Screening for Non-Significant Stenosis in Native Arteriovenous Fistula within the Maltese Population

CHRISTOPHER GAUCI

Dissertation submitted in part-fulfilment of the requirements for the degree of Master of Science in Radiography (Vascular Ultrasound) University of Malta

January 2015
University of Malta Library – Electronic Thesis & Dissertations (ETD) Repository

The copyright of this thesis/dissertation belongs to the author. The author’s rights in respect of this work are as defined by the Copyright Act (Chapter 415) of the Laws of Malta or as modified by any successive legislation.

Users may access this full-text thesis/dissertation and can make use of the information contained in accordance with the Copyright Act provided that the author must be properly acknowledged. Further distribution or reproduction in any format is prohibited without the prior permission of the copyright holder.
DECLARATION OF AUTHENTICITY FOR MASTER’S STUDENTS

Student's I.D. /Code: 0284185M
Student's Name & Surname: Christopher Gauci
Course: Master of Science in Radiography (Vascular Ultrasound)
Title of Dissertations:
Screening for Non-Significant Stenosis in Native Arteriovenous Fistula within the Maltese Population

I hereby declare that I am the legitimate author of this Dissertation and that it is my original work.

No portion of this work has been submitted in support of an application for another degree or qualification of this or any other university or institution of higher education.

I hold the University of Malta harmless against any third party claims with regard to copyright violation, breach of confidentiality, defamation and any other third party right infringement.

As a Master’s student, as per Regulation 58 of the General Regulations for University Postgraduate Awards, I accept that should my dissertation be awarded a Grade A, it will be made publicly available on the University of Malta Institutional Repository.

__________________________
Signature of Student

_________________________________________
Date

11.06.2015
Abstract

**Purpose:** To assess the feasibility of introducing a screening programme for patients with end stage renal disease undergoing haemodialysis through an autogenous arteriovenous fistula for the detection of asymptomatic stenosis of the feeding artery and/or fistula

**Objectives:** To scan using duplex ultrasound the autogenous arteriovenous fistulae of the patients with end stage renal disease and identify any asymptomatic clinical stenosis; identify any co-morbid disease that can increase the risk of a stenosis. Create and test a suitable data collection tool.

**Methodology:** Ninety nine patients that fulfilled the inclusion criteria were recruited for the study. Ten of these patients were enrolled for the pilot study and were not included in the main study. Eighty nine patients were asked a series of demographic questions and also underwent a duplex ultrasound examination where both the lumen diameter measurements and blood flow velocities were measured from the arterial and fistula segments. The results were then statistically analysed.

**Results:** The introduction of a screening programme is recommended as the results show that 36% of the patients had undetected, asymptomatic stenoses within their fistula. Fifteen percent from these undetected stenoses were significant. The remaining were non-significant in nature. No stenosis was detected in the arterial segment. All the stenoses were within the anastamotic area or in the fistula itself. The results also showed that 25% of the scanned population had already suffered from either a stenotic or thrombotic event. The mean flow velocity was slightly higher than what is published in the literature. Diseases such as diabetes and hypertension accounted to 71% of the scanned population but these diseases did not show an increased risk for the patients to develop a stenosis. A costing exercise is recommended in order to assess that screening and treatment costs as well as the additional burden of hospital resources are justifiable.

**Conclusions:** Thirty six percent of the patients currently undergoing haemodialysis with an autogenous arteriovenous fistula have an undetected stenoses. A screening programme would be beneficial for the patients undergoing haemodialysis using an autogenous arteriovenous fistula.
I would like to thank my wonderful wife Elena for her unfailing support and enthusiasm during this dissertation. For her patience and love I am deeply grateful.
Acknowledgements

Without the help of numerous people, the completion of this thesis would not have been possible.

My gratitude goes to my supervisor Dr. P. Bezzina, Head of Radiography Department and Senior Lecturer at the Faculty of Health Sciences for his continuous guidance and ceaseless support during the course of this study.

A huge word of thanks goes to my co-supervisor Professor K. Cassar, Consultant Vascular Surgeon at Mater Dei Hospital for his relentless technical guidance and help during this dissertation.

A special thank you goes to Professor L. Camilleri, Statistician and Senior Lecturer at the University of Malta for his help, advice and assistance on the statistical phase of my research.

I would like to thank the staff at the Renal Unit for their assistance during the data collection phase of this research study.

Last but not least I would like to thank all my family and friends for their encouragement during the course of this study.
# Table of Contents

1.0 Introduction .................................................................................................................. 1

1.1 Background to the study ............................................................................................. 2

1.2 Literature Review ........................................................................................................ 3

1.3 Aim and objectives ..................................................................................................... 5

1.4 Methodology ................................................................................................................ 6
   1.4.1 Research Design .................................................................................................. 6
   1.4.2 Data Analysis ..................................................................................................... 7

1.5 Limitations .................................................................................................................... 7

1.6 Ethical considerations ................................................................................................. 8

1.7 Outline of the study .................................................................................................... 8

2.0 Introduction ................................................................................................................... 10

2.1 End stage renal disease .............................................................................................. 11
   2.1.1 Dialysis ............................................................................................................. 12
   2.1.2 Haemodialysis ................................................................................................. 13

2.2 Autogenous arteriovenous fistula .............................................................................. 13
   2.2.1 Arteriovenous graft .......................................................................................... 14
   2.2.2 The purpose of an arteriovenous fistula ......................................................... 14

2.3 Stenosis ......................................................................................................................... 15

2.4 Thrombosis .................................................................................................................. 17

2.5 Co-morbidities ............................................................................................................ 18

2.6 Medical Screening ..................................................................................................... 19

2.7 Pre-emptive treatment ............................................................................................... 22
   2.7.1 The physical examination ............................................................................... 23
3.10 Data analysis .............................................................................................................. 58
  3.10.1 The Pearson’s Correlation ................................................................................. 59
  3.10.2 The One Way ANOVA ...................................................................................... 59

3.11 Strength and Limitations ...................................................................................... 60

3.12 Importance of Ethics in research ......................................................................... 60

3.13 Conclusion .............................................................................................................. 63

4.1 Introduction .............................................................................................................. 64

4.2 The patient sample ................................................................................................... 64

4.3 Patient demographics ................................................................................................ 64

4.4 Statistical analysis ................................................................................................... 66
  4.4.1 Mean follow up period ...................................................................................... 66
  4.4.2 Fistula complications and interventions .............................................................. 67
  4.4.3 Aetiology of end stage kidney disease ................................................................. 68
    4.4.3.1 Type of fistula ............................................................................................ 70
    4.4.3.2 Treatment .................................................................................................... 71
  4.4.4 Flow Volume ....................................................................................................... 72
    4.4.4.1 Pearson’s Correlation .................................................................................. 73
    4.4.4.2 Chi Squared test .......................................................................................... 73
    4.4.4.3 Results from the statistical tests .................................................................... 73

4.5 Stenosis ..................................................................................................................... 76
  4.5.1 Classification 1 .................................................................................................. 76
  4.5.2 Classification 2 .................................................................................................. 78
  4.5.3 Classification 3 .................................................................................................. 79
  4.5.4 Classification analysis ....................................................................................... 79
  4.5.5 Stenosis discussion ........................................................................................... 85

4.6 Co-morbidity ............................................................................................................. 86

4.7 Screening .................................................................................................................. 87
  4.7.1 Pre-emptive treatment ..................................................................................... 89

4.8 Justification for the use of hospital resources .......................................................... 91

4.9 Criteria for a screening programme ......................................................................... 93
4.10 Conclusions based on the findings ................................................................. 94

4.11 Limitations of this study .................................................................................. 95

4.12 Conclusion ....................................................................................................... 96

5.1 Introduction ....................................................................................................... 97

5.2 Conclusions based on the results ................................................................. 97

5.3 Recommendations .......................................................................................... 99

5.4 Final Comments ............................................................................................. 101

References ............................................................................................................ 102

Appendix A ............................................................................................................ 111

Appendix B ............................................................................................................ 129

Appendix C ............................................................................................................ 132
List of Tables

Table 1: Table showing the main articles and their findings in chronological order................................................................. 29
Table 2: Shows the different types of arteriovenous fistula...................... 65
Table 3: The table shows the different treatments given to the patients suffering from stenosis and/or thrombosis ......................... 67
Table 4: The table shows the predominant illnesses that led to the end stage kidney disease..................................................... 68
Table 5: Flow volume for both the fistula and feeding artery are shown with their respective minimum, maximum and mean.................... 72
Table 6: The table shows B-mode and Doppler measurements as well as flow volumes in the artery and radiocephalic fistula ............... 74
Table 7: The table shows B-mode and Doppler measurements as well as flow volumes in the artery and brachiocephalic fistula .......... 74
Table 8: The table shows B-mode and Doppler measurements as well as flow volumes in the artery and transposed brachiobasilic fistula. 75
Table 9: The table displays classification one and its 3 tiers.................... 77
Table 10: The table displays classification two and its 4 tiers ................... 78
Table 11: The table shows the 3 tier classification.................................. 79
Table 12: The table shows the Chi squared test result of classification one against classification two (with no stenosis column) .......... 80
Table 13: The table shows the Chi squared test result of classification one against classification two (without the no stenosis column) ...... 81
Table 14: The table shows the Chi squared test result of classification one against classification two (with no stenosis column) .......... 83
Table 15: The table shows the Chi squared test result of classification one against classification two (without the no stenosis column) ...... 84
Table 16: The table compares the percentage stenosis within each segment for both studies. ...................................................... 85
Table 17: The table shows the P value of both studies where the incidence of stenosis was tested against the co-morbidity which led to the end stage kidney disease..................................................... 87
List of Figures

Figure 1: Histogram showing the Age of the patient ................................................. 65
Figure 2: Histogram showing the mean follow up period for 88 patients (without outlier) .................................................................................................................. 66
Figure 3: Histogram showing the mean follow up period with 89 patients (with outlier) .................................................................................................................. 67
Figure 4: The relation between the type of fistula and the co-morbidity that led to the end stage kidney disease ................................................................. 70
Figure 5: The relation between the co-morbidity and different types of interventions ..................................................................................................................... 71
### Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>CVI</td>
<td>Content Validity Index</td>
</tr>
<tr>
<td>eGFR</td>
<td>Estimated Glomerular Filtration Rate</td>
</tr>
<tr>
<td>EU</td>
<td>European Union</td>
</tr>
<tr>
<td>$H_0$</td>
<td>Null Hypothesis</td>
</tr>
<tr>
<td>$H_1$</td>
<td>Alternative Hypothesis</td>
</tr>
<tr>
<td>I-CVI</td>
<td>Item Content Validity Index</td>
</tr>
<tr>
<td>KDOQI</td>
<td>Kidney Disease Outcomes Quality Initiative</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>N/A</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>NPV</td>
<td>Negative Predictive Value</td>
</tr>
<tr>
<td>PSV</td>
<td>Peak Systolic Velocity</td>
</tr>
<tr>
<td>PTFE</td>
<td>Polytetrafluoroethylene</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive Predictive Value</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised Control Trial</td>
</tr>
<tr>
<td>SD</td>
<td>Standard Deviation</td>
</tr>
<tr>
<td>SPSS</td>
<td>Statistical Package for the Social Science</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>US</td>
<td>Ultrasound</td>
</tr>
</tbody>
</table>
Definitions of Key Concepts

**Angiography**: radiographic imaging of the lumen of vessels after injection of radio-opaque contrast agents (Lee, 2010)

**Autogenous fistula**: a connection between an artery and a vein that is purposely created for the sole purpose of increasing the blood flow sufficiently in the venous system in order for the patient to have effective haemodialysis (Al-Benna, Deardon, Hamilton, & El-Enin, 2013).

**Duplex ultrasound**: the overlapping of both greyscale and colour Doppler imaging. Greyscale imaging (B-mode) provides the visualisation of the architecture of the body part under interrogation. Colour Doppler provides flow movement information of the structure, in this case the blood flowing through the vessels. (Hedrick, Hykes, & Starchman, 2005)

**End stage renal disease**: a chronic disease that results in severe impairment of renal function, with eGFR below 30ml/min/1.73 m² and is generally incompatible with life (Hall, 2010).

**Fistulography**: angiography of the fistula to detect any sites of narrowing or blockage (National Kidney Foundation, 2006).

**Graft fistula**: an arteriovenous graft works along the same principle of an autogenous fistula with the difference that a prosthetic graft usually made of polytetrafluoroethylene (PTFE) is used to create the fistula (Rabbani & Shojaeefard, 2006).
**Haemodialysis**: haemodialysis is the filtration and diffusion of blood and its constituents through an artificial semi permeable membrane (dialyser) in order to remove waste products such as creatinine, urea, potassium, phosphate and excess water from the human body (Hall, 2010).

**Monitoring**: monitoring consists of the physical examination as well as the clinical assessment of the access for any changes and/or dysfunction (National Kidney Foundation, 2006).

**Screening**: the presumptive identification of unrecognised disease by the application of tests which can be applied rapidly (Garvican, 2013) pg 81. Screening can be used to complement monitoring and it is used to enhance monitoring techniques and to provide a better picture of the functioning arteriovenous fistula (Paulson, Moist, & Lok, 2012).

