Improving the prevalence and treatment of diabetes in low-middle income countries

Individual Portfolio

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Abstract: **Background.** Diabetes mellitus is a common metabolic disease where patients suffer from high blood glucose levels over a sustained period of time. In LMICs the rate of diabetes incidences is growing at epidemic proportions, and the prevalence is estimated to increase by 108% between 2013 and 2030. **Methods.** The report took a systems engineering approach as means to improve the prevalence and treatment of diabetes in low-middle income countries. Desktop research was conducted as means to apply research and system perspectives on the topic. **Results.** It was found that developing a risk score analysis, will help to improve the awareness of diabetic patients, which will potentially result in a decreased prevalence in diabetes. Increasing the responsibility of nurses also resulted in a reduced pressure on physicians and an increased rate of addressing patients in hospitals. Finally, continuous subcutaneous insulin infusion (CSII) therapy was found to be the most cost effective and environmentally friendly option when compared to multiply daily injections, and sensor augmented pumps. **Conclusions.** From this report it was concluded that a non-governmental diabetes organisation could potentially implement a health care model into LMIC clinics with the approval and potential support of the local government. The recommended health care model should use a developed risk score assessment, an increased education of nurses, a cloud computing database system and a standardised treatment for CSII therapy.

ENGN2226 Research Portfolio Coversheet

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Portfolio Topic or Research Question:

Analysis Tools

Place an 'x' next to each of the eight research methods and system perspectives you have engaged with:

	Research methods		**System perspectives**
x	R01: Research question	x	S01: Social & cultural
x	R02: Surveys and interviews	x	S02: Safety & risk
x	R03: Quantitative & qualitative	x	S03: Anthropometrics
x	R04: Data organisation		S04: Planning approaches
x	R05: Research ethics	x	S05: Queue theory
	R06: Coding research data	x	S06: Process control
x	R07: Error types	x	S07: Control theory
x	R08: Descriptive statistics	x	S08: Material impact
x	R09: Hypothesis testing - populations		S09: Energy-mass balance
	R10: Hypothesis testing - categories		S10: Energy efficiency
x	R11: Simple linear regression	x	S11: Life-cycle cost
	R12: Confidence intervals	x	S12: Payback period

Any comments to the reviewer

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1. Introduction

1.1. Diabetes

Diabetes mellitus is a group of chronic metabolic diseases where patients suffer from high blood sugar levels over a sustained period of time (Alberti and Zimmet, 1998). Diabetes most commonly exist in two forms, as type 1 diabetes (T1D) and type 2 diabetes (T2D). T1D results from the destruction of pancreatic beta cells, which are responsible for producing insulin, the disease requires immediate exogenous insulin replacement where insulin treatment is required for survival and a patient's lifetime (Atkinson et al., 2014). T2D is globally more prevalent than T1D, accounting for approximately 90% of total cases (Maahs et al., 2010). In T2D the cells in your body either fail to use insulin properly or the pancreatic cells do not make enough insulin, patients however do not depend on insulin to live (American Diabetes Association, 2010). T2D is diagnosed in patients that develop a resistance to insulin or an inadequate insulin secretion response (Maahs et al., 2010). Obesity and increasing sedentary lifestyles have been found to be major risk factors for developing T2D in all age groups. It is most commonly found in patients with visceral obesity, which induces insulin resistance, and predisposes patients to the disease (Dagogo, 2006).

1.2. Motivation

Of the list of non-communicable diseases, the incidence of diabetes in low- and middle-income countries (LMICs) continue to rise at rates of epidemic proportions (Esterson et al., 2014). When comparing the rate of diabetes incidence in LMICs and high income countries (HICs) there is a marked difference, in low-income countries the number of diagnosed adult patients (aged 20-79 years) is estimated to increase by 108% between 2013 and 2030, additionally lower middle-income countries are expected to increase by 60%. In contrast the number of incidences in high income countries is expected to increase by 28%. (Guariguata et al., 2014). In addition, it is predicted that 50% of world's population are with undiagnosed diabetes (Dugee et al., 2015). These statistics underline the especially high burden in LMICs and emphasises the global issue of diabetes amongst the world's population (Guariguata et al., 2014). With expected increases in diabetes prevalence, it becomes timely to develop a strategy, that will facilitate the increase of care and decrease the overall prevalence of diabetes in LMICs.

1.3. Approach

The problem of diabetes existing in low-middle income countries can be attributed to a number of factors, including cost of treatment, social and cultural factors within the demographic, the cost of health care and substandard monitoring of the disease. These factors ultimately effect the 'Prevalence and treatment of diabetes' and this report will take a holistic systems engineering approach, as a means to address these issues. The report seeks to analyse the prevalence of diabetes and recommend possible health care treatment models that will improve overall treatment of the disease in resource poor settings. The qualities that define potential health care treatment approaches will be determined and validated using research methods and an analysis of time factors, human factors, material factors, cost factors an energy factors.

1.4. Outcomes and Solutions

The recommendations of this report included a refined type 1 and type 2 diabetes health care system that focuses on increasing awareness and education of diabetes in LMICs. It is recommended that the health care system uses, a risk score analysis as a low cost means to detect diabetes, as well as an increase in nursing responsibilities to reduce the pressure on physicians and ensure adequate management for diabetic patients. Additionally, it is recommended that a cloud computing system is developed to increase the monitoring of patients. It is also recommended that CSII therapy is the main type of insulin therapy recommend for patients in LMICs. It was concluded that, increases in nursing responsibilities will ensure that the complex management of CSII therapy is addressed correctly.

2. Research Methods

2.1. Researching Process and Problem Scoping

A focused and systematic search of the Australian National University online library was conducted to identify topical problems associated with diabetes. Initially 115 journal articles, 1 book and were found in the initial search, utilising these sources it was found that the dominant problems with diabetes, existed in low-middle income countries. Consequently, the research question formed was, "How can the prevalence and diabetic treatment be improved in low-middle income countries?". After the research question was defined, the systematic search of literature was refined based on a list of keywords and search terms: *diabetes, type1 diabetes, type 2 diabetes, developing countries, LMICs, diabetes care models, global diabetes.* In this portfolio access and communication with low-middle income countries was limited to desktop research, as a result a large majority of qualitative and quantitative data was utilised from the desktop research.

3. Health Care Models for Type 2 Diabetes

3.1. Qualitative and Quantitative Motivation

Addressing the problem of T2D is of paramount importance in the context of LMIC's. After conducting a safety and risk analysis of T2D it was found that many of the social, cultural and anthropometric perspectives of LMICs attributed to the development of the disease. From the 3 different tools utilised a final risk analysis was developed based on data organisation of multiple studies. These studies conducted risk assessments for T2D in LMICs and HICs, which assess the probability of developing T2D based on a number of risk factors. The associated impact that these factors have were determined via anthropometric measurements, questionnaire interviews and laboratory analyses. Although this study is focused on LMICs, a study was analysed for a HIC in order to reduce the skews in the demographics and account for the population residing in LMICs that have a high income. It is important to note that this analysis does not provide risk scores that are suitable for determining the probability of developing T2D in LMICs, rather it gives an indication as to what risk factors are of primary importance.

