must be supported by documentation(Teixeira, 2013). The final stage of the design control are manufacturing and completed through distribution(Gilman et al., 2009). This stage only ends for the simple medical device. However, according to the MDA, the process does not end here as their responsibility of the manufacturer ends after the product is being disposed of after the usage (Regulatory Framework.- Medical Device Authority.,2014).

2.3 Regulation in Malaysia

2.3.1 Medical Device Authority (MDA)

Medical Device Authority, an authorized body established under the Medical Device Act 2012 (Medical Device Act, 2012). Among their major tasks are setting rules and regulations regarding medical devices, monitoring already available medical devices and informing the healthcare professional as well as users about the issues related to medical device and a new product that available in the Malaysian market (Medical Device Authority).

2.3.2 Registration of the Medical Device in Malaysia

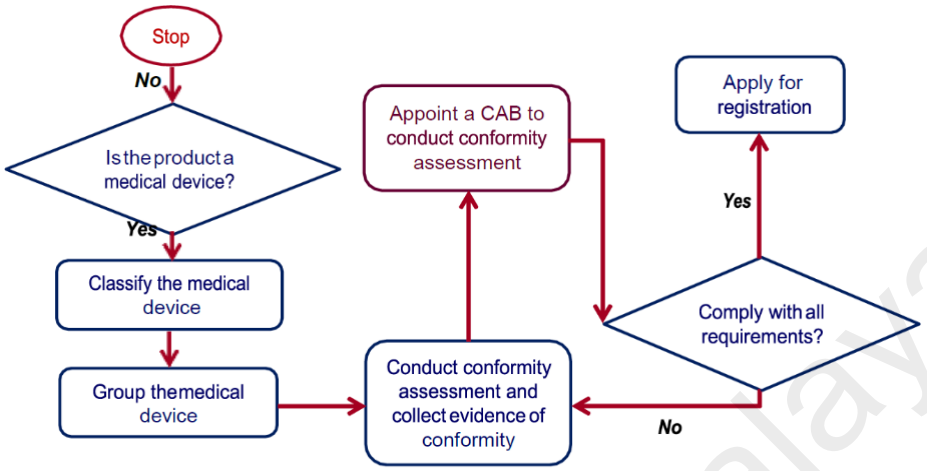

Figure 2.3: The regulation of the medical device (Medical Device Authority., 2014 -a)

According to the Section 5 (1) of Medical Device Act 2012, (Act 737) required the manufacturer or the authorized dealer (if device manufactured overseas) to register the medical device before the device can be placed in Malaysia market or exported outside the country. In the recent publication by the Medical Device Authority, the authorized body has outlined the flowchart as shown in figure 3 in order to serve as a guideline for the manufacturer to prepared the documentation before registration of their device (How to Apply for Registration- Medical Device Authority., 2019).

The first step is to define the medical device according to the definition of medical device as being described in chapter 2.1.1 (definition of the medical device). After the manufacturer has confirmed that their product is a medical device, then they need to classify the medical device as in chapter 2.1.2 (classification of the medical device). The first two steps are crucial because it acts as a foundation for the next step in the registration of the medical device. If the manufacturer unable to defined and classify the medical device properly the next step

will be complicated as they are required to group, the medical device (Guidance on the Product Grouping).

Consequently, the fourth steps that must be done by the manufacturer are to conduct a conformity assessment by Conformity Assessment Body (CAB) (How to Apply for Registration- Medical Device Authority., 2019).

Based on chapter 2.1.3 in the lifecycle of medical device, the process of conformity assessment considered as a preliminary stage, however, according to MDA is considered as an intermediate step that might be done by the manufacturer.

CAB is an independent body such as SIRIM QAS International, that carries out conformity assessment procedure, a procedure that ensures the device is safe and perform effectively as proposed by the manufacturer (Conformity-Medical Device Authority; Medical Device Act., 2012). The CAB will also issue a certificate to the establishment as part of the requirement for the registration of the medical device (How to Apply for Registration.,2019). After all the steps that have been elaborated had completed by the manufacturer, only then they can register their medical device using MeDC@St. MeDC@ST is standing for "Medical Device Centralized Online Application" a web-based online application that been set up by the MDA for the manufacturer to register their medical device (How to Apply for Registration.,2019).