**Stenosis**: a stenosis is a narrowing in the lumen diameter of an artery or a vein (Tessitore et al., 2011)

**Thrombosis**: thrombosis is the coagulation of blood within a blood vessel (Cronenwett & Johnston, 2014).

**Ultrasound dilution technique**: ultrasound dilution technique is a screening technique whereby the arteriovenous fistula is actively monitored by measuring the blood flow and blood flow volumes when the patient is actually being dialysed (Paulson et al., 2012).
Chapter 1

1.0 Introduction

End stage renal disease is a medical illness where the patient’s kidneys no longer function effectively and are unable to remove and filter toxins and excretory products that accumulate in the human body (Hall, 2010). End stage renal disease does not usually have a sudden onset (Roger et al., 2011). As the disease progresses, it allows for the patient to be evaluated and assessed by physicians who together with the patient may decide on the best form of long term dialysis. Dialysis is a treatment given to the patient where equipment is used to artificially replicate the kidney’s function by removing toxins and excess water from the blood stream. The two types of dialysis that may be performed are peritoneal dialysis and haemodialysis. This study will be focusing on one area: Haemodialysis using autogenous arteriovenous fistula. The difference between an autogenous and a non-autogenous fistula is that in the former the patient’s own vessels are used, whereas in the latter, a prosthetic graft such as polytetrafluoroethylene (PTFE) tube is used in order to create the connection between the artery and vein.
1.1 Background to the study

A well-functioning arteriovenous access is the life line of the patient with end stage renal disease and all necessary precautions should be taken in order to prolong its life as much as possible. Patients with end stage renal disease have to rely on haemodialysis as a replacement for their non-functioning kidneys (Teodorescu, Gustavson, & Schanzer, 2012). In order for haemodialysis to take effect, vascular access needs to be established (Malovrh, 2003). There are several types of accesses that may be used for haemodialysis: temporary haemodialysis such as tunnelled or non-tunnelled vascular catheters, or long term dialysis in the form of autogenous or non-autogenous arteriovenous fistula. All access options carry different types of risks and patency issues (Manns et al., 2005).

Once a mature fistula is deemed ready for use by the vascular surgeon and nursing staff at the renal unit, the arteriovenous access is needled to allow haemodialysis (Depner et al., 2006). These patients undergo haemodialysis approximately once every three days. Although the fistula is used on a regular basis, only when a problem is detected or encountered by the nursing staff would the patient be referred for medical investigations. If the problem is detected too late, the result may be that these patients can suffer from ineffective haemodialysis, lose treatment sessions and most likely would also need temporary access interventions which carry their own risks and complications (Tessitore et al., 2004). A screening programme would be able to detect such problems before they can cause difficulty with haemodialysis and therefore the patient may be offered an interventional
procedure such as angioplasty, thrombectomy or any other surgical intervention with the aim of preserving the fistula and allow for continuous use.

Certain medical co-morbidities such as peripheral vascular disease, hypertension, diabetes and coronary artery disease can increase the complication rates in arteriovenous fistulae (Shenoy, 2007). The Maltese population has among the highest rates of diabetes in Europe and the leading cause of death within the Maltese population is heart disease (Health Profile Malta, 2011; Rocchiccioli et al., 2005). Diabetic nephropathy constitutes the most common indication for haemodialysis in Malta (Cassar, 2012). The high prevalence of diabetes, hypertension, coronary artery disease and peripheral arterial disease in the local dialysis population increases the likelihood that the fistulae will develop complications, mainly stenosis followed by thrombosis (National Kidney Foundation, 2006).

At present, there is no screening programme to monitor the patency of autogenous arteriovenous access for patients being treated with haemodialysis using an arteriovenous fistula at the renal unit of a local general hospital.

1.2 Literature Review

An arteriovenous fistula or arteriovenous graft is when a connection or "bypass" is purposely created between an artery and a vein (Shenoy, 2007). This unnatural communication is created surgically by anastamosing an artery to a vein in order to increase the blood flow in the graft or fistula.
this new path bypasses the distal vascular bed, there is a significant reduction of pressure from the venous side which in turn allows some of the blood to flow directly from the artery into the vein and the main aim of this is to increase the blood flow and blood volume in the vein which is a requisite for maintaining haemodialysis (Hall, 2010). For adequate haemodialysis, the blood flow volume needs to be not less than 400ml/min (National Kidney Foundation, 2006). In the case of an autogenous arteriovenous fistula the native vein will mature over time to accommodate the increased blood flow and pressure (Konner, Nonnast-Daniel, & Ritz, 2003). The autogenous arteriovenous fistula has higher success rates and has fewer complications than other haemodialysis techniques. However, the commonest complications that plague autogenous arteriovenous fistulae are stenosis and thrombosis (Besarab, Asif, Roy-Chaudhury, Spergel, & Ravani, 2007; Pietura et al., 2005). Stenosis of a vessel is when the luminal diameter is abnormally reduced at a specific area/s. The stenosis of a vessel results in a disturbance in the laminar blood flow pattern and the development of turbulent flow as well as changes in blood flow and blood velocities (Weber, Lockhart, & Robbin, 2007). The progression of a stenosis can lead to increasingly significant changes and a higher risk for thrombosis which is the coagulation of blood inside a vessel that blocks off the fistula distal to the site of stenosis and renders the fistula useless (Thibodeau & Patton, 2006).

Screening for the detection of non-significant stenosis in patients with arteriovenous fistula includes monitoring on a regular basis for the incidence of minor stenosis (non-significant) that is not noticed either by the patient or nursing staff and does not hinder haemodialysis. A non-significant stenosis
is when the stenosis is less than 50% of the lumen diameter of the artery/fistula (National Kidney Foundation, 2006). If a non-significant stenosis of the artery/fistula is found in a patient, then this patient may be monitored more frequently for stenosis progression and may be offered less invasive treatment which would reduce the thrombosis rate and increase the secondary patency of the arteriovenous fistula. Less invasive treatment such as endovascular techniques offers minimal stress and the patient is exposed to lower risks (Tessitore et al., 2004).

Screening of these arteriovenous fistulae can be performed using duplex ultrasonography which has the capability not only to visualise the anatomy but also to calculate blood flow velocities and estimate the rate of blood flowing through the fistula (National Kidney Foundation, 2006). Although ultrasound has certain limitations such as operator dependency, it provides similar outcomes as the gold standard angiography without the ionising radiation penalty and possible intravenous contrast injection complications (Tessitore et al., 2004)

1.3 Aim and objectives

The aim of this study was to assess the feasibility of introducing a screening programme for the Maltese patient with autogenous arteriovenous fistula for detection of non-symptomatic and non-significant stenoses of the feeding artery or fistula.
The objectives were to:

- Use duplex ultrasound to assess the arteriovenous fistula and feeding artery of patients on haemodialysis and identify any asymptomatic clinical stenosis in the autogenous fistula and/or feeding artery
- Identify any co-morbidity that is likely to increase the risk of stenosis
- Create a data collection tool for demographic and physiologic data of patients undergoing haemodialysis through an autogenous arteriovenous fistula.

1.4 Methodology

1.4.1 Research Design

The study has a quantitative, non-experimental, prospective design with data collected over a three month period. A tool referred to as a proforma was designed, tested and used for the collection of the data. The ultrasound machine was the instrument used to collect the data. The numeric data consists of intraluminal diameters and blood flow velocities at various locations.

The target population consisted of all the patients with end stage renal disease who were undergoing haemodialysis treatment at the dialysis unit in a state hospital. Consecutive sampling was used. The inclusion and
exclusion criteria were drawn up and will be discussed in further detail in the methodology chapter.

1.4.2 Data Analysis

In this study, all the data was demographic as well as numerical and consisted mainly of measured values. The data was analysed by using inferential statistics and displayed with the aid of histograms and tables. Reliability and validity testing were carried out for the proforma and for the vascular scientist.

1.5 Limitations

A limitation was that the study only included patients with an autogenous arteriovenous fistula and patients with non-autogenous arteriovenous access and permanent catheters were omitted so as to eliminate different variables that can skew results. Non-autogenous arteriovenous access involves the use of mostly prosthetic grafts to create a fistula instead of a vein. Since the graft is essentially a foreign body, its physical properties are very different from an autogenous conduit. In particular non-autogenous arteriovenous access demonstrates increased pressures, an increased probability of stenosis, thrombosis and other complications over a native fistula (Cassar, 2012).
1.6 Ethical considerations

The study followed all the ethical rules that govern research studies. The patients were all informed and consented prior to the scans. The data was kept secure, encrypted and was destroyed at the end of the study.

All the necessary permissions (appendix A) to carry out the study were sought from the Hospital’s CEO and data protection officer, university research ethics committee, the head of the dialysis unit, four consultant nephrologists and a vascular surgeon.

1.7 Outline of the study

This study commenced in February 2014 and was finalised by January 2015. This study consists of five chapters which will be briefly described in this section.

The first chapter is the introductory chapter where an overview of the study is given. A brief literature review as well as the aims and research question are presented in this chapter. An outline of the methodology has been described here.

In chapter two an in-depth analysis of the available literature is presented. A critical evaluation on the available body of knowledge and research publications is also shown. This chapter laid the groundwork for research design and research tool used in this study.

The methodology of this study is presented in chapter three. This chapter presents the way the data was collected, analysed and how it was
tested. Validity and reliability testing is explained here as well as their significance and application within the study.

Chapter four presents the results of the study as well as a relevant discussion and analysis of the findings.

The final chapter summarises the study and presents any recommendations for future work.
Chapter 2

Literature Review
Chapter 2

2.0 Introduction

In this chapter a review of the relevant literature is presented.

The first autogenous arteriovenous fistula was created by James Ciminio and M.J. Brescia in 1966 (Brescia, Ciminio, Appel, & Hurwich, 1966). Since their first procedure, the arteriovenous fistula has become the most effective and reliable method for long term access for haemodialysis (Allon et al., 2013).

The arteriovenous fistula was the focus of research during the late 1990s and early 2000s and several papers from various reputable institutions on this subject were published but no studies relating to autogenous arteriovenous fistula performed at Maltese institutions have been found.

A comprehensive search was undertaken in both foreign as well as local online databases for relevant articles. The databases were http://www.um.edu.mt/library, www.sciencedirect.com and http://academic.research.microsoft.com. The initial inclusion criterion for the search was limited to articles published within the last ten years. However, as the number of published studies was low, the search was modified to incorporate articles that exceeded this ten year limit.

The keywords used in the search were; arteriovenous, fistula, duplex ultrasound, randomised controlled trial (RCT), native, autogenous,
haemodialysis, screening, stenosis and non-significant stenosis. The search strategy and keywords were recorded for future searches and Boolean operators such as and, or and not were also used. Authors who appeared in more than one journal were also included in the search strategy. In certain instances, snowballing was also used to further increase the search strength capabilities. This was conducted by analysing the reference list and researching other relevant journals found listed in these reference lists. The Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines issued by the National Kidney Foundation (2006) was sourced through snowballing. In fact the KDOQI guidelines appeared in the majority of journal’s reference list. The KDOQI guidelines were last updated in the year 2006 and they provide details about all aspects of haemodialysis.

2.1 End stage renal disease

The kidneys are vital for survival as their role is to filter the blood, remove any toxins, water and other excretory products produced by the human body (Hall, 2010). There are several conditions that may lead to renal failure. End stage renal disease is a chronic disease that results in severe impairment of renal function (Hall, 2010). Usually as the disease progresses the renal function becomes so diminished that eventually this is incompatible with life. It is at this stage that the patients are referred for haemodialysis. The KDOQI (2006) guidelines recommend that patients are referred for fashioning of an arteriovenous fistula once the estimated glomerular filtration rate (eGFR) drops below 30ml/min/1.73 m2 (Tordoir et al., 2007). The eGFR is a measure of the flow rate of filtered fluid inside the kidneys and is
accepted as the numerical indicator of the kidneys' physiological function (National Kidney Foundation, 2006).

2.1.1 Dialysis

Dialysis is the process by which toxins and excess water that is created in the human body are removed (Hall, 2010). Dialysis is used for those patients who suffer from acute kidney failure and for those with chronic kidney disease stage 5. Chronic kidney disease stage 5, also referred to as end stage renal disease, is the result of severe renal impairment whereby the kidneys' eGFR is decreased to a level that is ineffective for removal of all the by-products produced by the body (National Kidney Foundation, 2006). Dialysis acts on the principle of diffusion and ultrafiltration which replicates the kidneys' physiological function. There are two types of dialysis, peritoneal and haemodialysis (Hall, 2010). Peritoneal dialysis uses the peritoneal membrane as the semi permeable membrane while for haemodialysis, the patient's blood is passed through an artificial semi permeable membrane. Both types of dialysis have their advantages and disadvantages (National Kidney Foundation, 2006). Depending on the patient's needs, lifestyle and health, the type of dialysis is chosen after discussions between the patient and the nephrologist (Sidawy et al., 2008).
2.1.2 Haemodialysis

Haemodialysis is the filtration and diffusion of blood and its constituents through an artificial semi permeable membrane (dialyser) in order to remove waste products such as creatinine, urea, potassium, phosphate and excess water from the human body (Hall, 2010). The blood is passed through an extracorporeal dialyser and diffusion of the solutes occurs due to a concentration gradient. Excess fluid is removed by the pressure gradient that is generated across the membrane (Hall, 2010).

Access for haemodialysis can be achieved in various ways including central venous catheter, an autogenous arteriovenous fistula and an arteriovenous graft.

2.2 Autogenous arteriovenous fistula

An autogenous arteriovenous fistula is a connection between an artery and a vein. This unnatural connection, is purposely created for the sole purpose to sufficiently increase the blood flow in the venous system in order for the patient to have effective haemodialysis (Al-Benna et al., 2013). As this new path bypasses the distal vascular bed, there is a significant reduction in pressure from the proximal venous side of the fistula which in turn allows some of the blood to flow directly from the artery into the vein. This effectively increases the blood flow volume through the vein. Over time the vein will change both anatomically and physiologically in order to accommodate the increased blood flow and pressure (Cronenwett & Johnston, 2014)
2.2.1 Arteriovenous graft

An arteriovenous graft works along the same principle as that of an autogenous fistula with the difference being that a prosthetic graft usually made of polytetrafluoroethylene (PTFE) is used to create the fistula (Rabbani & Shojaeefard, 2006). The dynamics of the graft fistula are also different as it can sustain higher vascular pressures and the rate of complications such as infections and thrombosis increases when compared to the autogenous one (Zasuwa, Frinak, Besarab, Peterson, & Yee, 2010). The infection rate of arteriovenous grafts, which are essentially prosthetic, is tenfold higher than that of an autogenous arteriovenous fistula (Stolic, 2013).