In these studies, it is important to ensure research ethics is considered for all parties. For the studies analysed, ethical approval for surveys, questionaries and anthropometric measurements were obtained. Additionally, in many of the studies, participation was voluntary and consented, and the results for anthropometric and laboratory measurements were provided to participants directly after the testing occurred. The ethical approval for each study is outlined in the data organisation table, and include approvals from the Declaration of Helsinki., Ethical Committee of Diabetic Association of Bangladesh, Employees of Electric Generation Authority of Thailand, and the National Urban Diabetes Survey.

The risk factors in each study where derived based on the particular demographic in focus, and were validated based on questionnaires and anthropometric measurements. The scores for each risk factor were calculated using means, standard deviations, and cross referencing similar studies using p-values (hypothesis testing-population) and 95% confidence intervals (Dugee et al., 2015). The risk factors with higher weighted coefficients (risk scores) represent an increased impact and risk of developing T2D. The risk values are developed specifically for the target populations and are generally not applicable for other sample populations (Bhowmik et al., 2015), however, by analysing the risks in a number resource poor setting, will help to identify the risk scores for the generalised low to middle income population.

The results of the data research are summarised in table 1, where the accumulated risk score is associated with the impact of the risk, and the frequency is the amount of times the risk was found between the studies, representing the likelihood of the risk being a factor. Age, large waist circumference and high BMI's were

found to be most significant predictors of development of diabetes. In particular, for ages ≥41 there was an associated high risk score. It was also noticed that as age increased so did the amount of risk, this relationship is considered a preliminary conclusion due to the lack of data and skews in age demographics between each study. To validate this conclusion a study for LMIC found that an increase in age correlated to a proportional increase in the prevalence of T2D (Shen et al., 2016).

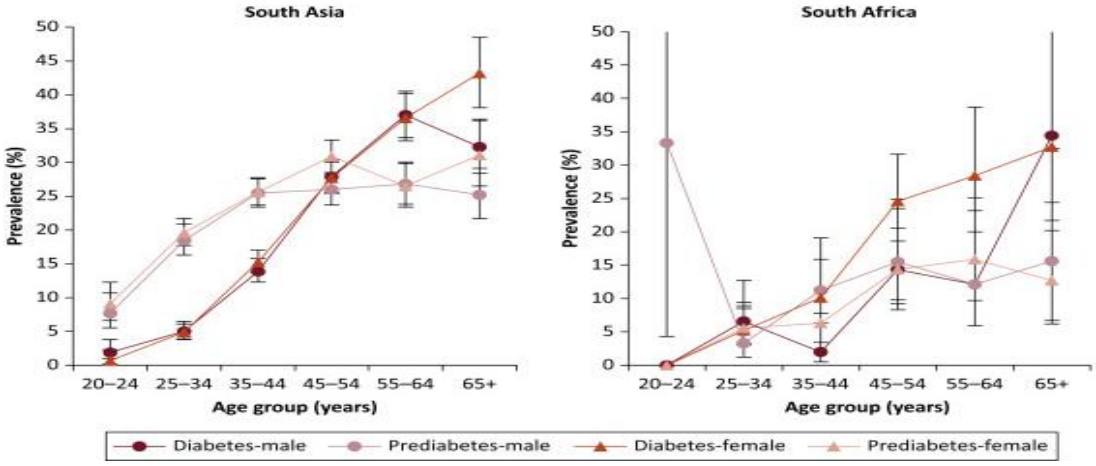

Figure 1, Age and sex specific prevalence of diabetes (Shen et al., 2016)

Other risks that were found throughout research included, history of elevated glucose and ethnicity. The risk factors that had the highest probabilities and appeared the most frequently in the studies were ones associated with unhealthy lifestyles and diets, that create high risk anthropometric and laboratory measurements. Similar conclusions were also made in a number of studies that found BMI (Tirosh et al., 2011), anthropometric measurement and a number lifestyle factors to be a significant predictor of diabetes (Bhowmik et al., 2014). In addition, it has been found that rapid changes in dietary practices and sedentary lifestyles has caused an increase of childhood obesity in developing countries, which predisposes them to, insulin resistance and T2D (Khuwaja, Khowaja and Cosgrove, 2009).

Table 1, Risk factors of developing type 2 diabetes, values were sourced from a detailed data organisation

Risk Factor	Accumulated Risk Score	Frequency
Age ≥ 70	36	4
Age 51-59	30	5
Waist Circumference Men ≥85 & Women ≥80	37	6
BMI (kg/m^2) ≥27.5	27	4
BMI (kg/m^2) 24-25	10	2
History/Presence of Hypertension	21	5
Genetic Predisposition	15	4
Sedentary Lifestyle	11	2
Men	9	4

One source of error that was encountered in these studies included skews in the demographics, an example was found in the Mongolian study, where the population sample ranged from only 35-64 years of age, neglecting the risks of diabetes for young adults and children. In addition, 62% of the sample population tested

were women (Dugee et al., 2015). A potential sample population error was also present in the Thailand study (Aekplakorn et al., 2006), with demographic consisting primarily of urban dwellers of middle-income social classes, thus neglecting all other social classes residing in Thailand. The requirement limits and criteria for each study were also defined differently which pose as a source of inconsistency, for example undiagnosed diabetes was defined for blood glucose levels at ≥7.0mmol/L for the Bangladesh and Thailand study and ≥6.1 mml/L for the Mongolian Study. Additionally, to simplify the analysis, the risks associated with age were divided into age groups, some of which did not directly correlate to the age groups defined in some studies. Similarly, it was assumed that the risk scores defined for ages greater than or equal to a certain value were accumulative for each proceeding age group.

Not only are there risk factors associated with developing T2D, but there is also a considerable amount of diabetic associated complications once you are diagnosed with T2D. It has been found that undiagnosed diabetes and disturbances in glucose metabolism has an associated increased risk of death of up to 3 times (Dugee et al., 2015). The symptoms of T2D are often associated with, metabolic syndromes, and development of micro- and macro-vascular complications (Dugee et al., 2015). A number of studies have indicated that 30-50% of patients with T2D usually present one or more micro- or macrovascular complications upon diagnosis (Bhowmik et al., 2015). These complications can be attributed to the early asymptomatic stages of the disease, causing delays in detection (Aekplakorn et al., 2006). For these reasons it is recommended that methods for early identification of T2D is developed. The risk score assessment method is a simple and effective tool that is measured based on a questionnaire and anthropometric measurements, which can be carried out at a primary care level or as a self-assessment. The tool has potential to be a cost effective solution for preventing, and reducing both the rising prevalence of T2D and impact it has on the health care budgets in resource constrained countries (Bhowmik et al., 2015). To reduce the errors and develop a valid risk score that is applicable for all LMICs, surveys, anthropometric measurements and laboratory data should be statistically analysed and validated, to directly determine the probabilities and coefficients of each risk factor. Developing a generalised risk score could potentially be used as an accurate low cost screening tool for identifying T2D in the early stages of the disease, which may also reduce the load on a number of health care systems. The tool may also present itself as an education tool on the risks of diabetes, both enhancing people's awareness of developing diabetes and potentially influencing lifestyle modifications.