2.4 Bioimpedance analysis (BIA)

2.4.1 Overview of BIA

BIA as a non-invasive, simple, affordable and reliable technique in measuring the body composition (Junji Kobayashi et al., 2006; Kim et al., 2011; Kyle et al., 2004). BIA has been studied in the past began in the year 1851, when the researcher studied the electrical properties of tissue. Thomasset et al had laid a foundation by pioneering in using electrical impedance to measure total body water (TBW) using two electrodes placed under

the skin. Later Hoffer et al changed into four adhesive electrodes (Dubiel. A., 2019; Kyle et al., 2004). In the 1970s, Nyboer et al. had pioneered in impedance plethysmography, which they studied the relations between impedance and hemodynamic of blood (Dubiel.A, 2019).

BIA has been classified according to the number of electrode and frequencies that it been used to operate. Generally, there are two main types of BIA which is single frequency BIA (SF-BIA) and multi-frequency BIA (MF-BIA) (Dubiel. A, 2019). U.G Kyle et al added there are three types added to the previous mentions which are Bioelectrical spectroscopy (BIS), segmental BIA and Bioelectrical impedance vector analysis (BIVA) (U.G. Kyle et al., 2004).

The parameters of the BIA are based on body composition to serve the purpose of the production. There are essentially four types of the parameter of BIA, which are fat-free mass (FFM), total body water (TBW) constitutes of extracellular water (ECW) and intracellular water (ICW) and body cell mass (BCM) (U.G. Kyle et al., 2004).FFM is also considered as anything inside the human body except fat. According to U.G. Kyle et al., this parameter can be determined by the SF-BIA. Meanwhile, the MF-BIA is shown to be better in predicting the TBW. Nevertheless, according to Patel et al., SF-BIA are able to predict TBW in very ill patients compared to MF-BIA which more precise in measuring ECW. BCM according to the U.G. Kyle et al constitute protein compartment (U.G. Kyle et al., 2004).

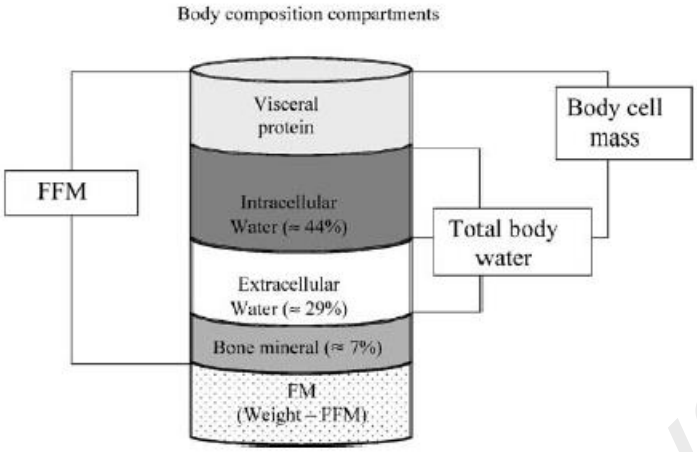

Figure 2.4: The body composition as measured by the BIA (U.G. Kyle et al., 2004).

2.4.2 Clinical Validation Study

The current study is concerning a newly developed SMARTMF which uses the principle of multi-frequency bioimpedance analysis (MF-BIA). MF-BIA as the name given used multiple frequencies with a range from 5 kHz- 200 kHz to evaluate FM, FFM, TBW, ECW and ICW (U.G. Kyle et al., 2004). In comparison with single frequency bioimpedance analysis (SF-BIA), MF-BIA is better in predicting the body composition in sick patients than SF-BIA which is useful for healthy subjects (Dubiel.A., 2019).

In order to validate the BIA, the validation study has to be done with the reference method as the equation used to develop BIA are varied between the age and ethnic group as well as clinical conditions (Kyle et al., 2004). The commonly used reference method such as dual-energy X-ray absorptiometry (DXA), air displacement plethysmography (ADP), skinfold thickness (Jebb et al., 2007; Kim et al., 2011; Rush, Chandu, & Plank, 2006). Hyeoijin Kim

et al mentions in their study that DXA is a popular method to measure body composition (Kim et al., 2011).