2.2.2 The purpose of an arteriovenous fistula

A well-functioning arteriovenous access is the lifeline of a patient with end stage renal disease (Pietura et al., 2005). For haemodialysis to take effect, access referred to as arteriovenous fistula is created in order for the dialysis equipment to work effectively, repeatedly and consistently. As previously explained, the fistula effectively increases the blood flow volume through the vein so that the minimum requirements for adequate dialysis are reached. The requirements are that the blood flow volume is not less than 400ml/min and not more than 1200ml/min (Alamdaran, Nazemian, & Taheri, 2008; Anatole Besarab, 2006). If the flow volume passing through the arteriovenous fistula is less than 400ml/min, effective dialysis would not be achieved.
Patients with end stage renal failure need frequent dialysis in order to increase their life expectancy and lead a relatively normal lifestyle (Anatole Besarab, 2006). In another study by A Besarab et al., (2007), the authors concluded that for haemodialysis, a mature autogenous arteriovenous fistula offers the best results in terms of minimal complications, long term use as well as a good life expectancy of the fistula.

Maintenance and screening of the fistula plays an important role in the preservation of this lifeline and a maintained fistula may be used for years without any major complications (Malovrh, 2011). Apart from the daily physical assessment performed by the patient and regular checks by nurses at the dialysis unit, several other screening methods are used in order to assess the patency of the fistula with the most commonly being ultrasound dilution technique, duplex ultrasonography and angiography (National Kidney Foundation, 2006). These screening techniques are discussed later on in this chapter, section 2.7

2.3 Stenosis

A stenosis is a narrowing in the lumen diameter of an artery or a vein and may be classified into two main categories:

- Significant stenosis where there is a reduction of the lumen diameter which is greater than 50%
- Non-significant stenosis where the reduction in diameter is less than 50% when compared to the adjacent segment

(National Kidney Foundation, 2006), (Tessitore et al., 2011)
The National Kidney Foundation, (2006) stated that a 50% reduction in the lumen diameter translates to approximately 75% loss of functioning vessel lumen. The larger the percentage of the stenosis, the higher the likelihood of access problems with/without complications, which is mainly thrombosis.

A significant stenosis may lead to failure of haemodialysis as the blood flow velocity and volume would be severely diminished. A stenosis may occur due to either external forces pressing on the vessel itself causing a reduction in the lumen diameter and/or as a result of changes in the internal dynamics of the vessel. The inside of the vessel is usually smooth and contains no protruding plaques. In the majority of cases, neointimal hyperplasia with smooth muscle proliferation which is the growth of the intimal layer of cells is the main cause of such reductions in the lumen diameter (Stolic, 2013). A degree of neointimal hyperplasia occurs when the vein undergoes maturation meaning that the vein will start to develop artery characteristics like increased wall thickness as a result of the increased pressure and blood volume passing through the fistula (Hall, 2010). The increased volume and pressure can create high shear stress flows which can exaggerate this neointimal growth which could result in the development of a stenosis (Ene-lordache & Remuzzi, 2012). Ene-lordache & Remuzzi, (2012) reported that the areas which are prone to increased intimal hyperplasia is where there is low, turbulent and oscillatory shear stresses. Since it is created surgically, the arteriovenous fistula’s physical dynamics automatically creates such areas of high and low shear stresses (Ene-lordache & Remuzzi, 2012). The area most commonly affected by intimal
hyperplasia is the anastamotic site where the shear stresses oscillate between their highest and lowest values (Ene-Iordache & Remuzzi, 2012). Salman (2010) pointed out that the anastamosis site could be a common area of aggravated intimal growth but further tests would be required to verify this physiological response.

2.4 Thrombosis

Thrombosis is the coagulation of blood within a blood vessel (Cronenwett & Johnston, 2014). Thrombosis can cause a reduction in the blood flow and sometimes can even create a complete occlusion of the blood vessel. There are two forms of thrombosis; arterial and venous (Hall, 2010). For the scope of this study, any references to thrombosis refer to arteriovenous fistula thrombosis.

The initiation of a thrombosis episode is usually due to some dynamic change within the fistula and thrombosis of the arteriovenous fistula may have a detrimental and debilitating effect on the patient undergoing dialysis and is considered as a medical emergency (Rustempaği & Solaković, 2010). In most cases, the thrombosis results in occlusion of the fistula rendering it unsuitable for dialysis and if left untreated thrombosis can lead to the loss of the fistula. Treatment for thrombosis is usually through an operation where the thrombus is surgically removed in order to try and restore the blood flow back through the fistula (Rustempaği & Solaković, 2010). In order to try and reduce the possibility of another thrombosis episode, the aetiology of the thrombotic episode is sought so that the
appropriate treatment may be delivered. Failure to identify the underlying cause for fistula thrombosis is likely to result in early re-occlusion since the underlying cause of thrombosis persists.

2.5 Co-morbidities

Certain medical co-morbidities such as diabetes, hypertension, coronary disease and peripheral vascular disease may increase the complication rates in arteriovenous fistulae (Shenoy, 2007; Tordoir et al., 2007). In Malta a higher incidence of these co-morbidities may exist as the Maltese population rates amongst the highest for diabetes in Europe and the leading cause of death within the Maltese population is heart disease (Ministry for Health, 2014; Rocchiccioli et al., 2005). Furthermore, diabetic nephropathy constitutes the most common indication for haemodialysis in Malta (Cassar, 2012). The high prevalence of diabetes, hypertension, coronary artery disease and peripheral arterial disease in the local dialysis population increases the likelihood that the fistulae may develop complications, mainly stenosis followed by thrombosis.
2.6 Medical Screening

Through screening, early disease traits may be identified, monitored and even possibly treated before the illness or disease becomes life threatening. Screening is:

\[\text{the presumptive identification of unrecognised disease}\] by the application of tests which can be applied rapidly....

(Garvican, 2013, pg 81)

Wilson & Jungner, (1968) set up four basic criteria specifically for the world health organisation (WHO). These criteria need to be satisfied in order for a screening programme to be set up and although the criteria are dated they are still applicable (Tidy, 2014).

These criteria are:

- **Knowledge of the disease**: The condition of the disease should be important to warrant the need of a screening programme. The disease aetiology must be understood and should be diagnosed early in the asymptomatic stage.
- **Knowledge of the test**: An adequate test or examination needs to be set up in order to adequately identify the disease. This test must be easily repeatable and is relatively acceptable by the target population.
- **Treatment for the disease**: The disease must be treated by using an acceptable treatment that is readily available.
• **Cost considerations:** The screening costs and treatment are acceptable and economically balanced.

In keeping with the criteria set by Wilson and Jungner (1968), the author Garvican, (2013) said that screening has to fulfil certain criteria in order for it to be beneficial. The tests need to be relatively quick, inexpensive, have high specificity and sensitivity and at the same time maximise the benefit whilst minimising the risk (Garvican, 2013). Paulson et al., (2012) claimed that although screening is sometimes necessary, different opinions exist as to which screening technique is the most adequate when taking into consideration the effectiveness, accuracy, reproducibility and cost implications.

The efficacy of the screening technique is calculated with respect to sensitivity and specificity (Basile, Ruggieri, Vernaglione, Montanaro, & Giordano, 2004). The sensitivity of the screening technique refers to how likely the technique is in detecting an abnormality when there is an actual abnormality. The higher the sensitivity the more accurate the technique (Gerrish & Lacey, 2013). Specificity is the opposite of sensitivity, as specificity of a screening technique measures how accurate the screening technique is in not detecting any abnormalities in patients who actually do not have any abnormalities (Gerrish & Lacey, 2013).

The main scope for screening is prophylactic/pre-emptive care which is the detection of early abnormalities within the arteriovenous circuit which have the possibility of inducing a thrombotic event and if necessary treating
such abnormalities (Work, 2011). There are a variety of ways through which screening can be conducted and these are discussed in the coming sections.

Screening is done at regular intervals which is not every time that the patient attends a dialysis session. Between one screening session and another, the patient is asked to monitor the fistula daily and this makes monitoring essential in dialysis care (National Kidney Foundation, 2006). Monitoring consists of the physical examination as well as the clinical assessment of the access for any changes and/or dysfunction. This assessment of the fistula is done by the patient as well as the dialysis nurse (National Kidney Foundation, 2006). Screening is different from monitoring as it utilises imaging techniques such as duplex ultrasound in order to complement monitoring and enhance monitoring techniques in order to provide a better picture of the functioning arteriovenous fistula (Paulson et al., 2012). According to Paulson & Work (2010) there is an absence of strong evidence to suggest that routine screening of fistulae results in higher patency rates but the National Kidney Foundation (2006) still recommends routine screening of arteriovenous fistulae. National Kidney Foundation (2006) argue that routine screening gives the possibility of planned, coordinated interventional procedures and possibly minimise the need for urgent interventions, such as on table thrombectomy. However, the National Kidney Foundation (2006) does acknowledge the fact that routine screening can be costly and possibly detrimental to the patient due to intervention complications.
2.7 Pre-emptive treatment

Pre-emptive treatment is the repair of a sub-clinical stenosis through an elective intervention with the intention of increasing the fistula’s life (Tessitore et al., 2004). The basis for pre-emptive treatment is that the survival and patency rates of the fistulas that are treated with prophylactic angioplasties are higher than those fistulas that are only treated once a complication has taken effect (Work, 2011). The National Kidney Foundation (2006) suggested that prophylactic treatment is still beneficial even though the published literature does not always show a net positive benefit. The reason for this is that angioplasty treatment tend to instigate an aggravated intimal hyperplasia response due to mechanical stress and injury caused by the angioplasty procedure (Allon & Robbin, 2009). The authors say that this aggravated response can be counterproductive as the fistula is likely to re-stenose at a faster rate. Furthermore, re-stenosis is a common occurrence in post angioplasties of fistulas with significant or non-significant stenosis (Allon & Robbin, 2009). Cronenwett & Johnston (2014) argue that a stenosis has no fixed aetiology and it can develop or progress at various intervals. There are no models available which predict which stenoses are likely to progress and which stenoses remain static. No published studies were found that explain/show an established pattern for the rate of progression of intimal hyperplasia. This lack of literature creates plausible benefit to the efficacy of pre-emptive treatment. Determining the rate of progression of a stenosis would enable better timing in the treatments and also avoid any unnecessary intervention (Kumbar, Karim, & Besarab, 2012)
2.7.1 The physical examination

The examination consists of physically examining the fistula (Beathard, 2005). The patient is encouraged to assess the fistula daily and report to the doctor immediately if any differences are noted. The physical examination is performed daily by the patient and also by the dialysis nurses before each dialysis session (National Kidney Foundation, 2006). The National Kidney Foundation (2006) noted that unfortunately these easy, cheap and basic skills of inspection, palpation and auscultation have been abandoned over the years as new technology has taken over. A big advantage of this type of examination is that it is easily performed anywhere and anytime (Gelbfish, 2008). The fistula is checked for any visual changes such as enlargement, redness, bruising or swelling which can be an indication of an infection or haematoma. Assessment for the fistula thrill is done using palpation and the fistula bruit using auscultation (Gelbfish, 2008).

The presence of a thrill and how the thrill feels under palpation may be indicative of a stenosis as well as the suspected location of that stenosis (Beathard, 2005). Gelbfish (2008) also commented on the fact that the physical examination is underutilised, even though it is an effective monitoring tool for the arteriovenous fistula. According to Gelbfish (2008) the physical examination has a high inherent potential to detect fistula abnormalities and coupled with other surveillance techniques, the arteriovenous fistula can be actively and closely monitored for the event of a stenosis. However, the physical examination requires a high level of skill.
and expertise in order to be a highly effective monitoring tool (Gelbfish, 2008).

2.7.2 Ultrasound Dilution Technique

Ultrasound dilution technique is a screening technique whereby the arteriovenous fistula is actively monitored by measuring the blood flow and blood flow volumes when the patient is actually being dialysed (Paulson et al., 2012). Flow parameters can be obtained on a regular basis and a blood flow/volume flow chart can be drawn up. Gradual and consistent changes in these parameters may be predictive of future problems with the arteriovenous fistula (Paulson et al., 2012). When the blood volume flow drops 20% below the normal, the patient is usually referred for an angioplasty as a stenosis is likely to be present which is inhibiting effectively the flow of blood. The National Kidney Foundation (2006) established and verified ultrasound dilution technique as a reliable and efficient way of screening for the arteriovenous fistula. In a RCT by Tessitore et al. (2004) the authors compared ultrasound dilution technique with angiography and ultrasound dilution technique was found to have a sensitivity of 95% and a specificity of 86%. The study did not give any sensitivity and specificity values for angiography as it was used as the gold standard. The aim of the study was to compare monitoring by ultrasound dilution technique of fistulae with a non-significant stenosis with other monitoring and clinical techniques like the physical examination. Despite the fact that the duration of this RCT was over five years, the authors still urged caution when interpreting the final results obtained as overall their sample size was small as this only included
79 patients. From their study, Tessitore et al., (2004) determined that it is feasible to treat patients with a non-significant stenosis in order to increase the life expectancy of the autogenous fistula. In a subsequent study the same authors concluded that ultrasound dilution technique monitoring led to a near fourfold reduction in thrombosis (Tessitore et al., 2008). The results show a net benefit when monitoring arteriovenous fistula, such as, a reduction in stenosis and thrombosis as well as reduction in the number of central venous catheters used and associated treatment costs (Tessitore et al., 2008). In another similar RCT study conducted by Polkinghorne, Lau, Sauner, Atkins, & Kerr, (2006) similar results were obtained with a sample size which was slightly larger (137 participants). Both studies by Polkinghorne et al., (2006) and Tessitore et al., (2004) identified the small sample size and a short follow up period as their major limitations, indicating that there is a need for studies with a larger sample size as well as longer follow ups in order to verify such findings. Polkinghorne et al., (2006) also suggested that the end point for screening during a study should be the actual failure of the autogenous fistula, irrespective of how long it takes to fail.