3.2. Modelling an Effective Health Care System

In most resource poor settings management of type 2 diabetes is sub-standard, diabetic complications are not prevented, treated or recognised, and interruptions in access to insulin is frequent (Allain et al., 2011). A successfully developed healthcare framework "DOTS" was based on five key principles: sustained political and financial commitment, quality assured diagnosis, standardised treatment, uninterrupted supply of high quality drugs and standardised monitoring (Allain et al., 2011). Due to limited communication, and little information on, political and health care situations in LMICs, the first factor will be excluded from this analysis. Many refined diabetic health care models have been developed by organisations, medical schools and businesses in industrialised countries (Esterson et al., 2014), thus, the model proposed here will be designed for implementation by non-governmental organisation residing in HICs, with the goal of future implementation with government support and involvement. The majority of monetary aid for these organisation is accrued from their own governments, and many United States based organisations have developed successful programs that are now implemented in current LMIC health care systems (Esterson et al., 2014). For these reason the cost associated factors associated with diabetic treatment will be sourced from HICs and converted to $USD.

Quality assured diagnosis and standardised monitoring and treatment will be addressed using the developed risk score assessment, an increased responsibility of primary care nurses, and implementation of an electronic

medical record or cloud computing database system. Due to the limited amount of physicians in resource poor setting the queues in hospitals and medical clinics are long and inefficient (Esterson et al., 2014). The limited amount of physicians and doctors can be modelled as a single channel and single phase system. By increasing the amount of primary nurses capable of managing diabetes will help to improve the speed at which patients are addressed, by modelling the system as a multiple channel, single phase system. The education of nurses can be achieved in a number of successful ways, including intensive courses, long term distance education using PowerPoint, video lectures or developed textbooks. The recommended method of education for nurses in this study, was used in a successful education program, implemented as a top down approach in the Ghana diabetes care model. It included two core teams consisting of a doctor, nurse and dietician who underwent training in the United States. Following the training the core teams returned to Ghana where they trained regional teams of doctors, nurses and dieticians, the regional teams subsequently trained the sub-regional teams. The trained regional teams were also active in regular workshops to maintain their training (Amoah et al., 1998).

Use of an automated database technology in health care clinics also has the potential to increase the efficiency of hospital queues, by reducing the delays in file transfer, misplacement of files and delayed decision making (Lederman, 2002). In a DOTS for diabetes model conducted in Malawi, EMF systems were developed for touch screen workstations, the system proved to be a more effective and efficient way of maintaining patient records, thus reducing the time spent on file administration (Allain et al., 2011). A cloud computing approach was conducted in Latin America, where a completely developed infrastructure for automated patient monitoring and self-care support was operated from a server located in the United States (Piette et al., 2011). This type of system shows feasibility and potential to reach patients in LMICs, which will significantly reduce the increasing queue pressure and utilisation value for nurses, doctors and physicians in hospitals.

A study conducted a queue theory analysis for nurse staffing in hospitals, as a means to appropriate nurse staffing levels. The model description consisted of a fixed number of occupied beds, which generate requests at a rate of, λ_n. Additionally, an outside source of requests arrived at a rate of, λ_b, which represents the workload associated with admissions. The patients were also modelled to arrive to the hospital according to a Poisson process, and all nurses are assumed to be equally trained and the requests are performed on a first-come, first served bias (Yankovic and Green, 2008).

The results of the analysis indicated that an increase in nurse's correlates to a decrease in inpatient delays and a decrease in nurse utilisation. The results are summarised in figure 2.

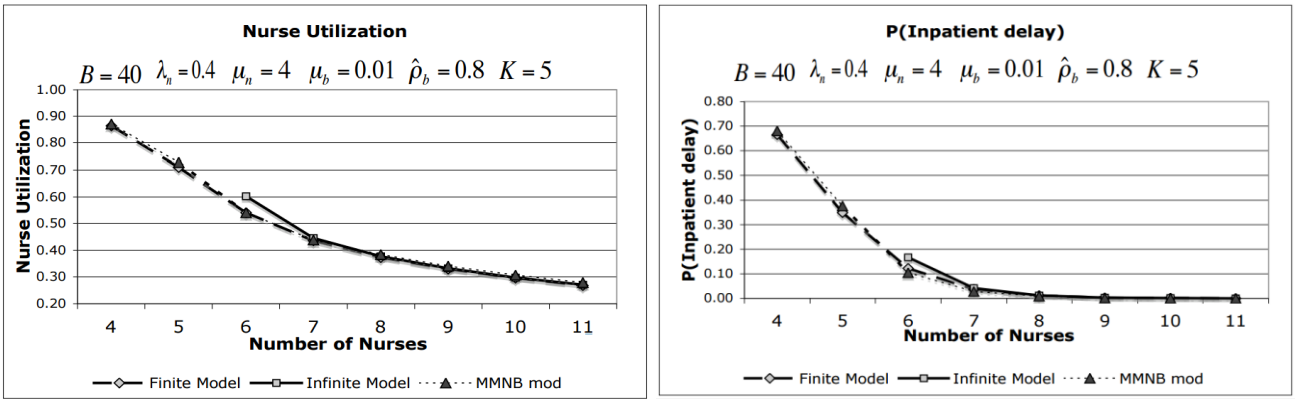

Figure 2, Nurse utilisation and inpatient delay trends for hospital queues (Yankovic and Green, 2008).

The results from the above study indicate that with more nurses comes an associated increase in service rate. Using a one dimensional simplified case for a hospital in an LMIC, we can theoretically determine an increased efficiency. With educated nurses being able to treat and manage patients with diabetes, there will be a noticeable increase in service rate (μ), this will consequently reduce the percentage of nurses and

physicians constantly being busy using the utilisation equation $\rho = \lambda/\mu$, where λ is the arrival rate of patients. A lower utilisation value will also lead to a lower average time spent in the queue. Thus allowing nurses to effectively treat all patients without being rushed. To ensure validity in increasing efficiency, a cost analysis should be conducted on the cloud computing system to determine whether or not the system is cost effective in increasing diabetes regulation. A cost analysis will also act as a means to appropriate the amount of nurses in each hospital, to minimise the amount of money wasted due to low nurse utilisation

4. Improving Access to Insulin for Type 1 Diabetes

4.1. Qualitative and Quantitative Motivation

It is important to consider the social and cultural factors that LMICs face when trying to improve the health care of diabetes. Although T1D is not as prevalent as T2D, it is important to analyse the treatment of both diseases. This ensures that the minority of the population is addressed and an inclusive health care system is designed. The rates of T1D, may be vastly underestimated, with 5-15% of adults diagnosed with T2D may in fact have T1D with autoantibodies (Atkinson, 2010). In contrast to T2D, T1D is most commonly diagnosed during youth (<20yr), accounting for ≥85% of all T1D cases worldwide (Maahs et al., 2010). The cause of T1D is currently unclear (American Diabetes Association, 2010), and there is no direct correlation between LMICs and an increasing rate of T1D, when compared to rates in HICs (Atkinson et al., 2014). The commanding problem in LMICs is not an increasing rate of T1D, rather, it is the poor availability and management of diabetic treatment.