Despite that, using DXA procedure are costly, tedious and produced radiation (Kim et al., 2011). U.G. Kyle added that the results of the DXA are varied from one manufacturer to another making it reasons for not an established gold standard method (Kyle et al., 2004). Even though so, there are still numerous studies that used DEXA as a reference method invalidating the bioimpedance analysis (BIA) (Jebb et al., 2007; Rush et al., 2006). Table 2.1 shown the clinical validation study that was conducted in the past, as shown in the table most of the study involves DXA and very few related to lipid profile.

In addition to using the machine as a reference for the validation, the anthropometric measurement must also be included. In a study that conducted in a Turkish adult, they have identified that by including anthropometric measurement into the validation study there are able to strengthen the estimation of the lipid profile parameter. In the previous study, they have included waist circumference for the women subject in order to estimate lipid profile parameter accurately (Meseri et al.,2012)

For validation of BIA, Hyeoijin Kim et al have conducted a study in Korean population to validate eight electrodes BIA model that is produced in their country. The author has used DXA as a reference method. Despite the usage of DXA, they agree that there are some disadvantages using this as reference method such as it required a well-trained person to operate the machine. The author added that there is also limitation using anthropometry such as BMI, as it was unable to measure body fat and fat-free mass separately. They agree that BIA can be a new way to measure body composition non-invasively. However, based on

their study there is some limitation of BIA expose which is the medical device is inaccurate to predict individual fat mass as they overestimated the amount of fat in man and underestimate fat mass in women (Kim et al., 2011).

On the other hand, EC Rush et al, able to produce a BIA equation for Asian Indian population to estimate FFM both in men and women(Rush et al., 2006). Despite the achievement, there are still not applicable to another population as the body composition differed between ethnicity as Asians have more percentage of body fat with the same BMI than Caucasians. In addition to that, a meta-analysis study has shown that even between Asians ethnicity has different in body composition (P.Deurenberg, 2002).

The validation study involving lipid profile in Malaysian are initiated by M.S Mokhtar et al. in 2005, the author had carried out a study that discovers an association between BIA and Coronary Heart Disease (CHD). The author added that there are eight predictors of BIA namely height, weight, body capacitance, fat mass, extracellular mass, BCM, BMR and ICW that able to predict the occurrence of CHD in obese subjects(M. S Mohktar et al., 2005). In addition, the same author, in the year 2007 has studied the effect of the abnormal total cholesterol level in the body composition parameter. From the study, it is shown that the abnormal group of total cholesterol has high BMI, weight, and height compared to the normal group (M. S. Mohktar et al, 2007).

Similarly, a study that was conducted on 1161 adult Japanese shown that BIA can predict the risk of having atherosclerosis using skeletal muscle parameter (Sato et al.,2018). This study has shown that decreased skeletal muscle mass has increased the risk of having atherosclerosis risk factors. An atherosclerosis risk factor is defined as diabetes with fasting

plasma glucose levels ≥110mg/dL, dyslipidemia was defined as increased in triglyceride level and or decreased in HDL-C and hypertension(Sato et al.,2018).

A previous validation study has proved that the bioimpedance analysis is able to predict lipid profile parameter (Junji Kobayashi et al., 2006; Masahiro Noguchi et al., 2015; Nayak et al, 2018). According to the Masahiro Noguchi et al. there is a relationship between body composition parameter measured by BIA and the lipid profile parameter in a dialysis patient. In addition, the author specified that there was a significant correlation between the per cent body fat (%BF) and high-density lipoprotein cholesterol level. The author cited Kobayashi et al, as a foundation to support their evidence (Junji Kobayashi et al., 2006; Masahiro Noguchi et al., 2015). However, according to a study conducted in Turkish adult, there are a weak association between percentage body fat and total cholesterol and LDL-C (Meseri et al.,2012). Thus, this signifies that there finding are varied in between BIA parameter in estimating the lipid profile parameter. Therefore, there is a need for the SMARTMF to be validated in the diseased population residing in Malaysia.