2.7.3 Angiography

Angiography is considered as the gold standard in terms of vessel imaging (Chandra et al., 2010). With angiography all of the vessels are imaged including those in the thoracic cavity which is advantageous when compared directly with ultrasound (Scaffaro et al., 2009). For example, with ultrasound, resolution is limited by the increasing depth and the presence of
air in the apex of the lungs (National Kidney Foundation, 2006). However, Chandra et al., (2010) stated that angiography is generally less cost effective, needs to make use of an angiography suite along with radiologists and a supporting team. Also, the procedure is invasive and may result in bleeding from the access site as well as the possibility of infection at the puncture site. Angiography also requires the use of ionising radiation as well as a nephrotoxic contrast agent. Despite these disadvantages the majority of the studies (mentioned later on in this chapter) used angiography as the gold standard and compared the various parameters, such as specificity and sensitivity, of the other imaging techniques to angiography.

2.7.4 Duplex Ultrasound

Duplex ultrasound is a very convenient way to visualise an arteriovenous fistula (Chandra et al., 2010). Salman et al., (2010) concluded that with a sensitivity of 98% and specificity of 91%, duplex ultrasound closely compares to the gold standard angiography. Ultrasound has the ability to visualise the necessary anatomy, measure dimensions of the fistula as well as assess blood flow patterns with minimal discomfort to the patient. (Alamdaran et al., 2008). Although ultrasound is an excellent screening tool for fistulas, it has its own limitations as it is highly user dependant and in certain instances, the angle of insonation required for duplex ultrasound can be difficult to achieve as it is dependent on the patient’s anatomy and the way the fistula is fashioned. The angle of insonation is the angle which the sound waves make when they interact with the red blood cells and should not exceed 60 degrees to allow for accurate measurements (Hedrick et al.,
Chapter 2

The anastamotic site, also called juxta anastomosis, is the area where the correct angle of insonation is the most difficult to be achieved and special care should be taken so that the angle does not exceed 60 degrees (Pietura et al., 2005). However, duplex ultrasound is still regarded as an efficient, safe and successful instrument in monitoring and screening of arteriovenous fistulas (Tessitore et al., 2011).

2.8 Limitations in the literature

Research on autogenous fistulas is limited and the number of published papers on this subject is small (Kumbar et al., 2012). Substantial amount of research and publications have been produced on arteriovenous grafts (Dember, 2011). During the literature search for this study, the majority of the publications on arteriovenous fistula were from the United States of America (USA) and the majority were related to arteriovenous grafts. In fact Polkinghorne and Kerr (2002), in their collective review for predicting vascular access failure stated that in the USA, up to 80% of patients with end stage renal disease had arteriovenous grafts. The reasoning behind this, according to Tordoir et al., (2007) could be that the population health profile and particular co-morbidities would have led to the unsuccessful maturation of several autogenous fistulas and subsequently aided in the development of the arteriovenous graft mentality. However, the conclusions drawn up by Polkinghorne & Kerr, (2002) may be out of date as things have changed significantly since then with a drive to increase the proportion of patients dialysed through an arteriovenous fistula in the USA. In fact, Dember, (2011) mentioned that this drive contributed to an increase of 20% in patients being
dialysed through an arteriovenous fistula over a five year span. It is also apparent that quite a significant number of studies such as Bonforte et al., (2010); Shahin et al., (2005); and Tonelli et al., (2001), including the five year RCT by Tessitore et al., (2004) focused mainly on ultrasound dilution technique measurements/flow monitoring techniques and not duplex ultrasound which means that there was and possibly still is a general lack of available research on arteriovenous fistula using duplex ultrasound.
2.9 The research findings

The table below shows the main articles in chronological order with their main findings displayed for easier reference.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Design</th>
<th>Number of patients</th>
<th>Modalities used</th>
<th>Negative predictive value (NPV)</th>
<th>Positive predictive value (PPV)</th>
<th>Sensitivity %</th>
<th>Specificity %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schnitz et al., 2003</td>
<td>Prospective, UDT &amp; Angiography</td>
<td>69</td>
<td>US, UDT &amp; Angiography</td>
<td>N/A</td>
<td>89</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Asf et al., 2005</td>
<td>Interventional</td>
<td>158</td>
<td>Angiography</td>
<td>N/A</td>
<td>N/A</td>
<td>97</td>
<td>N/A</td>
</tr>
<tr>
<td>Pietra et al., 2005</td>
<td>Multicentre, Prospective Cohort study</td>
<td>139</td>
<td>US</td>
<td>N/A</td>
<td>N/A</td>
<td>91</td>
<td>N/A</td>
</tr>
<tr>
<td>Deelman et al., 2005</td>
<td>Prospective</td>
<td>49</td>
<td>US, MRI &amp; Angiography</td>
<td>N/A</td>
<td>91</td>
<td>97</td>
<td>N/A</td>
</tr>
<tr>
<td>Alambran et al., 2008</td>
<td>Prospective</td>
<td>78</td>
<td>US</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Solomon et al., 2010</td>
<td>Prospective</td>
<td>103</td>
<td>US &amp; Angiography</td>
<td>N/A</td>
<td>98</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Chandra et al., 2011</td>
<td>Retrospective</td>
<td>83</td>
<td>Angiography</td>
<td>N/A</td>
<td>98</td>
<td>N/A</td>
<td>85% - 93%</td>
</tr>
<tr>
<td>Canso et al., 2013</td>
<td>Prospective</td>
<td>41</td>
<td>US, CT &amp; Angiography</td>
<td>N/A</td>
<td>90</td>
<td>N/A</td>
<td>90.7</td>
</tr>
</tbody>
</table>

Table 1: Table showing the main articles and their findings in chronological order
Arteriovenous fistulas are the preferred dialysis access with their major complication being stenosis and/or thrombosis (Pietura et al., 2005). This accounts for the majority of maturation/failure rates of arteriovenous fistulas (Pietura et al., 2005). Research has been carried out regarding the need of screening and monitoring through various instruments, such as, ultrasound dilution technique in order to try and predict if, when or where the fistula will develop stenosis. However, there is a paucity of research on duplex ultrasound in this context and in fact no RCT using duplex ultrasonography was found in the literature search conducted. An RCT is regarded as the gold standard of scientific experiments (clinical trials) (Zhou, Obuchowski & McClish, 2009). Studies like those published by Pietura et al., (2005) and Salman et al., (2010), used duplex ultrasound as their modality of choice but their study design was varied. The studies did not use RCT design but the majority of the other studies (as seen in table 1) had a prospective cohort design. One study was retrospective and a study by Alamdaran et al., (2008) did not describe the methodology used. Regardless of the design, one important factor evident in all of the studies is that the sample size was relatively small. The authors Pietura et al., (2005) and Salman et al., (2010) recognised this limitation, however, both studies failed to justify the use of small sample size. Both studies Pietura et al., (2005) and Salman et al., (2010) referred to cost as a major potential deterrent for screening. Time constraints could also be a limitation, but it does not seem to be a major deterrent since most of these studies took place over a number of years. One major limitation of a small sample size is the weakness of statistical analysis, difficulty for extrapolation, generalisation and overall validation of
the study (Zhou et al., 2009). A small sample size is capable of yielding statistical results but the strength would be relatively weak (Gerrish & Lacey, 2013).

Salman et al. (2010) conducted a prospective study on the detection of inflow stenosis of arteriovenous fistulae. In the study patients with a dysfunctional autogenous fistula were referred to an interventional laboratory and each patient underwent both a duplex scan and an angiogram (fistulogram). In order to minimise the reporting bias, the angiograms were read by different examiners who were experts in their respective field. Based on the analysis of the data, Salman et al. (2010) concluded that duplex ultrasound had a high degree of accuracy when compared to the gold standard angiography. As previously mentioned, this is because angiography was used as the denominator i.e. ultrasound picked up 70% of the stenosis picked up by angiography. Salman et al., (2010) reported the following values for duplex ultrasound: sensitivity 91%, specificity 98%, negative predictive value 90% and positive predictive value of 98%. Based on these values Salman et al. (2010) were of the opinion that especially for the inflow segment, duplex ultrasound is very accurate. The study only considered the inflow segment as the most likely site where a fistula can develop a stenosis or failure to mature (Salman et al., 2010). The authors explained that the inflow segment consisted of only the arteriovenous anastamosis and two centimetres of juxta-anastamotic area. Even though the study had one hundred and three patients, it still remains apparent that patient inclusion criteria established for this study could have contributed to the small sample size. When compared to the other studies such as Asif et
al., (2005); Cansu et al., (2013); Chandra et al., (2010); Doelman et al., (2005), to name a few, Salman et al., (2010)’s study was the only article that acknowledged bias and took it into consideration and calculated the relative bias and precision of ultrasound with respect to their study. As the results showed positive findings for bias and precision, the authors suggested that inflow stenosis should be frequently monitored by duplex ultrasound due to the increased likelihood of stenosis progression (Salman et al., 2010).

A similar study to Salman et al’s., (2010) was one by Chandra et al., (2010) with the main difference between the two being the fact that the study by Chandra et al., (2010) was retrospective as opposed to a prospective study. The ninety three patients who underwent both duplex ultrasound and angiography examinations due to a known dysfunctional fistula were reviewed. Similar to Salman et al., (2010), the examinations were reported by different professionals who were blind to each other’s reports and their reports were reviewed by a third independent investigator who compared both reports that were submitted by the two physicians. Another difference to the study by Salman et al., (2010) was that the study was on the whole arteriovenous circulatory system and not just limited to the inflow segment. The fact that the analysis carried out by Chandra et al., (2010) was on the whole arteriovenous segment, meant that the data gathered was covering the whole aspect of the fistula and not only the juxta-anastamotic area. This could account for Chandra et al., (2010)’s study reporting a lower congruence percentage when compared to Salman et al., (2010) for the sensitivity percentages between ultrasound and angiography. The authors, Chandra et al., (2010), used the congruence and agreement (Kappa)
between angiography and ultrasound to demonstrate the comparability of duplex ultrasound to angiography. The congruence for the different zones of the arteriovenous circuit was between 85% and 96%. Even though the percentages were lower than those obtained by Salman et al., (2010), the figures still indicate that ultrasound is highly comparable to angiography and very accurate in the identification of the location of the stenosis. Chandra et al., (2010) considered ultrasound to be very useful as a first line of investigation for arteriovenous fistulas. Unlike other studies, Chandra et al., (2010) challenged the normal established standard of calculating the difference between a significant and non-significant stenosis. They argued that through their experience, the concept of taking a 50% reduction in the lumen diameter to define the transition point between a significant and non-significant stenosis does not always work in practice due to the high variability in the autogenous fistula’s calibre as this varies from one patient to the next. Studies, such as, Alamdaran et al., (2008); Asif et al., (2005); Cansu et al., (2013); Doelman et al., (2005); Salman et al., (2010) and the guidelines published by the National Kidney Foundation, (2006) followed the 50% reduction of the lumen as the transition point. Chandra et al., (2010) then set precise values in millimetres to denote the degree of stenosis. A non-significant stenosis was when the stenosis calibre was greater than 3mm. A 50% to 75% stenosis was when the measured stenosis was between 1.5mm and 3mm. When the calibre was less than 1.5mm, this signified a greater than 75% stenosis. To have consistency, the authors Chandra et al., (2010) applied the same millimetre criteria for the angiography examination. The authors state that this analogy is based on
the fact that autogenous fistula dysfunction depends on the blood flow volume that is flowing through the fistula. It is not uncommon to find a significant stenosis in large calibre fistulas but the residual lumen could be still large enough so as not to cause a significant reduction in the blood flow volume. This implies that most of these stenoses could go unnoticed unless the patient is scanned and unless the strictures are tight enough to be problematic as they will cause a reduction in blood flow volume and inhibit effective haemodialysis (Chandra et al., 2010). This issue Chandra et al., (2010) to use the 0mm to 1.5mm, 1.5mm to 3mm and greater than 3mm ranges in their study in order to differentiate between a significant and non-significant stenosis and not just a 50% reduction in the lumen diameter.