There are major risks associated with incorrect management of exogenous insulin replacement, including a number of disease associated complications, including neuropathy, nephropathy, hypoglycaemia, retinopathy, ketoacidosis, foot complications and cardiovascular disease (Atkinson et al., 2014). These diabetic complications continue to be a primary cause of morbidity and mortality in T1D, with cardiovascular disease prevailing as the leading cause of death (Maahs et al., 2010). It has been found that individuals with T1D have ten times higher risk of experiencing a cardiovascular event (Atkinson et al., 2014), and up to 40 times more likely to require lower limb amputation, than non-diabetics (Khuwaja, Khowaja and Cosgrove, 2009). Indicating that cardiovascular disease, and lower limb amputation has a high impact and likelihood of occurrence, for patients with T1D. The proceeding sections detail methods for reducing the risks of these complications.

4.2. Physiology

After the insulin releasing β-cells in the body are degraded the body is no longer able to regulate the glucose levels in their blood to produce energy, consequently the glucose tends to build up in the blood stream (Eren-Oruklu et al., 2009). When this occurs the haemoglobin protein in the body attaches to the glucose and becomes glycated haemoglobin (HbA_{1C}) (American Diabetes Association, 2010). The optimum glycaemic levels ($\mathrm{HbA_{1C}}$) are commonly thought to be between 4.0 and 7.8mmol/L (Diabetes Australia, 2016), the main objective of diabetic therapy is to maintain blood glucose concentration within this range and reduce concentration variability (Eren-Oruklu et al., 2009). After conducting a safety and risk analysis it was found that minimising glycaemic variability correlates to a decrease in a number of diabetic complications listed previously (Rayfield, 2015).

4.3. Multiple Daily Injections

Multiple daily insulin injections (MDI) are the most common method used to optimise metabolism and treat diabetes in LMIC's (Kesavadev et al., 2010). This type of diabetic treatment is strict, time consuming and without the correct monitoring of glycaemic levels, it becomes dangerous for the user. The MDI method consist of long acting insulin, which is commonly administered during periods of fasting (sleeping), and rapid-acting insulin which is administered before each meal (Atkinson et al., 2014). In addition to 3-5 daily insulin

injections, type 1 diabetics, commonly take 3-7 daily blood glucose measurements (Eren-Oruklu et al., 2009). It has been found that patients that use injection therapy experience high levels of glycaemic variability, which is commonly attributed to the difficulty in optimising the insulin amount/rate and timing of injections (Eren-Oruklu et al., 2009). This becomes particularly difficult for type 1 diabetics residing in LMIC's, who commonly experiences changes in their diets and lifestyles (Misra et al., 2011).

Reviewing the anthropometric, social and cultural perspectives of insulin therapy found that the amount, and type of insulin that should be used for treatment, is dependent on common human measurements and lifestyles. Prescribing insulin is dependent on the patient's height, weight, metabolic rate, physical maturity, blood glucose level, exercise and diet (Kamaraj, Gandhimathi and Ramesh, 2014). In addition, insulin must be injected into subcutaneous tissue only, including, the abdomen (except within 2 inches of the navel), the outsides of the upper arms, anywhere on the buttocks, and the front and outside areas of the thighs (Figure 3) note that shots should only be administered to thighs if there is a sufficient amount of fat present. (Figure 4).

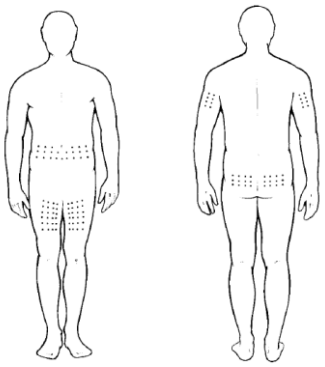

Figure 3, Sites for Insulin Injections. (American Diabetes Association, 2010).

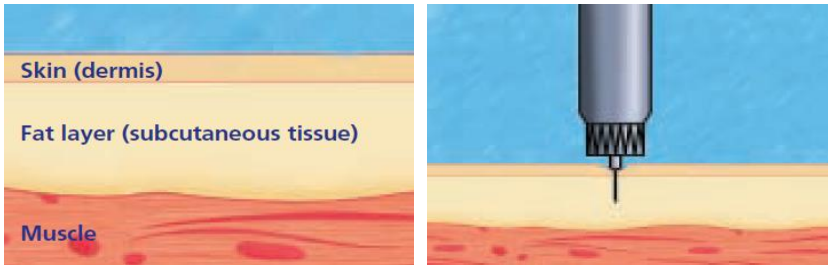

Figure 4, Subcutaneous layer where insulin should be administered. (Becton Dickinson Canada, 2016)

It is important to also consider which sections of the body absorb insulin at faster rates, this will help to determine where you should inject the and at what time. From the recommended area the abdomen has a high rate, followed by arms, buttocks and thigh (American Diabetes Association, 2010).

4.4. Pump Device

Many high income countries over the past decade have adopted the use of continuous sub-cutaneous insulin infusions (CSII), commonly referred to as insulin pumps (Atkinson et al.,2014). Standard insulin therapy most commonly involves continuous or intermittent insulin delivery; this insulin is administered continuously by predetermined basal rates (Ly et al., 2014). These basal rates are made of small insulin doses based on the basal insulin production of the pancreas (Ly et al., 2014). Additional insulin can be delivered in a Bolos dose, which is used to correct the glucose levels based on carbohydrate intake (Ly et al., 2014). These rapid acting insulin analogues are specifically adjusted to the patient's lifestyle and needs, and consequently act as a more physiological method of insulin d (St Charles et al., 2009). The increased use of this method has found to decrease the risk of hypoglycaemia, which continues to pose the largest barrier in maintaining glycaemic control (Maahs et al., 2010). The below figure describes the open loop feedback system of CSII therapy and Insulin Injection therapy (Figure 5).