Another study by Nayak et al. has found an association between the body composition parameters in predicting the conditions known as prediabetes. The author identifies, by finding an association between body fat and combine with waist circumference measurement, extracellular water and dry lean weight, they can predict the occurrence of the prediabetes(Nayak et al., 2018). On the other hand, in a study conducted by Tuzun et al which has done on the type 2 diabetes mellitus (T2DM) patient show, there is no relationship between the body fat mass and LDL-C (Sabah Tuzun.,2017)

Table 2-1: The previous validation study

References	Design of study	BIA Parameter	Reference method	Study population	Analysis technique	Findings
Hyeoijin Kim et al.,2011	Cross-sectional	FM, %Fat, FFM	**DEXA** FM, BMC, FFM Soft lean body mass	Healthy adults	Pearson correlation coefficient Bland-Altman analysis	Correlation between BIA_%fat and DEXA_% fat mass = 0.956 in men
Junji Kobayashi et al., 2006.		PBF	**Lipid Profile** TC, TG, HDL-C, LDL-C	Healthy adults Japanese	Pearson correlation coefficient	BF able to predict serum lipid except for TC
EC Rush et al., 2006	Cross-sectional	FFM	**DEXA** Total Body Fat, Fat-Free Soft Tissue, BMC	Migrant Asian Indian	Tukey's test	FFM prediction equation is applicable to the studied population
SA Jebb et al., 2007	Longitudinal	BF	ADP, Deuterium dilution, DEXA, SFT	Overweight women	Bland-Altman method	The BIA system can be used as a tool to monitor body composition
Masahiro Noguchi et al., 2015	Cross-sectional	BMI, BW %BF, %SM	**Lipid profile** HDL-C, TC, LDL-C, TG level	Dialysis patients	Spearman's rank correlation coefficient	HDL-C, BMI, BF% and SM% were strongly correlated
Nayak et al.,2018	Case-control	LBM, FM, DLW TBW, ICW, ECW	**Blood samples routine**	Prediabetic and Normoglycemic patients	Regression method	BF% and WC can screen and diagnosed PD

			Plasma glucose, HbAIC, TC, HDL-C, TG **Anthropometric** BMI, WC, HC			ECW and DLW as an adjunct to predict PD

BMI-Body mass index , BMC -Body mass cells, BW-Body Weight, FFM-Fat free mass, FM-Fat mass, HC-Hip Circumference, HbA1C-Glycated Hemoglobin, TC-Total Cholesterol, WC-Waist Circumference, ECW-Extracellular Water, ICW- Intracellular water DLW-Dry lean weight , LBM-Lean body mass, PD-Prediabetes, %SM- Percent skeletal muscle, LDL-C Low density lipoprotein cholesterol, HDL-C-High density lipoprotein cholesterol, SFT-skinfold thickness

CHAPTER 3: METHODOLOGY

The study began with the application of ethical approval to the University of Malaya Medical Center Ethics Committee. Series of documentation supplied to the UMREC committees to request for their consent and permission for the study to be carried out in the University Malaya Medical Centre (UMMC). Among the document that is provided are patient information sheet in Bahasa Malaysia and English, patient informed consent form similarly has two editions and data collection form. The ethical approval was approved on 22nd August 2018 (MREC ID No:201882-6562).

The study was conducted at Pusat Setempat Pengambilan Darah at University of Malaya Medical Centre from 23rd January until 15th May 2019. The study population consists of adult range 30-80 years old. According to the literature review by EC Rush et al.,2016 the targeted subject for the study was 211.

3.1.1 Patient recruitment

The potential subjects were identified based on blood cholesterol investigation test that will be undergone by them. Upon subject recruitment, the patient was explained using the patient information sheet either in Malay or in English depending on the comfortability of the patient. The patient information sheet contained information regarding the study being carried out to the volunteers. The protocol of the study was also being explained to the potential subject and the consent was asked prior to the measurement.