Doelman et al., (2005) and Cansu et al., (2013) made use of three imaging modalities in their studies as opposed to Chandra et al., (2010) and Salman et al., (2010) where they compared two imaging modalities. Doelman et al., (2005), were the first to compare three modalities: duplex ultrasound, magnetic resonance angiography and digital subtraction angiography together for assessment of arteriovenous fistulae. In their study, Cansu et al., (2013) compared duplex ultrasound, computed tomography and the gold standard angiogram against each other. The main limitation for both of the studies by Doelman et al., (2005) and Cansu et al., (2013) was the cohort size, as Cansu et al., (2013) included forty one and Doelman et al., (2005) had forty nine patients. The reason behind the relatively small cohort sizes was due to a variety of factors. The small sample size can be partly due to the reluctance of the investigators to expose patients to unnecessary radiation as well as the fact that each patient had to undergo three different
examinations increasing the time and cost requirements of both studies. In the study by Doelman et al., (2005) a specificity of 91%, sensitivity of 97%, positive predictive value of 91% and a negative predictive value of 97% was obtained for ultrasound. These figures are highly comparable to the study performed later by Salman et al., (2010) even though the sample size was much smaller in the study by (Doelman et al., 2005). Although ultrasonography showed the poorest results amongst the different modalities, its practicality, portability, cost effectiveness and availability makes it more practical and convenient for routine screening (National Kidney Foundation, 2006). Furthermore, the main drawback of duplex ultrasound is that the results depend highly on the experience of the operator (Doelman et al., 2005). Duplex ultrasound may be performed on all the patients without modality restriction since it is safe for each and every patient. Magnetic resonance angiography is not indicated in patients with a cardiac pacemaker and ferrous objects inside the patient (Doelman et al., 2005). Computed tomography uses ionising radiation which contributes to a radiation dose being given and both computed tomography and magnetic resonance imaging need to make use of potentially nephrotoxic contrast agents in order for angiography to be successful. Duplex sonography is free of such limitations (Cansu et al., 2013).

The study by Schwarz et al., (2003) compared three modalities namely ultrasound dilution technique, duplex ultrasound and angiography together. This study despite being dated and not originally fulfilling the search strategy, it was the only study that compared the most used non-invasive techniques. In their study, Schwarz et al., (2003) compared ultrasound dilution technique
and duplex ultrasound, for screening of the autogenous fistulas. These two modalities were then compared against angiography which was considered to be the gold standard for imaging of the arteriovenous fistula. The study design by Schwarz et al., (2003) was prospective, observational and had an interventional nature unlike the studies by Cansu et al., (2013); Chandra et al., (2010); Doelman et al., (2005); Salman et al., (2010), where the patients were not selected due to a failing autogenous fistula but on the type of fistula that patients had. Only patients with autogenous forearm fistula were considered resulting in a total of fifty nine patients that were enrolled in their study. Each patient had to undergo all three investigations within one week (Schwarz et al., 2003). The results show that ultrasound dilution technique and duplex ultrasound had similar performance characteristics between each other in the detection of stenosis of an autogenous fistula. With a specificity of 76% and a sensitivity of 78%, these percentages were slightly lower when compared to the later studies by Doelman et al., (2005) and Salman et al., (2010). A possible reason for this could be the way the blood flow volume (ml/min) was calculated for the duplex ultrasound examination was less accurate since ultrasound dilution technique measurements are in ml/min, the duplex ultrasound scan needed to have the same units as ultrasound dilution technique. Therefore, Schwarz et al., (2003) calculated the blood flow volume through extrapolation of the PSV of the blood. The blood flow volume at ml/min was calculated using the following equation:

$$\text{Access Volume (ml/min)} = \text{PSV} \times \text{radius}^2 \times \pi \times 60.$$  

(Schwarz et al., 2003 pg 540)
The extrapolation of the blood flow could have led to the minor reduction in the specificity and sensitivity of duplex ultrasound. However, despite this reduction ultrasound dilution technique and duplex ultrasound are still closely comparable (Schwarz et al., 2003). As ultrasound dilution technique has already been established as an adequate way of screening fistulas National Kidney Foundation, (2006), and duplex ultrasound has closely comparable results to ultrasound dilution technique as published by Schwarz et al., (2003), duplex ultrasound can be an adequate screening tool for arteriovenous fistulas. In fact, Schwarz et al., (2003) commented that duplex ultrasound is more reliable in detecting access stenosis as the stenotic area can be directly visualised.

Asif et al., (2005) used angiography to determine if inflow stenosis has a higher incidence than what was previously reported in the literature prior to their study. Asif et al., (2005) used a multicentre, prospective cohort design for their study in order to reduce the possibility of bias and also to have a larger sample size for better statistical analysis. The sample size consisted of one hundred and fifty eight patients. All the patients were referred to a laboratory due to a dysfunctioning fistula. Patients had undergone a total of two hundred and twenty three angiography procedures for both arteriovenous grafts (122) and autogenous fistulas (101) and it appears that some patients had more than one intervention but this was not specifically mentioned. The authors Asif et al., (2005) did not consider arteriovenous grafts statistics but considered only the data for the 101 autogenous fistula angiograms. The results showed that inflow stenosis occurred in forty one patients and a total of fifty eight lesions were found. Asif et al., (2005)
remarked that the incidence of inflow stenosis for autogenous fistula is higher than arteriovenous grafts.

Although the reason remains unclear, a possible explanation for the high incidence of inflow stenosis could be that the mobilisation of the vein during surgery in order to create the anastomosis may lead to local fibrosis and stenosis (Vassalotti, 2004). Vassalotti, (2004) explained that the physical mobilisation of the vein onto the artery, also known as the swing-point, is an area which is prone to stenosis. This mobilisation can cause damage to the vein itself through shear stresses and intimal hyperplasia can be induced (Ene-Iordache & Remuzzi, 2012; Vassalotti, 2004). Asif et al., (2005) used the gold standard investigation technique for their data collection and a relatively high incidence of stenosis was found around the inflow area. Despite the fact that Salman et al., (2010) used a different methodological approach and performed their study after Asif et al., (2005), the results of the two studies showed a high incidence of inflow stenosis in the arteriovenous segment.

Assessment of asymptomatic autogenous fistulas can be effectively carried out through duplex ultrasound (National Kidney Foundation, 2006). Pietura et al., (2005) reported ultrasound to be effective in determining several characteristics such as anatomical and vascular features. The authors conducted a study on one hundred and thirty nine patients who had asymptomatic arteriovenous fistulas and were scanned using duplex ultrasound only. The results showed that sixty four percent of the autogenous arteriovenous fistulas had a stenosis with fifty seven percent of these stenoses being at the anastomotic area (Pietura et al., 2005).
Although the modalities used in the studies by Asif et al., (2005) and Pietura et al., (2005) were different, the results had similar findings. By using duplex ultrasound Pietura et al., (2005) obtained higher percentages in stenosis detection than Asif et al., (2005). Pietura et al., (2005), took into consideration blood flow volume, however, they could not find a link between high flow volume, stenosis and fistula age. A few years later, Alamdaran et al., (2008) conducted a cross sectional study on sixty nine patients with autogenous fistulas using only duplex ultrasound with the focus being blood flow volume. Same as Pietura et al., (2005), Alamdaran et al., (2008) could not establish a link between high flow volume and stenosis development, but high flow autogenous fistulas could be linked with other complications such as tortuosity, aneurysms and steal syndrome. However, both studies did agree on the fact that even though there is a high incidence of abnormalities in autogenous fistulas, the time and cost requirements do not justify screening asymptomatic autogenous fistulas. Contrary to the results published by Alamdaran et al., (2008); and Pietura et al., (2005), authors, such as, Tordoir et al., (2007) and Allon, (2007), stated that screening and pre-emptive repair was deemed as beneficial. Quarterly screening of arteriovenous fistulas can reduce the morbidity and mortality rates of patients with end stage renal disease and also possibly reduce the overall cost in the long run, (Tordoir et al., 2007). Tordoir et al., (2007) acknowledged the fact that there are significant gaps and limitations in their research and they recommended further studies especially for autogenous fistulas. A summary of their observations are seen overleaf:
• Advancement in the detection methods used so that failing autogenous fistulas are detected more accurately.

• Newer imaging techniques with high quality images and new imaging modalities used in order to improve the diagnosis rate of access stenosis.

• The study on the prevention of neointimal hyperplasia both for arteriovenous and graft fistulas

(Tordoir et al., 2007)

2.10 Conclusion

Haemodialysis is an integral part of the treatment of patients with end stage renal disease. Without dialysis they are unable to survive which is why considerable effort, time and money are devoted to the renal impaired patients. The most effective and long term solution to date is the autogenous arteriovenous fistula when compared with permanent catheters and graft fistulas. Still the autogenous fistula has limitations and the main complication is stenosis followed by thrombosis. Stenosis is usually caused by neointimal hyperplasia and this may occur at different rates as each patient is different. No published study could be traced that accurately determines the rate of stenosis progression, if and when there is any. This unknown rate of intimal hyperplasia progression leaves plausible benefit with respect to pre-emptive treatment due to the costs of such treatments. However, it has been established that patients suffering from co-morbidities such as diabetes and
hypertension are more likely to have aggravated signs of intimal hyperplasia when compared to patients without such co-morbidities.

Screening and monitoring techniques have been developed in order to try and minimise such complications. These techniques vary from physical examination to imaging modalities such as duplex ultrasound and angiography. Although angiography is currently the gold standard in fistula imaging for the detection of stenosis, studies have shown that duplex ultrasound is highly comparable with angiography in terms of specificity and sensitivity and at the same time does not make use of ionising radiation. No studies were identified that had a longitudinal RCT with a large sample size using duplex ultrasound. Such a study would contribute to invaluable findings with regards to screening of autogenous arteriovenous stenosis to the established current body of knowledge.

In the next chapter the method for data collection and analysis will be discussed.
Chapter 3

Methodology
Chapter 3

3.0 Introduction

A research methodology chapter is a detailed and systematic way of presenting the entire search strategy method (Wood & Ross-Kerr, 2010). This chapter presents the selection of the study design, the rationale for the choice of methodology and its application in the development of this study.

3.1 Aim and Objectives

The aim of this study is to assess the feasibility of introducing a screening programme for the patient with autogenous arteriovenous fistula for detection of asymptomatic stenosis of the feeding artery and/or fistula.

The objectives were to:

- Use duplex ultrasound to assess the arteriovenous fistula and feeding artery of patients on haemodialysis and identify any asymptomatic clinical stenosis in the autogenous fistula and/or feeding artery.
- Identify any co-morbidity that is likely to increase the risk of stenosis
- Create a data collection tool for the collection of demographic and physiologic data.
3.2 The study design

A quantitative study focuses on the collection of factual evidence in the form of numerical data and establishing a cause-and-effect relationship between variables by using mathematical based methods (Trappen, 2010). The quantifiable data collected for the study had numerical values and was collected using a formal, objective and systematic process.

A prospective designed study is stronger than a retrospective designed study (Gerrish & Lacey, 2010). The study is regarded to be stronger as the data that was collected was chosen specifically and according to the relevance of the study. A prospective study lends a more exploratory element to the research study as the start of the study usually has a presumed cause and finishes with a measured effect (Polit & Beck, 2012). A limitation of a retrospective study would have been that the interpretation of the available information can be a source of bias as it could be inaccurate and missing. Even so, to the best of the researcher’s knowledge, the available data that was collected from the local renal unit was not useful for this study. The above mentioned reasons were the basis for choosing a prospective study.

Apart from having a prospective nature, a non-experimental design was implemented which involves the collection of data that is necessary to provide an answer without the need of an intervention, through manipulation or implementation of variables by the researcher (Polit & Beck, 2012).
A cross-sectional design was also applied as the data was collected during a particular point in time (Wood & Ross-Kerr, 2010). Through the use of a cross-sectional study, the assessment for particular features or possible prevalence of a population was possible (Wood & Ross-Kerr, 2010). This type of study design due to:

- The time constraint of the research study
- A cross-sectional study has the capability of assessing if a particular co-morbidity can be associated in the prevalence of a clinical asymptomatic stenosis within the population.

### 3.3 The research setting

In certain instances, the setting where the data is collected can influence the type of data that is being collected (Gerrish & Lacey, 2010). Quantitative studies need an adequate location where the data is being collected. The data was collected from patients with an autogenous arteriovenous fistula who undergo dialysis approximately once every three days. The study was performed at the main teaching hospital. For this research study an ultrasound room was needed and two locations were analysed for their advantages and disadvantages with respect to feasibility options for data collection. The first room was in a radiology department where the ultrasound room was purposely set up for ultrasound scans. The second room was a general room within the renal unit where it had to be converted into a scanning room prior to the scans. The renal unit is open every day and offers services at all hours in order to make it easier for the
patients to manage the dialysis within their weekly schedule/commitments. Option two was chosen because it was available for use any time during the day and also since it was much more convenient for the patient undergoing dialysis to stay in the same location within the hospital.

The data was collected prior to a dialysis session. Permission was sought from the nurse in charge and a room for scanning with all the required necessities such as a height adjustable stretcher, sheets and hand washing amenities were provided. The ultrasound machine (Esaote MyLab70xvg) was the instrument used to collect the data.

3.4 Target population and Sampling technique

For the purpose of this study, all the patients who suffered from end stage renal disease and undergoing haemodialysis were considered. These patients are dialysed through permanent catheters, autogenous fistulas or prosthetic fistulae. Through the use of an inclusion and exclusion criteria, the target population was established. The inclusion criteria and exclusion criteria were set on the basis of the literature review and will be explained in detail further on in this chapter. Purposive sampling was used so as to stay within the confines of the study and only the patients with autogenous fistulas were eligible to participate in the study. There were one hundred and three patients (103) that had an autogenous arteriovenous fistula.
3.4.1 Inclusion and exclusion criteria

The inclusion and exclusion criteria are characteristics that are used to establish whether a patient suffering from end stage kidney disease was eligible to participate in the study.

3.4.1.1 Inclusion criteria

- The patient needed to have a functioning arteriovenous fistula that had been successfully needled for a minimum of five consecutive dialysis sessions.
- Patients had to be between 18yrs and 90yrs of age.
- Patients had to be able to read and write in either Maltese and/or English as they had to read and understand the information letter and afterwards sign a consent form.