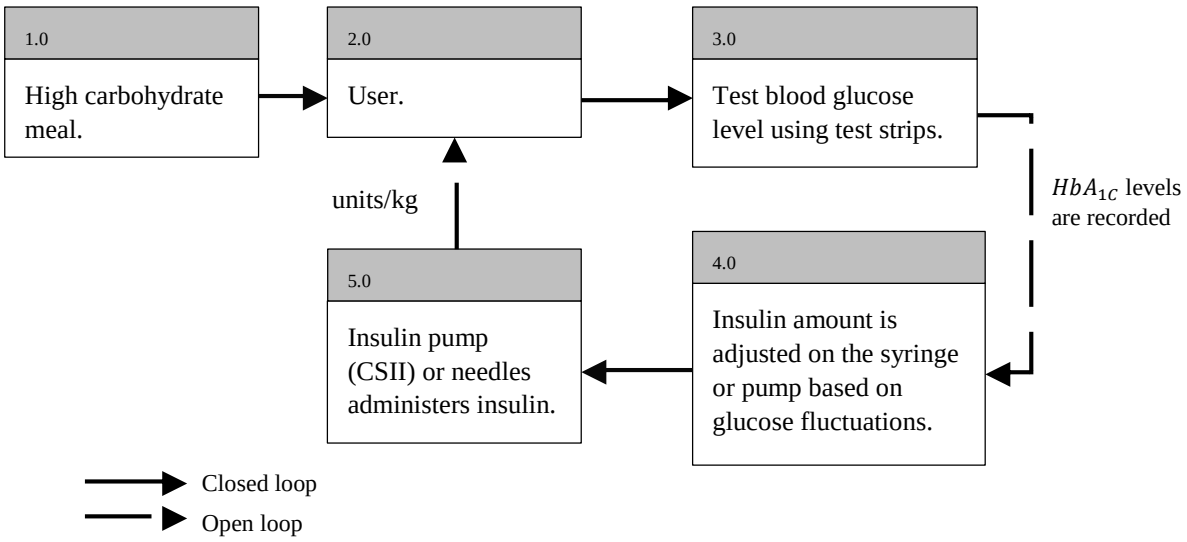

Figure 5, Open Loop feedback system for CSII and Daily Injections

4.5. Sensor Augmented Pumps

In addition to enhancements in insulin delivery systems, improvements have been made to glycaemic control, via, self-monitoring blood glucose report software and real time continuous glucose monitors (CGM) (Atkinson et al., 2014). The CGM device provides blood glucose concentrations at high frequencies, and provide detailed information on patient's glucose profiles throughout the day (Eren-Oruklu et al., 2009). In a study using the CGM system, there was a noticed decrease in the amount of time spent in hypoglycaemia (<4mmol/L) and a lowered HbA_{1c} for patients that previously had higher HbA_{1c} concentrations (Tamborlane and Beck, 2009). The system has also shown to reduce nocturnal hypoglycaemia (during sleep) in children (Anon, 2010). The CSII pumps and CGM technologies are starting to be used in conjunction, as a sensor augmented pump therapy (SAP) (Atkinson et al, 2014). This kind of therapy uses the two devices independently in a closed feedback loop system, similar to the open loop system displayed in figure 5. Closed loop systems are currently being investigated. One system that has been developed, is the low-glucose suspend (LGS) system, which monitors glucose levels and stops administering insulin for 2 hours when blood glucose levels fall below certain thresholds, thus preventing hypoglycaemic episodes (Rayfield, 2015). This type of insulin therapy has been trialled, and it showed a significant improvement in lowering HbA_{1C} levels and patients showed a decrease in hypoglycaemia episodes, when compared to injection therapy (Álvarez et al., 2010).

The closed loop feedback system shown below (Figure 6) is potentially the most effective way to emulate the physiological role of the pancreas. The system is autonomous and which will not only help to manage blood glucose levels, but will improve the patient's lifestyle and prevent complications. The system operates based on the user's reaction foods that contain glucose. Each food will have a different effect on the user's blood glucose levels, the blood glucose sensor will determine the HbA_{1C} levels and send this data to the algorithm controller which determines how much insulin needs to be administered. Finally, the insulin pump dispenses the required insulin as the measured output of the system.

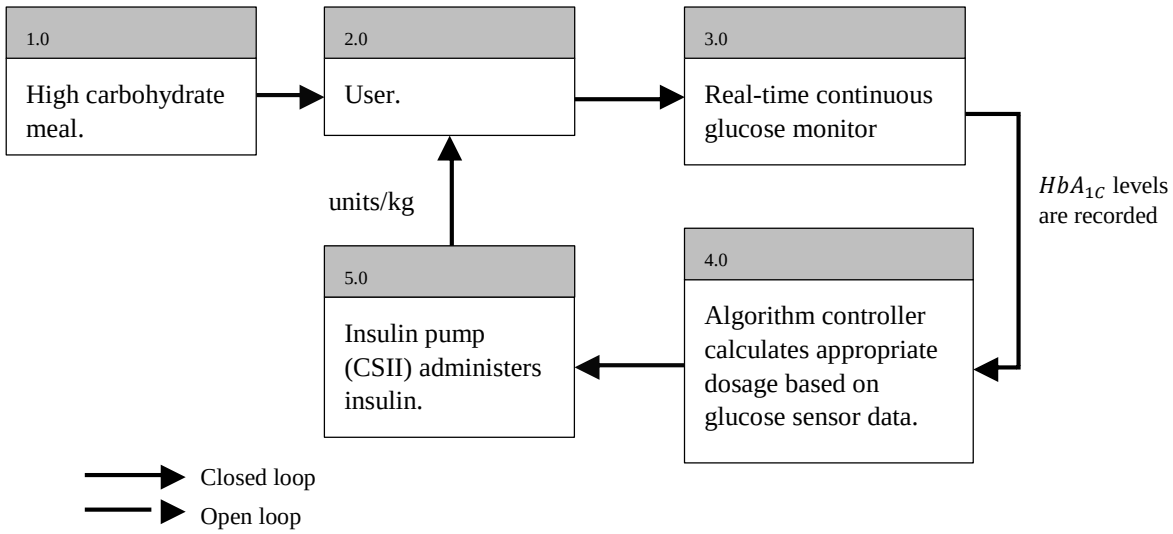

Figure 6, Components for a closed loop sensor augmented pump system.

The limitations associated with a sensor augmented pump device includes the subjective variability of metabolisms between patients, delays in insulin delivery due to the time consuming control processes an increased risk of human error when manually entering meal consumption and daily exercise (Eren-Oruklu et al., 2009).

5. Recommended Therapy for LMICs

The system of insulin therapy that is most suitable for LMICs will be determined by using both a cost analysis process control tools, and material impact analysis tools. As stated in the previous sections the goal of diabetic therapy is to maintain normal glycaemic levels. In cases where hypocalcaemia occurs, hospitalisation or a medical check-up may be necessary, in these situations there is an associated cost. In the following analysis, the life cycle costs of patients with T1D will analysed, based on the acquisition phase, where the cost of the necessary equipment will be detailed, the operations and use phase, the renewal phase and the costs associated with diabetic complications. The life cycle costs of each type of diabetic therapy will be investigated, and converted into a payback period graph, as a means to determine which method of treatment is the most cost effective in the long term.

Evidence from a study has shown that CSII is associated with improved glycaemic control and reductions in hypoglycaemic events, when compared to MDI (St Charles et al., 2009). The same study also found, that there was an improved quality of life and a reduction in diabetic complications (St Charles et al., 2009). CSII therapy commonly requires more equipment and more training at initiation when compared to MDI therapy, and thus CSII therapy tends to be more expensive at the acquisition phase, however these costs may potentially be offset by reduced insulin requirements and a reduced risk in complications due to improvements in glycaemic control (St Charles et al., 2009). CSII was found to be a cost-effective treatment when compared to MDI in a number of countries (Roze et al., 2015). The objective of this cost analysis, is to validate which diabetic therapy would be most beneficial and cost effective for LMICs, to reduce the extra pressure imposed on individuals with T1D and the healthcare system of the country.