3.1.2 Subject criteria

The inclusion criteria of the subject are the patient who was diagnosed with metabolic or endocrine disorder particularly diabetes mellitus, hypertension and hyperlipidemia and any

patient who undergoes blood investigation to measure cholesterol level. The study excluded any subject that are pregnant women, disabled patient and patient with a cardiovascular-related illness.

Figure 3.1: The location of data collection

3.1.3 Anthropometry and Bioimpedance Analysis measurement

The anthropometric measurement was recorded at the nearest 0.1 cm for height and 0.1 kg to the nearest weight. The patient was asked to remove shoes to do the procedure. The subject was instructed to lie down in a supine position for the placement of the adhesive electrode. The adhesive was then placed on the subject's right hand, one at the metacarpophalangeal joint and another at the wrist. In addition, two electrodes were then placed on the right foot, between the metatarsophalangeal of the great toe and the second toe and another at ankle joint.

Figure 3.2: The adhesive electrode on the right hand

Figure 3.3 The adhesive electrode on the right leg

After that, the SMARTMF device is switch on and the SMARTMF application on the mobile device is open. The Bluetooth setting on the smartphone is enabled and the information such as name, height, weight, hours of fasting and gender are being inserted through the SMARTMF app. The SMARTMF app is then connected and paired with the SMARTMF device and the result are displayed within 10 seconds. The procedure was repeated three times(Sajaratulnisah Othman, 2018).

Figure 3.4: SMARTMF measurement.

3.1.4 Biochemical parameter

The subject was then assisted to the withdrawal of blood procedure and blood taking procedure was conducted by the nurses in the PSPD. The results of the lipid profile are then were retrieved from the database with the help of the primary care consultant.

3.1.5 Statistical method

Statistical analysis was performed. The descriptive statistics for the four lipid profile parameter were performed using SPSS software. Further independent t-test and multiple logistic regression analysis were done to find the association between the lipid profile parameter and SMARTMF.

CHAPTER 4: RESULTS AND DISCUSSIONS

4.1 Descriptive Statistics

The validation study of BIA that was done in diseases subjects with a different diagnosis from hyperlipidemia, diabetes mellitus and hypertension. The patient also be selected from those who done the lipid profile test regardless of their diagnosis. A total of 48 subjects are recruited with the age range from 30 to 80 years old. From this, both female and male subject is divided into 24 each based on gender as shown in figure 4.1.

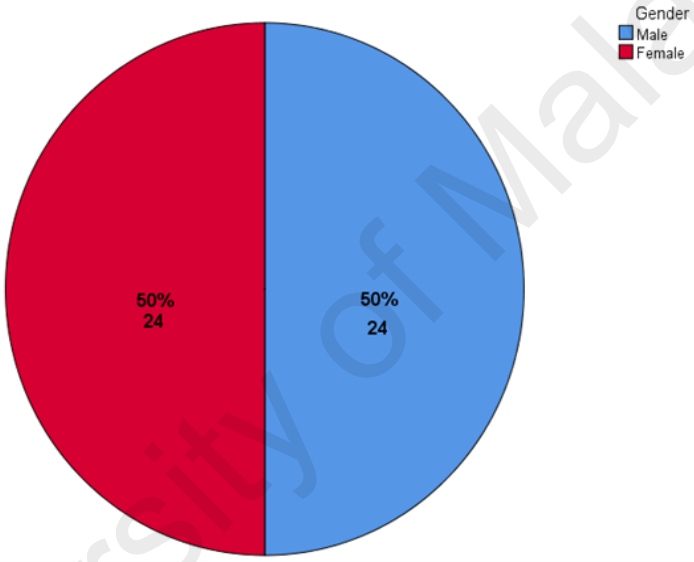

Figure 4.1: The distribution of gender

The 48 subjects are then be grouped according to lipid profile parameter which is total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol(LDL-C) and high-density lipoprotein cholesterol (HDL-C) according to MIMS Malaysia guidelines (MIMS, 2019). The number of subjects that divided for each classification will be described as further detailed in each section respectively.