3.4.1.2 Exclusion criteria

- Patients with permanent catheters were excluded from the study. A permanent catheter is a tube that is inserted into the central veins which can be a source of stenosis and central vein thrombosis/occlusion. Although the study is aimed at detecting stenosis, ultrasound has a low specificity and sensitivity score when it is used to image the central vessels.
- Patients with prosthetic fistulas were omitted from the study. The main reasons why these patients were excluded are:
  - They operate at higher venous pressures
II. Are more susceptible to infections as the graft is essentially a foreign body

III. Are more likely to stenose at the anastamosis sites and have the capability to thrombose at a higher minimum blood flow threshold when compared to an autogenous fistula.

- If during the data collection period the patient required treatment in the form of an angioplasty and/or thrombectomy, the patient would be excluded unless the fistula had been successfully needled for a minimum of five consecutive dialysis sessions.

3.5 The research tools

The renal unit at the local general hospital collects information such as patient blood pressures, machine blood pressures (arterial and venous) and the volume of excreted fluid, to name a few. Even though this information is valuable for the renal unit, this data was not relevant for this study. In order to be able to collect the necessary data, an ultrasound machine and a proforma were used. The ultrasound machine was the instrument to collect the data and a data collection sheet where all the data was documented. The data collection sheet is called the proforma for the purpose of this study.

3.6 The ultrasound machine

In order to ensure consistency, the same ultrasound machine (Esaote MyLab70xvg) was used throughout the study. This was done in order to rule out any possible variations between ultrasound equipment. Since the same
ultrasound machine was used to gather all the data, reliability and validity testing of this instrument was not necessary. The operator (vascular scientist) was tested for reliability and validity and this will be explained later on in the chapter.

3.7 The data collecting tool (proforma)

The proforma was formulated from various sources encountered during the literature review. The literature review provided the basis for questions that were necessary for this study. With the help of a vascular surgeon and a statistician, these questions were then amended and structured in order to create a more homogenous structure and facilitate the data collecting phase. The proforma was used as the basis of the scanning protocol.

The proforma (see appendix C) was the data recording tool that assisted the researcher to record structured observational data and subsequently allowed this data to be analysed statistically. The demographic data section was collected through a structured interview where the patient was asked nine closed ended questions and the answers were noted in the proforma. The remaining eleven data questions were collected during an ultrasound scan and the necessary information was documented in the proforma.

Reliability and validity of the data collection tools are essential in order for the research study to be truthful and credible.
3.7.1 Validity of the research tool

The validity of an instrument corresponds to the degree that the instrument is accurate and valid in its work and measures what it is supposed to measure (Gerrish & Lacey, 2010). The proforma was validated for content-related validity where content of the research tool is examined for its construct and ascertains that all the required aspects of the study are covered. This type of validity was established through the content validity index (CVI) (Gerrish & Lacey, 2010). The proforma was analysed and critiqued by two consultant vascular surgeons and a general ultrasound sonographer with more than ten years of scanning experience. The personnel were asked to rate each question individually and they were also given the opportunity to bring forward any remarks and suggestions. Each question on the proforma was given a score on a four point scale for relevance. The number one on the scale was the least relevant/appropriate with four being highly relevant and appropriate. The item content relevance of each question (I-CVI) was measured by calculating the average score of each question. The acceptable minimum value of the I-CVI is 0.80. Two questions did not reach the 0.80 value and were removed from the proforma. Suggestions from the expert panel were included into the proforma and the amended proforma underwent re-evaluation for content validity. These suggestions were:

- To add an 'On table angioplasty' tab under the section called: *If yes, what treatment?*
• To add an “Other” tab under the section called: *What was the predominant illness that led to the end stage kidney disease?*

### 3.7.2 Reliability testing of the research tool

Reliability of a study is a measure of the consistency and reproducibility of a result (Burns & Grove, 2005). The reliability of the proforma was tested for internal consistency. This is used to check how the questions relate to each other. The Cronbach’s Alpha is used to calculate the average inter-item correlation (Gerrish & Lacey, 2010). A score of 0.70 or above is considered acceptable and shows that the research tool had good internal consistency (Burns & Grove, 2005).

### 3.7.3 Reliability testing of the vascular sonographer

Testing for the reliability of the vascular scientist’s scanning technique is an important process as the consistency in the scanning is crucial in obtaining reliable data. All the data was collected by one vascular scientist who followed a scanning protocol. This was done so as to eliminate any variances that could exist between operators and ensure rigour. Since the measurements are obtained through scanning, it was imperative that the vascular scientist scanned the patients and used the data collecting tools in a consistent manner.
3.7.4 Intra-observer reliability testing

To ensure rigour, intra-observer reliability was tested by using the test-retest method. Intra-observer reliability testing was used to check that the vascular scientist was collecting the required data in a reliable way. The test-retest was done by scanning the patients taking part in the pilot study twice with the scans being one week apart. It was assumed that any changes in the fistula dynamics (if any) were minimal and would be averaged out over the ten patients. The data collected was then compared and the Kappa statistic was measured.

The value of the Kappa statistic can range from zero to one. A score of zero means that there is no agreement and that the vascular scientist collected very different data during the second scan. A value of one means that the vascular scientist collected exactly the same data during both scans. A score of 0.75 or more indicates excellent agreement. The Kappa statistic score for the scan was 0.85 showing excellent agreement between both scans and meant that the vascular scientist was scanning reliably.

3.7.5 Validity testing of the vascular scientist

Validity testing ensures that the data that is being collected by the vascular scientist is not distorted and is without bias. To test for validity, the vascular scientist conducted an ultrasound scan under the observation of two personnel with more than ten years of ultrasound scanning experience. Each observer had a proforma sheet and each question was ranked from zero to ten accordingly. A score of zero meant that the data collected by the
vascular scientist was not accurate. A score of ten meant that the data for that particular question was highly accurate. Pearson’s correlation was used to compare the means of each question and paired sample t-test was used to test the significance of the scores. Pearson’s correlation measures the correlation between sets of data and measures how they are related (Fitzpatrick & Kazer, 2011). Paired sample t-test was used for the validity testing and the null hypothesis ($H_0$) established that the average difference between the two samples was zero and that the p-value was less than 0.05 (Fitzpatrick & Kazer, 2011). The statistical test showed that the means of the observer’s answers were related and $p$ was 0.01. This meant that the vascular scientist was collecting data in a valid way.

### 3.8 Data Collection

#### 3.8.1 The scanning protocol

A scanning protocol was used during the data collection phase and it served as a guide so that all the necessary measurements were taken in a consistent manner. The proforma was structured in a way that apart from being a data recording tool, the proforma also served as the scanning protocol. The vascular scientist would follow the proforma and sequentially fill the required information ensuring that no section was omitted.
3.8.2 The data collection

Data was collected between January 2014 and March 2014, both included. All the patients participating in the study had already been informed and agreed to participate in the study. This will be explained in detail under the ethics section 3.12 in this chapter.

All the required information was obtained through an ultrasound examination and the data was recorded on the proforma. On the day, after a brief re-introduction, the patient was escorted to the scanning room. The first phase of the data collection was through a structured interview. The patient was then given the opportunity to ask any further questions if necessary. The patient was then asked to lie down on the couch and extend the arm with the arteriovenous fistula over towards the vascular scientist.

The ultrasound scan consisted of scanning the artery, from the axilla to the anastamotic area, and the arteriovenous fistula. Measurements made during the scan, such as diameters and blood flow velocity were documented on the proforma. The scanning was split into three phases.

3.8.3 Phase 1

The scanning of the whole area under investigation was initially done in B-mode in both transverse and longitudinal orientation. B-mode, or greyscale imaging gives the vascular scientist the possibility to get a general overview of the artery and arteriovenous fistula. This is essential as an autogenous arteriovenous fistula may have various configurations in the way that it was surgically created. In B-mode, the vascular scientist also has the
ability of identifying areas which may be stenotic due to the visibility of atherosclerotic plaque in the artery that could be the cause of a stenosis. Stenosis created from outside of the vessel due to extrinsic pressure, usually from oedema or haematoma within the surrounding tissues due to a complication of dialysis, could also be identified with a high degree of specificity and sensitivity in B-mode imaging. The calibre of the vessels was measured in B-mode. Calibre measurements were obtained in transverse from various segments of the system. Measurements were acquired from three sites; the axillary artery, one centimetre proximal to the anastamosis (arterial side) and mid fistula (excluding aneurismal segments). All the measurements were taken in millimetres (mm) using the inbuilt electronic calliper. Before taking any diameter measurement, it was visually ascertained that the vessel was circular in shape as this is the most accurate way to acquire the diameter of the vessel under interrogation.

3.8.4 Phase 2

Colour flow mode was used in the second phase of the ultrasound scan as it has the capability of supplementing the B-mode imaging with additional information. Colour flow Doppler works on the principle of movement, in this case the blood flowing through the artery or fistula. The blood flow is assigned a colour hue according to the direction of flow and which is superimposed on the B-mode image. The advantage of using colour flow is that any filling defects are easily detected as these filling defects will not get any colour fill. These filling defects are generally due to solid atherosclerotic plaques protruding in the lumen of the vessel which cause said stenosis. Any
filling defects were always collaborated with B-mode imaging as atherosclerotic plaques may not always be visible in B-mode imaging. However, colour flow overcomes this problem as echolucent or echogenic plaque does not influence colour flow mode as the colour flow depends only on the blood flow around the plaque. Another advantage of colour Doppler flow in the detection of stenosis is aliasing. Since the blood flow accelerates within a stenosis, aliasing occurs. High blood flows can exceed the Nyquist limit that is set by the PRF and these high blood flows create aliasing. This aliasing creates different colour hues within the vessel and this can be used as a reliable indicator in the detection of a stenosis. To avoid accidental aliasing between patients, the PRF setting was set individually according to the patients circulatory dynamics. The PRF was adjusted so that no aliasing was present in the axillary artery and a colour map baseline was established for each patient. Any aliasing seen during the scan was indicative of a stenosis and was noted in the proforma.

3.8.5 Phase 3

Doppler was the final step used as part of the scanning protocol. In ultrasound Doppler mode, ultrasound equipment is able to measure the blood velocity at any area that the user requires by calculating the velocity of the red blood cells as they pass through the sampling gate. The measurements were taken according to the established protocol. One measurement was at the axilla and another was 2cm away from the anastamosis. The measurement was taken two centimetres instead of one centimetre away from the anastamosis in order to reduce turbulent
arteфactual measurements. The final measurement was taken mid fistula between the anastamosis and the axilla.

If at any point throughout the scan changes were noted which indicated a possible stenosis, additional measurements were taken. These measurements were one centimetre proximal to the stenosis, at the stenosis (the narrowest part visible on B and colour mode) and one centimetre post-stenosis. The reason for the documentation of these three measurements is so that the degree of stenosis can be established. The velocities before and at the stenotic lesion are used to determine if the stenosis is significant or non-significant. The measurement post stenosis was taken as in this area a blood flow jet can be found and the PSV of this jet can be higher than the PSV at the stenotic lesion. In cases where the PSV in the jet was higher, this PSV was used in the calculation to determine the degree of stenosis.

3.9 Pilot Test

Wood & Ross-Kerr, (2010) explained that unforeseen problems may arise during the research study which may be either unimportant or may have disastrous effects on the study. A pilot study is a dry run for the actual study and it should address all the aspects of the data collection phase, preparation, recruitment and also the actual data collection phases.

A pilot study was carried out for this research study. All aspects of the study such as the proforma layout/sequencing, scanning procedure, patient positioning and recording of the measurements were replicated in order to be able to maximise the benefit out of the pilot study. Ten participants were
enrolled in the pilot study. This amounted to 10% of the sample population. The patients were informed that they would not be able to participate in the main study. After each scan, the vascular scientist noted down any difficulties or problems encountered during any part of the ultrasound scan.

Although no major design flaws were found, some amendments were made in order to better streamline and facilitate the data collection process. These are:

- Font change in the proforma to be more user friendly
- Date of fistula creation was obtained from the patient’s history for better accuracy of fistula age. It was first thought that the patient would supply this information, however, it turned out that only one out of the ten patients actually knew the exact date of the operation.
- The aetiology for the end stage kidney disease was also verified from the patient’s history for the same reason that is mentioned in the previous point.
- An additional section for comments was added to the proforma. This was used to note down any vascular anomalies that were noted during the scan. These patients were referred for follow up to the consultant nephrologist.
- Another new section was also added to cater for those cases where the ultrasound scan identified more than one stenosis.
- Patient scanning position was initially sitting but this configuration made it difficult to obtain accurate data from the axillary artery. The patient position was modified and standardised so that the patient
would be lying down with the fistula arm extended away from the body.

### 3.10 Data analysis

Data analysis is a process where raw data is organised systematically and statistical tests are applied to better describe and evaluate the data (Trappen, 2010). The quantitative data gathered was first inputted into a spreadsheet and then imported into the statistical analysis program SPSS version 20. The data consisted of both metric and categorical data. Categorical data is data that can be segmented into their respective categories, for example *gender*. Metric data is numerical data only, for example, the diameter in mm of the fistula.

The statistical tests chosen were determined by an expert statistician. For this study both descriptive and inferential statistics were used. Descriptive statistics were used to provide a statistical summary of the population data in both numerical and graphical format. Furthermore, descriptive analysis provided the statistical information relating to dispersion such as mean, range and the standard deviation of the data. Inferential statistics were used to infer the data parameters and model relationships within the data itself. Throughout the study, three statistical tests were used. These are:

- The Pearson’s Correlation
- The One Way Anova
- The Chi Squared Test.
3.10.1 The Pearson’s Correlation

The Pearson’s correlation test was used to measure the strength of the relationship between two metric variables, such as, age and weight. This association can have either a positive or a negative correlation. Pearson correlation is one method of estimating the association of the two variables that are scored on an interval or ratio level and the level of significance (P) of a Pearson’s correlation test should be less than 0.05 in order to prove that the test was statistically significant (Trappen, 2010).