5.1. Life Cycle Costs for SAP, CSII and MDI

Table 2, Life Cycle Costs for Type 1 Diabetes Therapies

Resource	Unit	Frequency of unit turnover	Cost Per Unit ($USD) ($AUD) (€)	Annual Costs ($USD)	SAP	CSII	MDI	Study
CSII Pump	1 pump	1/7 y	4739.98 USD	677.14	-	x	-	(St Charles et al., 2009)
LGS Pump	1 pump	1/6 y	9,949.76 AUD	1,263.29	x	-	-	(Ly et al., 2014)
Syringes and Needles	1 needle	4/d	0.314 USD	459.04	-	-	x	(St Charles et al., 2009)
Batteries for Insulin Pump	1 battery	1/5 wk	0.87 AUD	6.89	x	x	-	(Ly et al., 2014)
CGM Transmitter and battery charger	1 transmitter and charger	1/2 y	522.62 AUD	199.07	x	-	-	(Ly et al., 2014)
Transmitter Battery	1 battery	1/12 wk	0.87 AUD	2.87	x	-	-	(Ly et al., 2014)
Autonomous Glucose Sensor (Enlite)	1 sensor	1/6 d	78.55 AUD	3,640.23	x	-	-	(Ly et al., 2014)
Infusion Set	1 infusion set	1/3 d	15.27 AUD	1,415.31	x	x	-	(Ly et al., 2014)
Insulin Reservoir	1 reservoir	1/3 d	4.40 AUD	407.814	x	x	-	(Ly et al., 2014)
Lancets	1 lancet	5/d	0.16 AUD	222.45	x	x	x	(Ly et al., 2014)
Glucose Test Strips	1 strip	5/d	0.56 AUD	778.56	x	x	x	(Ly et al., 2014)
Freestyle Optium Neo Glucose Meter	1 meter	1/4 y	69.00 AUD	13.14	x	x	x	(Diabetes Queensland, 2016)
Insulin	0.71 units/kg/day	1 y	2047.60 USD	2,047.60	x	-	x	(St Charles et al., 2009)
	0.53 units/kg/day	1 y	1421.94 USD	1,421.94	-	x	-	(St Charles et al., 2009)
Outpatient	5 Visits	1 y	372.43 USD	372.43	x	x	-	St Charles et al., 2009)
	4 visits	1 y	312.10 USD	312.10	-	-	x	St Charles et al., 2009)
Complication Costs	60-year lifetime	60 y	102,212 USD	1703.54	-	x	-	St Charles et al., 2009)
	60-year lifetime	60 y	121,296 USD	2021.60	-	-	x	St Charles et al., 2009)
	60-year lifetime	60 y	27397 €	500.27	x	-	-	(Roze et al., 2016)

The total annual and lifetime costs for each therapy were summed and the results are summarised in table 3. The highest annual cost was achieved by the SAP, calculated to be $10,244, this was expected due to the high

capital costs upon acquisition, and the constant costs of operations, use and renewal. The mean lifetime cost was set at 60 years, as a means to capture the patents lifetime and ensure that development of complications was included in the analysis (St Charles et al., 2009). The lifetime totals for SAP, CSII and MDI therapy were calculated at, $614, 655, $421,153 and $351,269 respectively. The analysis showed that the high cost of SAP treatment was significantly offset by a reduction in complication costs, for the SAP when compared to CSI and MDI, however the offset was not large enough to provide a payback period. A limitation in this analysis, was each study focused their analysis on a separate country based on separate cohorts. Due to these limitations, the costs for each resource and factor was adjusted using inflation conversion rates to 2016 USD ($), calculated using data from the world bank (Data.worldbank.org, 2016). Additionally, currency exchange rates were converted to $US using XE (Xe.com, 2016). It should be noted that the inflation rates are not a precise indications of fluctuations in medical expenses, which vary independently based on the health care system of the country. It is also acknowledged that using separate cohorts for each study will provide inconsistencies when determining the costs associated with diabetic complications.

Table 3, Annual and Lifetime Costs of Therapies

	SAP	**CSII**	**MDI**
Totals ($USD)	10,244	7,019	5,854
Lifetime Totals (60y) ($USD)	614,655	421,153	351,269

5.2. Measuring the Cost-Effectiveness

Although there was no payback period for SAP and CSII when compared to MDI, the cost effectiveness of the treatments should be measured based on the performance of the therapy. Data was extracted for total lifetime diabetic therapy costs and quality-adjusted life years gained, to facilitate comparisons the data was converted based on inflation and exchange rates. Seven different settings were analysed in the following analysis, the skews in each of the demographics, and varying health care systems provided a wide spread of lifetime cost values, as indicated by the standard deviation. HICs were also analysed in this study to effectively determine the costs for non-governmental organisations, and due to the little reliable information about incident and treatments outcomes in LMICs. The measure of cost effectiveness is determined using an incremental cost effective ratio, given by,

$$ICER = \frac{\Delta Cost}{\Delta QALY}$$

Table 4, Cost Effectiveness based on total lifetime costs and quality-adjusted life years for 7 studies,

	Quality-adjusted Life Expectancy (years)				Lifetime Costs ($USD)				
Study	SAP	CSII	MDI	**Δ** QALY	SAP	CSII	MDI	**Δ** Cost	**ICER ($US 2016)**
USA-(St Charles et al., 2009)	-	12.85	11.79	1.06	-	237,193	216,259	20,934	**19,749**
UK-(Roze et al., 2005)	-	12.03	11.27	0.76	-	144,223	89,823	54,400	**71,578**
Denmark-(Nørgaard et al.,2010)	-	12.52	11.56	0.96	-	348,822	345,671	3,151	**32,448**
Canada-(Charles et al., 2009)	-	10.03	9.37	0.66	-	145,196	131,291	13,905	**21,068**

Australia-(Cohen et al., 2004)	-	7.95	7.48	0.47	-	152,138	109,429	42,709	**90,870**
Australia- (Ly et al., 2014)	N/A	N/A	-	N/A	N/A	N/A	-	N/A	**32,554**
France- (Roze et al., 2016)	10.55	9.36	-	1.19	93,226	53,948	-	39,278	**33,006**
Mean	**10.6**	**10.8**	**10.3**	**0.9**	**93,226**	**180,253**	**178,494**	**29,062**	**43,039**
Standard Deviation	**0.0**	**2.0**	**1.8**	**0.3**	**0.0**	**100,924**	**105,160**	**19,492**	**27,234**

In agreement with the life cycle cost analysis conducted above, each study found that the reported lifetime costs were higher for SAP vs. CSII therapy. Similarly, the lifetime costs for CSII where greater than those for MDI. A higher lifetime cost was associated with a with a higher quality-adjusted life expectancy. SAP therapy has an associated HbA_{1c} benefit which lead to delays in diabetic complications and consequently improved the QALY of patients (Roze et al., 2016). Similarly, CSII vs MDI studies showed a noticed benefit in HbA_{1c} levels and a reduction in hypoglycaemic events (Roze et al., 2015). The studies determined whether or not the therapies were cost effective or not, by plotting the data on an acceptability curve, by assessing the probability of cost-effectiveness according to the customer's willingness to pay. An acceptability curve was replicated using MATLAB for the study conducted in the USA, it was noticed that there was a 1000% probability that CSII would be cost-effective relative to MDI for patients willing to pay $US50,000/QALY (Figure 7) (St Charles et al., 2009). The willingness to pay threshold, total lifetime cost for each therapy will vary between each setting and health care. It is evident however from these studies that increased glycaemic control using the SAP and CSII therapy, leads to a lower incidence of complications and in turn, an increase quality adjusted life expectancy. A limitation and source of error that is prevalent in these studies, is the model does not consider many real life social factors, such as compliance, effectiveness and dropout rate.