4.2 Total Cholesterol

Table 4.1**:** SMARTMF parameter according to TC

Lipid Profile Parameter	Means ± Standard deviation	
Total cholesterol (TC)	Group 1 (n=29)	Group 2 (n=19)
SMARTMF parameter		
Age	59.79 ±12.36	62±12.88
Weight	70.28±19.47	64.63±12.03
Height	163.69±9.37	158.68±5.92
BMI	26.13±6.65	25.73±4.82
Impedance $(5kHz)$	538.64±112.63	527.26 ±58.98
Impedance $(50kHz)$	544.52±90.27	564.16± 88.24
Impedance$(100kHz)$	523.72±95.46	524.16±100.782
Impedance $(200kHz)$	488.72±92.74	479.79±100.87
Phase Angle	13.84± 34.25	7.50±1.05
Resistance (R)	551.37±91.18	553.07±98.02
Reactance (Xc)	74.52±21.77	72.89±16.56
Capacitance	45.85±12.07	45.67±9.57
Body capacitance	776.89±173.17	763.61± 156.03
FFM	44.17± 11.95	39.32±7.95
FM	26.55±10.89	25.30±7.95
TBW	32.21±8.95	29.09±6.24
ECF	15.86±3.21	14.82±1.94
ICF	16.34±5.87	14.27±4.43
BMR	1378.12±372.1	1227.53± 248.17

For the total cholesterol, the respondents are classified according to group 1 consists of subjects TC≤5.2 mmol/L considered as normal TC level and group 2 with TC >5.2 mmol/L representing the abnormal level. And the results are tabulated as shown in table 4.1. However, the result for the independent t-test shown there is no significant difference between TC level and the SMARTMF parameter with p-value>0.05. The independent t-test shows there is no significant difference in TC for both genders with (p=0.213). However, the mean value for the TC level shows that female have high TC level compare to male counterpart with the mean value of 5.31 mmol/L and 4.81 mmol/L respectively. From the table, it is shown that Group 1 shows higher body capacitance (BC) than group 2. BC means

total energy stored in the body cell mass compartment. According to the literature, high TC indicates high BC (M. S. Mohktar et al., 2007), however, this study contradicts the finding as it is shown that the group1 with low TC level has high BC than group 2.

4.3 Triglyceride

Table 4.2: SMARTMF parameter according to TG

Lipid Profile Parameter	Means± Standard Deviation	
Triglyceride (TG)	Groups 1 (n=32)	Groups 2 (n=16)
SMARTMF Parameter		
Age	60.22±13.13	59.88±13.07
Weight	66.75±18.30	70.63±13.32
Height	162.59±9.17	159.94±6.8
BMI	25.12±6.15	27.66±5.26
Impedance ($5kHz$)	544.41±107.68	512.88±49.72
Impedance ($50kHz$)	567.53±99.27	521.81±54.75
Impedance($100kHz$)	539.06±97.63	493.56±89.59
Impedance ($200kHz$)	501.44±95.69	452.69±87.82
Phase Angle	13.26±32.60	7.46±0.99
Resistance (R)	566.20±93.84	523.74±87.00
Reactance (Xc)	76.68±22.04	68.28±12.73
Capacitance	44.66±12.15	48.02±8.3
Body capacitance	755.94±159.64	803.02±176.30
FFM	41.96±11.54	42.83±9.2
FM	24.78±9.62	28.60±9.85
TBW	30.55±8.60	31.82±7.03
ECF	15.36±3.13	15.63±2.06
ICF	15.19±5.61	16.18±5.03
BMR	1309.21±360.07	1336.52±287.26

For the Triglyceride the group was divided according to normal TG level which is Group 1 with TG ≤1.6 mmol/L and Group 2 high TG level >1.7mol/L. The results are tabulated as shown in the table. The result for the independent t-test shown only impedance ($50kHz$) has significant difference (p=0.046).