3.10.2 The One Way ANOVA

The One way ANOVA statistical test was used to compare the means scores, such as, blood volume between several independent groups clustered by, for example; Stenosis. For the statistical test to work, a hypothesis had to be established for each statistical test. The H₀ specifies that the mean scores differ marginally between the groups and is accepted if the p-value exceeds 0.05 level of significance and the alternative hypothesis (H₁) specifies that the mean scores differ significantly between the groups and is accepted if the p-value is less than the 0.05 criterion (Trappen, 2010).

3.10.3 The Chi Squared test

The Chi Square test was used to assess the association between two categorical variables. A hypothesis had to be established for each statistical test. H₀ specifies that there is no association between the two categorical variables and is accepted if the p-value exceeds 0.05 level of significance.
H₁ specifies that there is a significant association between the two categorical variables and is accepted if the p-value is less than the 0.05 criterion (Trappen, 2010).

3.11 Strength and Limitations

The main strength of the study was that all the patients, not a sample of these, with an autogenous arteriovenous fistula that attended the local renal unit for dialysis were recruited. A limitation of the study was that only the patients with an autogenous arteriovenous fistula were used and therefore patients with graft fistulas and permanent catheters were omitted.

Another limitation was the cross-sectional nature of this study. Due to time limitations, the researcher was only able to gather and analyse the data of one collection point. Although his data is sufficient and can be extrapolated, this is by no means as accurate as a longitudinal study whereby multiple collection points offer a higher accurate data collection method due to the analytic possibility of the progression of disease.

3.12 Importance of Ethics in research

All ethical issues and their implications were addressed throughout this study. The participants, in this case the patients with an autogenous arteriovenous fistula, were not approached initially by the researcher so that the patient would not feel pressured or coerced in any way to participate in this study. Instead a nurse who works at the renal unit approached the
patient during one of the dialysis sessions. The nurse handed the patient the information sheet so that the patient could inform him/herself about the scope of the research study. The information sheet (appendix B) was provided in both official languages Maltese or English languages so as to try and avoid any language barriers. If the patient decided to participate in the research study, he/she would inform the nurse who in turn would contact the researcher. The researcher was then able to approach the patient and introduce himself. The researcher was then able to verbally explain the purpose of the study and give all the information pertaining the study. The patient was also given the opportunity to ask any questions. The consent form (appendix B) was also provided in both languages. The patient had the right to refuse participation at any time during the ultrasound examination and was not obliged to give a reason for doing so. A convenient date for the patient was then established so that the ultrasound examination could take place prior to a dialysis session.

The proforma was designed so that no personal information such as names and identification numbers were collected. This meant that no data could be linked to a particular patient. All the data was kept secure in a locked drawer until the data was inputted on the computer. The computer files containing the study’s data were encrypted and password protected.

A strength of the study was that the patients were not exposed to any risks such as ionising radiation or any harm by participating in the study. The ultrasound scanning required measurements of blood velocities from the forearm. As explained in the data collection section, the blood flow measurements were taken from the axilla, the junction between the artery
and vein (anastomosis) and the fistula itself. All of the fistula circuit was imaged using ultrasound. All the resident consultant nephrologists and a vascular surgeon were informed and agreed to provide support and treatment should a problem or anomaly be detected during the ultrasound scan.

Permission was sought and obtained from the University Research Ethics Committee (appendix A). Other permissions necessary for this research study were obtained and are listed below:

- The hospital CEO for approval to perform a research study within the hospital and the use of hospital equipment.
- The head of the dialysis unit for providing the scanning room with all the required necessities.
- The data protection officer in charge.
- Four (4) consultant nephrologists
- Vascular surgeon
- Director and the manager of the Medical Imaging Department for permission to use the facilities in the Medical Imaging Department if the room provided by the renal unit was not available.
- The head of the Department of Radiography, of a University in Malta for the provision of the ultrasound machine.
3.13 Conclusion

This chapter highlights the methodology and the technique used to obtain the data necessary to fulfil the aims of this research study. A detailed analysis and discussion of the data will be provided in the next chapter.
Chapter 4
Results and Discussion
Chapter 4

4.1 Introduction

This chapter presents the results of this study as well as a discussion of the results.

4.2 The patient sample

The patient sample consisted of all the patients undergoing haemodialysis at the renal unit of a state hospital through an autogenous arteriovenous fistula. A total of 103 patients were eligible to participate out of which 10 were selected to take part in the pilot study. Four (4) patients refused to participate in the study. The final patient count was 89. These 89 patients were scanned according to the established protocol (section 3.8.1) and the data pertaining to this study was collected.

4.3 Patient demographics

The population sample consisted of 53 males and 36 females. As seen in figure 1 overleaf, the mean age was 62 years with a median of 64 years. The youngest patient was 20 and the oldest patient was 84 years old. The standard deviation (SD = 14.886) curve shows that the age distribution is slightly skewed to the right with the majority of the population sample being over the age of 50 years.
Chapter 4

Results and Discussion

Three types of autogenous arteriovenous fistula were present amongst the sample population. Table 2 illustrates the different types of fistula.

![Histogram showing the Age of the patient](image)

**Figure 1:** Histogram showing the Age of the patient

<table>
<thead>
<tr>
<th>Type of Fistula</th>
<th>Number</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiocephalic</td>
<td>25</td>
<td>28.1%</td>
</tr>
<tr>
<td>Brachiocephalic</td>
<td>61</td>
<td>68.5%</td>
</tr>
<tr>
<td>Transposed Brachiobasilic</td>
<td>3</td>
<td>3.4%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>89</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

**Table 2:** Shows the different types of arteriovenous fistula
4.4 Statistical analysis

4.4.1 Mean follow up period

The mean follow up period is the time interval between first haemodialysis session using the fistula until the time of data collection. A histogram depicting this data can be found in Figure 2. The mean follow up period for the cohort of patients recruited to the study was 27 months with a range of 116 months and the SD was 21.823. The minimum mean follow up period was of 2 months and the maximum follow up period was of 118 months. One patient was omitted from this descriptive test as the data point was classified as an outlier (refer to the arrow in figure 3 overleaf). This individual had a follow up period of 204 months. This was significantly higher than the other mean follow up periods and following consultation with a statistician data pertaining to this patient was omitted so that a holistic representation of the mean follow period of all the fistulas could be obtained.

![Histogram showing the mean follow up period for 88 patients (without outlier)](image)

Figure 2: Histogram showing the mean follow up period for 88 patients (without outlier)
4.4.2 Fistula complications and interventions

Within the population sample, 24.7% of the patients had a history of complications in their fistula. These included stenosis with or without associated thrombosis. All 24.7% of the patients underwent intervention as shown in Table 3 without loss of dialysis access through the fistula. All interventions were performed prior to the data collection period. Table 3 below illustrates the treatment given to the 24.7% of these patients.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number</th>
<th>Percent %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angioplasty and/or stenting</td>
<td>18</td>
<td>60.0</td>
</tr>
<tr>
<td>Open Thrombectomy</td>
<td>2</td>
<td>6.7</td>
</tr>
<tr>
<td>Open thrombectomy and on table angioplasty</td>
<td>10</td>
<td>33.3</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>30</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>

Table 3: The table shows the different treatments given to the patients suffering from stenosis and/or thrombosis.
4.4.3 Aetiology of end stage kidney disease

The data showed that forty seven (47) patients (52.9%) had one co-morbidity and forty two patients (47.1%) had two co-morbidities that were likely to have led to their end stage kidney failure. Table 4 illustrates the primary co-morbidity and the respective percentages.

<table>
<thead>
<tr>
<th>What was the predominant illness that led to the end stage kidney disease?</th>
<th>Number of patients</th>
<th>Percent %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>37</td>
<td>41.6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>31</td>
<td>34.8</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>5</td>
<td>5.6</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>3</td>
<td>3.4</td>
</tr>
<tr>
<td>Genetic disorder</td>
<td>7</td>
<td>7.9</td>
</tr>
<tr>
<td>Other a</td>
<td>6</td>
<td>6.7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>89</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>

*Table 4*: The table shows the predominant illnesses that led to the end stage kidney disease. a: refers to Nsais abuse, drug abuse and unknown cause.

Table 4 shows that the two most predominant predisposing conditions for end stage renal failure are diabetes and hypertension. Collectively these diseases constitute the underlying aetiology in 76.4% of the scanned population. The National Kidney Foundation (2006) explains that people with diabetes and hypertension are more susceptible to suffer from end stage kidney disease. In Malta, the prevalence of diabetes and hypertension is higher than in the other EU-27 countries (Ministry for Health, 2014) and this is reflected in this study as seen in table 4.
The co-morbidity variable was tested for statistical significance by the Chi-squared statistical test against other categorical variables such as gender, the type of fistula, any previous treatment and presence of stenosis and the location of stenosis. $H_0$ specifies that there was no association between the two categorical variables. $H_1$ specifies that there was an association between the two categorical variables.

No statistical significance was found for gender ($p = 0.436$), presence of stenosis ($p = 0.241$) and location of the stenosis ($p = 0.450$). Statistical significance was found for the type of fistula present ($p = 0.013$) and whether any treatment was given ($p = 0.001$).
4.4.3.1 Type of fistula

The histogram below shows the correlation between the type of fistula and all the co-morbidities that may lead to the end stage kidney disease. The diagram shows that the majority of patients who suffer from the two predominant illnesses, namely diabetes and hypertension, have a brachiocephalic fistula. Patients with diabetes mellitus have the highest number of brachiocephalic fistulas when directly compared to radiocephalic fistulas which may be the result of calcific atherosclerotic disease in diabetics which preclude patients from having a distal fistula (Cassar, 2012).

![Type of fistula](image)

Figure 4: The relation between the type of fistula and the co-morbidity that led to the end stage kidney disease.
4.4.3.2 Treatment

The histogram below represents the correlation between any treatment given and the type of co-morbidity that led to the end stage kidney disease. The diagram depicts that for this cohort, twelve (12) diabetic patients have had an angioplasty to treat a stenosis.

![Histogram](image)

**What was the predominant illness that lead to the end stage kidney disease?**

**Figure 5:** The relation between the co-morbidity and different types of interventions
4.4.4 Flow Volume

A fistula is intended to achieve high flow rates for the patient to receive effective dialysis. The literature is not consistent in the flow rates required and different studies have published varying ranges of blood flow. According to Alamdaran et al., (2008) the ideal flow rate should be between 400ml/min and 1200ml/min but Tonelli, James, Wiebe, Jindal, & Hemmelgarn (2008), in their review quote a higher flow rate of 1801ml/min and a median of 1108ml/min. San Miguel and Chow (2009) claim that the ideal flow rate is between 500 ml/min and 1000ml/min, however, the authors also point out that flow rates can be higher in upper arm and thigh fistulas. Even though the flow rates stipulated by the different authors are different, the blood flow ranges are similar except for those quoted by Tonelli et al., (2008) which are higher.

The flow rates of both the arterial and the fistula segment were calculated. The table below presents all the results. The mean flow rate in the fistula is 1580ml/min and the SD is 1.061. The lowest working fistula flow rate was 200ml/min and the highest was 4280ml/min. The results show that for this cohort, the blood flow in the fistula is higher when compared to the studies by (Alamdaran et al., 2008; San Miguel & Chow, 2009; Tonelli et al., 2008).

<table>
<thead>
<tr>
<th>Flow volume L/min</th>
<th>N</th>
<th>Minimum</th>
<th>Maximum</th>
<th>Mean</th>
<th>Std. Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flow volume - Fistula</td>
<td>89</td>
<td>0.20</td>
<td>4.28</td>
<td>1.5866</td>
<td>1.06085</td>
</tr>
<tr>
<td>Flow volume - Artery</td>
<td>89</td>
<td>0.47</td>
<td>3.50</td>
<td>1.5226</td>
<td>0.71936</td>
</tr>
<tr>
<td>Valid N (list wise)</td>
<td>89</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 5: Flow volume for both the fistula and feeding artery are shown with their respective minimum, maximum and mean.
To assess the significance of the flow rate of the fistula two statistical tests were used. These were the Pearson's correlation and the Chi Squared test.

4.4.4.1 Pearson’s Correlation

The Pearson's correlation was used to test for statistical significance between the means of metric variables such as age and weight. \( H_0 \) states that there is no association between the two variables. \( H_1 \) states that there is a significant association between the two variables.

4.4.4.2 Chi Squared test

The Chi Squared test was also used to assess for statistical association between the flow rate and a categorical variable such as fistula type and previous treatment. The test used the same hypothesis as stipulated in section 4.4.3.

4.4.4.3 Results from the statistical tests

Univariate analysis of the blood flow rate in the fistula did not show any statistical significance in relation to gender \( (p = 0.634) \), age \( (p = 0.964) \), weight of the patient \( (p = 0.311) \), height of the patient \( (p = 0.462) \) and previous treatment for stenosis or thrombosis \( (p = 0.415) \). However, statistical significance was established for the type of fistula \( (p = 0.049) \), the diameter (mm) of the fistula \( (p < 0.01) \) and blood flow rate (cm/s) of the fistula \( (p < 0.01) \). These results indicate that the type of fistula (radiocephalic, brachiocephalic or brachiobasilic) is a significant factor in the total flow rate of blood in the fistula. In this study, radiocephalic fistulas have the smallest
diameters when compared to the two other types and subsequently had the lowest mean flow rate. The tables 6 and 7 below and table 8 overleaf show the mean and median of all the measurements taken by duplex ultrasound for the three different types of fistula found in this cohort.