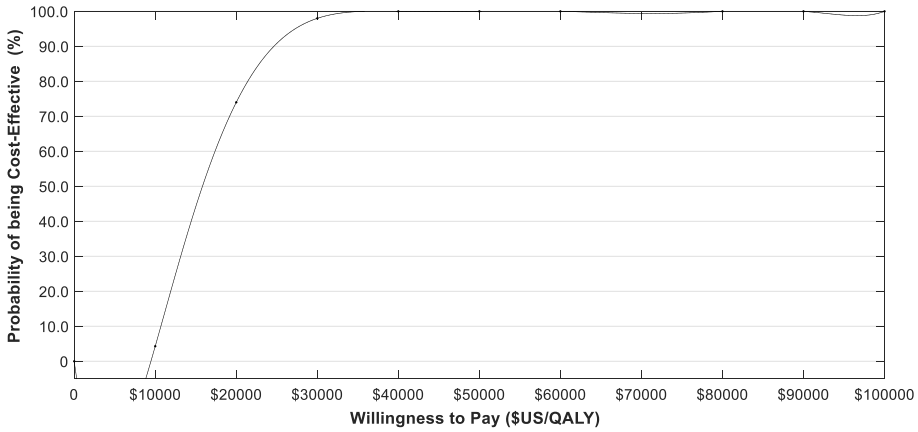

Figure 7, Cost-effectiveness acceptability curve for type 1 diabetes in the US. (St Charles et al., 2009)

When comparing the average lifetime cost from table 4 and table 3, there is a significant overestimation of cost with the life cycle analysis. This is likely due to overestimations in complication costs, equipment cost, and renewal costs caused by inaccurate inflation rates. It can be argued that the lifetime costs defined in table 3 are the upper bounds of lifetime diabetes cost.

Two studies were conducted for SAP vs. CSII, however only one study provided sufficient detailed information, it showed that SAP had the largest increase in QALY when compared to CSII, however, without substantial data, no sufficient conclusions can be made about the products validity. The life cycle costing results summarised in table 3 also found, that SAP therapy was the most expensive option, and although it may be a cost effective therapy, it is cannot be concluded that it is the most suitable therapy for LMICs. The

average lifetime cost for MDI therapy, was calculated to be, $178,494±105,160 with a QALY of 10.3 years. The mean lifetime cost for CSII therapy was calculated to be $180,253±100,924 with a QALY of 10.8 years. With such minor discrepancies between the cost and, an overall improved quality of life for CSII patients, it is recommended that CSII therapy is introduced and utilised in LMICs. Furthermore, these two types of therapies will be validated based on HbA_{1C} control and environmental impact.

5.3. Control of HbA_{1C} for CSII and MDI

To further validate which of the two types of therapies were most effective in treatment, two interviews were conducted on two different patients in the Canberra region. One patient who used CSII therapy and the other who used MDI therapy, during the interview blood glucose data was retieved from each pateint, using the associated software for their blood glucose meters. The interviewee using CSII therapy used an Accu-Chek mobile glucose meter and provided 90 days of data, in contrast the interviewee using the MDI therapy used the Optium Neo glucose meter, which provided a years worth of data. The HbA_{1C} process control graphs were created using the Free-Style Auto-Assist Neo software and th Accu-Chek 360 Mobile Report software, and can be seen in figures 8 and 9. Consent was given by both patients to use their data and responese in this report.

To facilitate comparison between the two data sets, 90 days were used for both patients and where recorded from 12 July 2016 to 9 October 2016. Prior to conducting a p value tests, it was hypothesised that the CSII therpay would improve glucose control. The following calculations were made using the values calculated from the data, note that data set 1 is CSII therapy and data set 2 is MDI therapy,

$$\text{Z Value} = \frac{(\overline{x_1} - \overline{x_2})}{\sqrt{\frac{\sigma_1^2}{n_1} + \frac{\sigma_2^2}{n_2}}} = \frac{(10.15 - 10.7)}{\sqrt{\frac{4.82^2}{376} + \frac{3.89^2}{258}}} = 1.58$$

The corresponding P-value was found using Graphpad.com (2016), giving a value of 0.1132. This indicated that the difference between the two data sends are not considered statistically significant. Indicating that CSII in fact does not significantly improve the glycaemic control of patients when compared to MDI.

This statistical conclusion should be validated, using the criteria that that studies in table 4 used. This primarily included reductions in hypoglycaemic events. When comparing the CSII and MDI data it was found that for MDI the blood glucose levels ranged from 2.1-22.2mmol/L, for the CSII patient the levels ranged from 2.6-26.5mmol/L. Additionally, it was found that 64.6% of the time the CSII patient was above the target range (>7.8mmol/L), 27.1% of the time the patient was within the target range (3.9-7.8mmol/L) and 8.3% of the time the patient was below their target range (0.0-3.9mmol/L). For the patient using MDI therapy it was found that 77% of the time the patient was above the target range (>7.8mmol/L), 20% of the time they were inside the target range (4.4-7.8mmol/L). and 3% of the time they were below the target range. These statistics suggest that CSII therapy does not improve glycaemic control and there is a higher likelihood of hypoglycaemic events. This may be due to the discrepancies between target values and high and low blood glucose indexes, for example a hypoglycaemic event for the MDI patient is values below 3.9mmol/L and for the CSII patient the hypoglycaemic index is 1.5 and below. As mentioned by both of the interviewees, diabetic therapy is subjective to every patient, this can be seen by the different process control boundary limits set for each patient. The subjective nature of each treatment, and the limited amount of patients analysed, posed as a source of error in the analysis. Due to these discrepancies it cannot be concluded that CSII therapy does not improve glycaemic variability.