4.4 Low-Density Lipoprotein Cholesterol (LDL-C)

Table 4-3**:** SMARTMF according to LDL-C

Lipid Profile Parameter	Means±Standard Deviation	
Low-Density Lipoprotein (LDL-C)	Group1 (n= 26)	Group 2 (n=18)
SMARTMF parameter		
Age	60.31±14.08	61.28±12.43
Weight	65.88±11.59	65.17±15.95
Height	160.92±8.28	162.11±9.39
BMI	25.47±4.43	24.72±5.44
Impedance $(5kHz)$	528.00±52.47	557.22±129.41
Impedance $(50kHz)$	563.04±91.67	552.89±80.43
Impedance$(100kHz)$	526.46±89.00	542.33±96.47
Impedance $(200kHz)$	483.62±88.66	503.67±103.88
Phase Angle	7.41±1.02	17.71±43.47
Resistance (R)	555.13±86.64	568.22±90.06
Reactance (Xc)	72.42±15.63	77.69±24.12
Capacitance	45.87±9.55	44.14±11.73
Body capacitance	747.81±140.37	757.18±169.82
FFM	40.79±8.74	41.16±10.51
FM	25.08±7.37	24.72±10.36
TBW	29.95±6.42	29.92±7.73
ECF	15.17±2.09	15.02±2.90
ICF	14.78±4.44	14.89±5.04
BMR	1272.82±272.70	1284.38±328.07

For the Low density-Lipoprotein Cholesterol(LDL-C) The subject is also classified according to the group, which is group 1 with LDL-C ≥ 2.6 mmol/L and group 2 ≤2.59 mmol/L. Similar to TC, there is no significant difference between the SMARTMF parameter and the LDL-C level with the p-value>0.05 in the independent t-test. In addition, the multiple logistic regression analysis also showed similar findings.

4.5 High-Density Lipoprotein Cholesterol (HDL-C)

Table 4-4 SMARTMF according to HDL-C

Lipid Profile Parameter	Means ± Standard Deviation	
High-Density Lipoprotein (HDL-C)	Group 1 (n=36)	Group 2 (n=12)
SMARTMF Parameter		
Age	59.36±13.32	62.33±12.13
*Weight	72.53±16.01	54.58±11.03
*Height	163.00±8.61	157.83±7.01
*BMI	27.36±5.97	21.81±3.46
*Impedance $(5kHz)$	509.19 ±47.07	608.00±148.08
Impedance $(50\ kHz)$	547.28±88.79	567.33±92.02
*Impedance $(100kHz)$	501.97±80.66	589.67±113.23
*Impedance $(200kHz)$	463.75±73.44	549.50±124.29
Phase Angle	7.39±0.94	23.15±53.14
*Resistance(R)	530.55±79.27	616.53±104.13
Reactance(Xc)	68.91±14.27	88.77±26.22
*Capacitance	48.09±9.82	38.83±12.01
Body capacitance	782.19±159.98	739.96±182.90
*FFM	44.70±10.00	34.91±9.75
*FM	28.18±9.68	19.67±7.06
*TBW	32.78±7.48	25.54±7.53
*ECF	16.23±2.42	13.10±2.61
*ICF	16.55±5.15	13.10±2.61
*BMR	1394.65±312.00	1089.29±304.29

*significant value $p<0.05$

The above table shown the descriptive statistics for the HDL-C. The subjects are divided into two which is group 1 HDL-C≤1.59 mmol/L and group 2 which is HDL-C ≥1.6 mmol/L. Independent t-test are conducted and the significant p-value ($p<0.05$) are given as weight ($p=0.0001$), height ($p= 0.049$) , BMI ($p=0.004$), impedance $(5kHz)$ ($p=0.043$), impedance $(100kHz)$ ($p=0.026$), impedance $(200\ kHz)$ ($p=0.041$), resistance ($p = 0.019$), reactance ($p= 0.026$), capacitance ($p=0.028$), FFM (0.007), TBW ($p=0.002$) ECF ($p=0.002$), ICF ($p= 0.027$), BMR ($p=0.007$)

These findings contradict with the study done by Kobayashi et al. whereby the estimated the PBF to be accurately measured TG, LDL-C and TC in the healthy adults (Junji Kobayashi et al, 2006). However, since this study is involving diseases subject there are shown that BF can estimate only HDL-C.