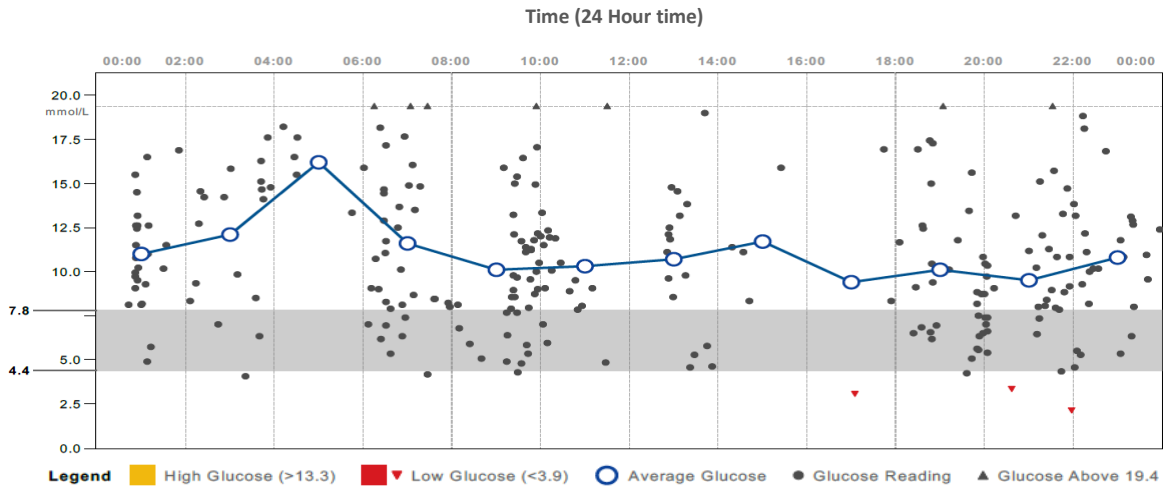

Figure 8, Process control graph for interviewee using MDI therapy.

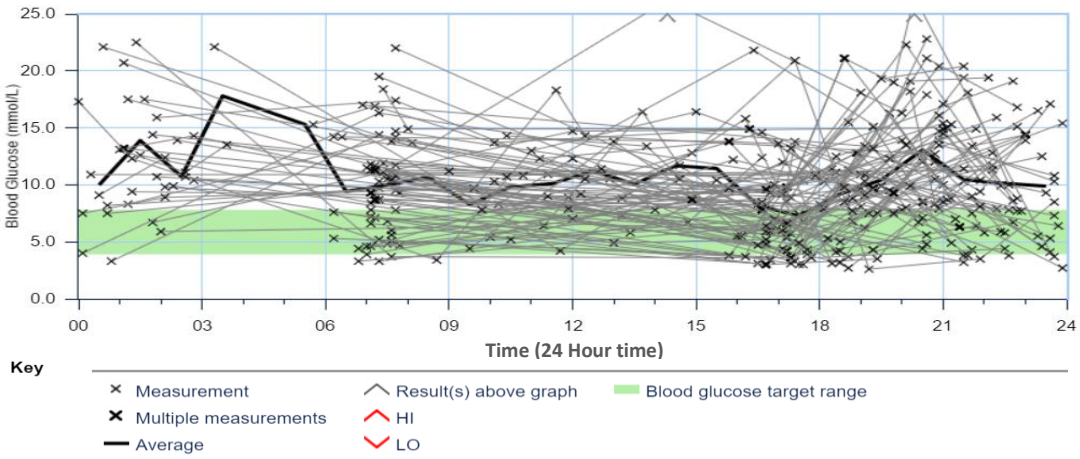

Figure 9, Process Control graph for interviewee using CSII therapy.

It could be argued based on the information provided on SAP therapy that these process control graphs would not display as much glycaemic variability, and show no signs of hypoglycaemia or high glucose level patterns. Due the small amount of people using SAP therapy, it was difficult to find a patient willing to participate in this study. It is recommended that before further implementation of CSII or MDI therapy, a process control on SAP therapy should be conducted and compared.

5.4. Material Impact of CSII and Needles

With such high rates of disposal and renewal of diabetic equipment, it is important to consider the potential environmental impact of pharmaceuticals. To moderate this issue, medicinal product companies are forced to analyse the potential environmental impact of disposed products as waste, with the intention of minimising the release of medicinal chemicals into the environment (Pfützner et al., 2011). The main source of waste from MDI therapy are syringes, test strips, injection caps, and lancets, patients take approximately 4 injections a day (Gold, 2011), which demonstrates the usefulness in analysing the environmental impact. The main source of waste disposal associated with CSII therapy are the infusion sets, lancets and test strips however unlike MDI therapy infusion sets only require replacement every 2-3 days (Pfützner et al., 2011). The equipment detailed above, are commonly polymeric materials, which are reliable and represent efficacious functioning of drug delivery systems, however there are several consequences associated with the degradation of the products with the environment (Pfützner et al., 2011). An environmental impact analysis of insulin

infusion sets, was conducted by Pfützner et al. (2011), and looked at the loss of natural resources as a burden to the environment when disposed of as waste rather than recycling.

The analysis focused on a number of ordinary insulin infusion products, and a tubing free insulin infusion system (Omnipod) (Table 5). The resource consumption for 1 year was calculated and compared to the waste of a disposable cup of coffee and an aluminium can. Additionally, waste information for insulin pen needles were included in the analysis, assuming the number of pen needs used per day was 4. The results of each infusion set are summarised in table

Table 5, Weight Based Loss of Resources, infusion set data was sourced from (Pfützner et al., 2011), and pen needle data was sourced from (Diabetes WA shop, 2016)

Product	Number of Units Consumed after 3 days	Recycling (%)	Metals (g)	Plastics (g)	Paper/wood (g)
Infusion sets					
Inset 30	1	0	0.05	22.14	1.49
Insetll	1	0	0.02	23.62	0.09
Comfort	1	0	0.06	8.11	0.89
Quick-set	1	0	0.02	11.32	0.87
Cleo	1	0	2.10	27.13	1.00
Omnipod	1	0	11.83	30.31	1.06
Pen needles					
BD Ultra-Fine	12	0	31*	-	-
Novo-Fine Plus	12	0	32*	-	-
Unifine pentips	12	0	31*	-	-
Novo-Fine	12	0	30*	-	-
BD Microfine	12	0	29*	-	-
Coffee Cup	3	0	0	12.09	44.80
Aluminium Can	3	52	18.82	0	0

** Weight is inclusive of metal, plastic and paper/wood.*

In the above table it is assumed that all infusion sets are discarded after use, some of the energy of the plastics are recovered, on the large scale though the plastics are not recycled. Due to the small portion of metallic material in the components there was also no large scale recovery, after incineration (Pfützner et al., 2011). It is concluded that the environmental waste of infusions sets is similar to that of one cup of coffee per day, and far lower than the loss of one aluminium can per day. In contrast the pen needles have a far greater impact on the environment, when compared with ordinary insulin infusion sets, there is a noticed increase in resource consumption by over 5 times. The associated higher amount of resource consumption may also expose sanitation workers to needle stick injuries in LMICs, to reduce this risk, safe needle disposal programs should be introduced in LMICs (Gold, 2011). This analysis concludes that CSII has a much lower environmental impact when compared to pen needles, the analysis should act as a preliminary validation for introducing CSII into LMICs. Further evaluation should be conducted on every piece of equipment, CSII and MDI equipment to determine whether or not CSII is a more environmentally viable option.

In conclusion it is recommended that CSII therapy is implemented in the recommended diabetic health care model outlined in section 3.2. With a potential reduction in percentage of nurse utilisation in the developed health care model, more time during patient check-ups can be dedicated to educating patients on CSII treatment and the associated risk factors of developing diabetes. This will potentially decrease the prevalence of diabetes in LMICs.

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