The phase angle is predictors for cellular health, the higher the phase angle indicates the cell is in good conditions and the lower the phase angle indicates the cells are in a worse state of health (Mariana De Souza Dorna et al.,2013). Thus, in this study, the value of the phase angle is significant as those in the group 2 which have high HDL-C also known as good cholesterol with the phase angle value which is 23.15 compared to group 1 which is 7.39.

The SMARTMF parameter is grouped according to the similarity which is impedance, electrical components and body compositions. This is being done in order to analyse the data according to multiple logistic regression analysis and in order to find an association between each of the parameters with the HDL-C. The results are shown in table 4.5 for the impedance group, table 4.6 for the electrical components group and table 4.7 for the body compositions group.

Table 4-5: Multiple logistic regression analysis for HDL-C

SMARTMF parameter	HDL-C	
	Standardized β coefficient	p-value
Impedance ($5kHz$)	0.278	0.01
Impedance ($100kHz$)	-0.293	0.016
Impedance ($200\ kHz$)	0.163	0.020

The table above shows the value for the HDL-C parameter that is significantly based on the multiple logistic regression analysis. Statistical analysis has shown that the other parameters are insignificant in predicting the LDL-C, TG, and TC. The result of the study shown that the impedance in multiple frequencies ($5,100,200\ kHz$)can estimate the HDL-C level in the subject with the accuracy of 75%. The further table shows multiple logistic regression analysis for phase angle, resistance and capacitance. This parameter is able to measure HDL-C with 85.4% accuracy. From the three parameters in table 4.6 shows that phase angle is more sensitive in detecting the HDL-C. This finding contradicts to a study that was done in 2013 whereby there shown that there is no association between the lipid profile of patients, however, according to the previous study, there are significant relations between the phase angle and anthropometry measurement (Mariana De Souza Dorna et al.,2013).

Table 4-6: Multiple logistic regression analysis for HDL-C

SMARTMF Parameter	HDL-C	
	Standardized β-coefficient	p-value
Phase Angle	26.782	0.053
Resistance	0.219	0.037
Capacitance	0.647	0.043

As for the TBW and ICW, the accuracy of the parameter is similar to the previous table which is 85.4% accuracy. However, there is a negative association between the TBW and HDL-C as shown in table 4-7.

Table 4-7: Multiple logistic regression analysis for HDL-C

SMARTMF Parameter	HDL-C	
	Standardized β-coefficient	p-value
TBW ICF	-7.638 7.751	0.015 0.011

The finding is significant in the clinical setting as based on the definition of hyperlipidemia, there is an elevation of the TC and there is decreased in the HDL-C. The ability of the SMARTMF to estimate the HDL-C parameter is the initiative for future work to be carried out.

Chapter 5: Conclusions

5.1.1 Limitations

The current study has several limitations, a small number of sample size. The larger sample size is needed to validate a new medical device and to test the sensitivity and specificity of the study. These are important to test the validity of the diagnostic test. This requires 400 subjects to get the sensitivity and specificity of 80%. (Rajeev Kumar Malhotra and A Indrayan., 2010). The second limitations of the study are the recruitment of the patient was done on anyone who does the lipid profile test. By doing this it reduced the accuracy of the device. To get the accuracy of the SMARTMF the device should only be tested on the hyperlipidemic patient who already been diagnosed by the clinician. This is because the function of the device is to estimate the lipid profile rather than measuring the lipid profile. The third limitation of the study is the fasting hours of the subject are varied between one another and there are subject even though there are not fasting the measurement are been measured as well. This will have an effect on body composition measurement.

5.1.2 Future work

In the future, the aim of the study can be narrowed to estimating the lipid profile in hyperlipidemic patients and SMARTMF as a smart application to help patient monitor the cholesterol level regularly. In addition, the study can be carried out in the larger population among especially for hyperlipidemia patient to improve the accuracy of the device. Other than that, the fasting hours of the patient will be considered and only those fast for at least 6 hours will be recruited

In conclusion, the study shows that the objective of the study has been achieved. One out of four lipid profile parameter can predict by the device. The independent t-test and multiple

logistic regression analysis has shown that the SMARTMF have an association with the HDL-C.

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