<table>
<thead>
<tr>
<th>Radiocephalic Fistula</th>
<th>B-mode measurement - middle of the Fistula (mm)</th>
<th>Doppler measurement - middle of the Fistula (cm/s)</th>
<th>Flow volume in Artery (ml/min)</th>
<th>Flow volume in Fistula (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>24</td>
<td>24</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Mean</td>
<td>6.648</td>
<td>86.6958</td>
<td>1.3364</td>
<td>1.2205</td>
</tr>
<tr>
<td>Median</td>
<td>6.890</td>
<td>82.9500</td>
<td>1.1210</td>
<td>0.9090</td>
</tr>
<tr>
<td>Std. Deviation</td>
<td>0.16009</td>
<td>49.4058</td>
<td>0.70338</td>
<td>0.91960</td>
</tr>
</tbody>
</table>

Table 6: The table shows B-mode and Doppler measurements as well as flow volumes in the artery and radiocephalic fistula

<table>
<thead>
<tr>
<th>Brachiocephalic Fistula</th>
<th>B-mode measurement - middle of the Fistula (mm)</th>
<th>Doppler measurement - middle of the Fistula (cm/s)</th>
<th>Flow volume in Artery (ml/min)</th>
<th>Flow volume in Fistula (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>61</td>
<td>61</td>
<td>61</td>
<td>61</td>
</tr>
<tr>
<td>Mean</td>
<td>8.374</td>
<td>102.2344</td>
<td>1.5894</td>
<td>1.7071</td>
</tr>
<tr>
<td>Median</td>
<td>8.100</td>
<td>86.7000</td>
<td>1.5450</td>
<td>1.4170</td>
</tr>
<tr>
<td>Std. Deviation</td>
<td>0.20787</td>
<td>60.74068</td>
<td>0.72990</td>
<td>1.08976</td>
</tr>
</tbody>
</table>

Table 7: The table shows B-mode and Doppler measurements as well as flow volumes in the artery and brachiocephalic fistula
### Transposed Brachiobasilic Fistula

<table>
<thead>
<tr>
<th></th>
<th>B-mode measurement - middle of the Fistula (mm)</th>
<th>Doppler measurement - middle of the Fistula (cm/s)</th>
<th>Flow volume ì Artery (ml/min)</th>
<th>Flow volume ì Fistula (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Mean</td>
<td>8.900</td>
<td>193.3000</td>
<td>1.6400</td>
<td>2.4010</td>
</tr>
<tr>
<td>Median</td>
<td>9.700</td>
<td>204.4000</td>
<td>1.8000</td>
<td>2.8400</td>
</tr>
<tr>
<td>Std. Deviation</td>
<td>0.24980</td>
<td>72.88669</td>
<td>0.72339</td>
<td>0.78037</td>
</tr>
</tbody>
</table>

Table 8: The table shows B-mode and Doppler measurements as well as flow volumes in the artery and transposed brachiobasilic fistula

A non-significant stenosis in small diameter fistulas will have a greater impact on the total flow rate which makes it more likely that the minimum threshold of 400ml/min is reached and will result in ineffective dialysis sessions resulting in a possible thrombotic event (National Kidney Foundation, 2006). Only one patient had a blood flow volume of 200ml/min and this was half of the minimum threshold (400ml/min). This was due to a significant stenosis in the brachiocephalic fistula which was not thrombosed at the time of data collection. The patient was still being dialysed effectively through this fistula despite the low flow rate but upon completion of the duplex scan the patient was immediately referred to the caring consultant for follow-up investigations.
4.5 Stenosis

One of the study’s objectives was to use duplex ultrasound to assess the arteriovenous fistula and feeding artery of patients on haemodialysis and identify any asymptomatic clinical stenosis in the autogenous fistula and/or feeding artery. The data that was collected during the study consisted of measurements in mm for diameters and cm/s for PSVs. These data measurements alone were in an unprocessed form and the researcher was unable to classify the asymptomatic stenosis as significant or non-significant. Therefore, the data was post processed three times according to the classifications used. These three classifications use different parameters (diameter in mm or PSV in cm/s) to determine the cut-off point where a non-significant stenosis transitions into a significant one. These classifications are explained in the following sections.

4.5.1 Classification 1

Classification one is that recommended by the National Kidney Foundation, (2006). The stenoses identified are classified into two categories namely significant and non-significant (National Kidney Foundation, 2006). A minimum of 50% decrease in normal vessel diameter (artery or fistula) is needed for the stenosis to be considered a significant stenosis. If the stenosis does not exceed 50% of the lumen diameter, then the stenosis is classified as non-significant. The National Kidney Foundation, (2006) also point out that a 50% reduction in the lumen diameter corresponds to an area reduction of approximately 75%.
The percentage stenosis was calculated by averaging the lumen distances proximal and distal to the stenosis. This figure was then divided by two. This result was then compared to the residual lumen distance taken at the stenosis level. If the stenosis measurement was more than this the stenosis was classified as a non-significant stenosis. If the measurement was less or equal to half the average of the diameter proximal and distal to the stenosis then the stenosis was classified as a significant stenosis. The results of this type of classification are displayed in the table below.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Number</th>
<th>Percent %</th>
</tr>
</thead>
<tbody>
<tr>
<td>No stenosis</td>
<td>57</td>
<td>64.0</td>
</tr>
<tr>
<td>Non-significant stenosis</td>
<td>19</td>
<td>21.4</td>
</tr>
<tr>
<td>Significant stenosis</td>
<td>13</td>
<td>14.6</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>89</strong></td>
<td><strong>100.0</strong></td>
</tr>
</tbody>
</table>

*Table 9: The table displays classification one and its 3 tiers*

The previous table shows that based on this classification 36% percent of the patients had a previously undetected stenosis and 14.6% had a significant stenosis which according to the guidelines should ideally undergo some form of intervention (Ministry for Health, 2014; Tordoir et al., 2007).
4.5.2 Classification 2

Classification 2 used the criteria which were established by (Chandra et al., 2010). Fistula stenoses are classified into 4 tiers based on the diameter as follows.

These are:

- No stenosis
- A stenosis which is more than 3mm diameter is classified as a non-significant stenosis
- A stenosis ranging between 1.5mm and 3mm is classified as a significant stenosis
- A stenosis less than 1.5mm is classified as a highly significant stenosis

<table>
<thead>
<tr>
<th>Classification</th>
<th>Number</th>
<th>Percent %</th>
</tr>
</thead>
<tbody>
<tr>
<td>No stenosis</td>
<td>57</td>
<td>64.0</td>
</tr>
<tr>
<td>Stenosis greater than 3mm (not significant)</td>
<td>14</td>
<td>15.7</td>
</tr>
<tr>
<td>Stenosis between 1.5 - 3mm (significant)</td>
<td>15</td>
<td>16.9</td>
</tr>
<tr>
<td>Stenosis less than 1.5 mm (highly significant)</td>
<td>3</td>
<td>3.4</td>
</tr>
<tr>
<td>Total</td>
<td>89</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Table 10: The table displays classification two and its 4 tiers

Using Classification 2, 36% of the patients had an undetected stenosis and 20.3% had a significant stenosis which according to the guidelines
should undergo some form of treatment (Ministry for Health, 2014; Tordoir et al., 2007).

### 4.5.3 Classification 3

Classification 3 used the PSV criteria established by Stolic, (2013). This classification is based on the PSV in the arterial and venous segments. Velocities greater or equal to 400 cm/s indicate the presence of a significant stenosis.

<table>
<thead>
<tr>
<th>Classification three</th>
<th>Number</th>
<th>Percent %</th>
</tr>
</thead>
<tbody>
<tr>
<td>No stenosis</td>
<td>66</td>
<td>74.1</td>
</tr>
<tr>
<td>Significant stenosis</td>
<td>23</td>
<td>25.8</td>
</tr>
<tr>
<td>Total</td>
<td>89</td>
<td>100.0</td>
</tr>
</tbody>
</table>

**Table 11:** The table shows the 3 tier classification

Based on classification three, seventy four percent (74.1%) of the cohort did not have a stenosis. Twenty six (25.8%) percent of the cohort had a significant stenosis which according to the guidelines should be referred for intervention (Ministry for Health, 2014; Tordoir et al., 2007).

### 4.5.4 Classification analysis

The data collected for this study included lumenal diameter measurements and blood flow velocities. Classification one and two use lumenal diameter measurements to stratify a stenosis into either a significant or non-significant one. Based on these two classifications there was agreement that 64% percent of the scanned population did not have a
stenosis. The remaining 36% of the scanned population had a stenosis classified as either a non-significant or as a significant stenosis. When comparing the results of the two tiers (significant and non-significant) a difference of 5.7% is noted. Classification one shows that more patients have a non-significant stenosis when compared to the results of classification two. The Chi squared statistical test was used to test if there was an association between the classifications. $H_0$ specifies that there is no association between the two categorical variables and $H_1$ specifies that there is an association between the two categorical variables. The results in the table below shows that there was a high level of association between classification one and classification two ($p < 0.01$).

<table>
<thead>
<tr>
<th>Classification II ~ Classification I Crosstabulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classification II</td>
</tr>
<tr>
<td>No stenosis</td>
</tr>
<tr>
<td>No stenosis</td>
</tr>
<tr>
<td>Stenosis greater than 3mm (not significant)</td>
</tr>
<tr>
<td>Stenosis between 1.5 - 3mm (significant)</td>
</tr>
<tr>
<td>Stenosis less than 1.5 mm (highly significant)</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

Table 12: The table shows the Chi squared test result of classification one against classification two (with no stenosis column)

Table 12 shows that there is a very high association between classification 1 and classification two, especially for the no stenosis column.
(100%). Upon review by the statistician, it was pointed out that the no stenosis column was so statistically strong and that it could be influencing the result. Another Chi Squared test was done with the no stenosis column omitted from the test and $p$ was 0.548. The result can be seen below in table 13.

<table>
<thead>
<tr>
<th>Classification II</th>
<th>Classification I</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Non Significant Stenosis</td>
</tr>
<tr>
<td>Stenosis greater than 3mm (not significant)</td>
<td>Count</td>
</tr>
<tr>
<td>Stenosis greater than 3mm (not significant)</td>
<td>% within Classification I</td>
</tr>
<tr>
<td>Stenosis between 1.5 - 3mm (significant)</td>
<td>Count</td>
</tr>
<tr>
<td>Stenosis between 1.5 - 3mm (significant)</td>
<td>% within Classification I</td>
</tr>
<tr>
<td>Stenosis less than 1.5 mm (highly significant)</td>
<td>Count</td>
</tr>
<tr>
<td>Stenosis less than 1.5 mm (highly significant)</td>
<td>% within Classification I</td>
</tr>
<tr>
<td>Total</td>
<td>Count</td>
</tr>
<tr>
<td>Total</td>
<td>% within Classification I</td>
</tr>
</tbody>
</table>

Table 13: The table shows the Chi squared test result of classification one against classification two (without the no stenosis column)

Table 13 shows that there is no association between the non-significant and significant stenosis as $p$ was more than 0.05. The results of both table 12 and table 13 show that classification one and classification two agree only on the “no stenosis” criteria but differ on the “non-significant stenosis” and “significant stenosis”

Classification two is a four tier classification, which unlike classification one, stratifies the significant stenosis tier into two more groups, significant
and highly significant. The additional tier caters for a section which Chandra et al., (2010) called highly significant. Chandra et al., (2010) state that their way of distinguishing between a significant and a non-significant stenosis is more accurate than the other methods. They argue that the purpose of an autogenous arteriovenous fistula is to increase the blood flow volume for the patient to have effective dialysis and that it is not uncommon to find a 50% stenosis in a large calibre fistula. This will not reduce the blood flow rate significantly as the residual lumen is more than capable of delivering adequate blood flow for effective dialysis. Chandra et al., (2010) are more concerned with the higher percentage stenoses (above 75%) as these have the potential to limit effective dialysis. Table 10 shows that three patients (3.4%) from this cohort had an undetected, highly significant stenosis. Highly significant stenoses are more likely to lead to a thrombotic episode (National Kidney Foundation, 2006). When combining the percentages of the significant tiers, the results indicate that 18 patients (20.3%) have a significant stenosis based on the criteria of classification 2.

Classification three is different from classification one and two as it uses blood flow velocity (cm/s) to detect stenoses. Classification one and two use luminal diameter measurements (mm). Classification three is different from the other two classifications as it does not have a non-significant stenosis tier. Patients whose blood flow velocity exceeds 400 cm/s are stratified directly into the significant stenosis category. Any patient whose blood flow velocity is less than 400 cm/s is stratified into the no stenosis list. When compared to the other classifications, classification three identified 10.1% less stenoses when compared to the other classifications. Classification
three was tested against the other two classifications to check if there was any association between them. The table below shows the results and that there is a high level of association between the classifications as $p$ was less than 0.01.

<table>
<thead>
<tr>
<th>Classification III</th>
<th>Classification I</th>
<th>Non-stenosis</th>
<th>Non-significant Stenosis</th>
<th>Significant Stenosis</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No stenosis</td>
<td>Count</td>
<td>57</td>
<td>6</td>
<td>3</td>
<td>66</td>
</tr>
<tr>
<td>% within Classification I</td>
<td>100.0%</td>
<td>31.6%</td>
<td>23.1%</td>
<td>74.2%</td>
<td></td>
</tr>
<tr>
<td>Velocities are significant</td>
<td>Count</td>
<td>0</td>
<td>13</td>
<td>10</td>
<td>23</td>
</tr>
<tr>
<td>% within Classification I</td>
<td>0.0%</td>
<td>68.4%</td>
<td>76.9%</td>
<td>25.8%</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>Count</td>
<td>57</td>
<td>19</td>
<td>13</td>
<td>89</td>
</tr>
<tr>
<td>% within Classification I</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

Table 14: The table shows the Chi squared test result of classification one against classification two (with no stenosis column)

Table 14 shows that there is a very high association between classification 1 and classification three, especially for the ’no stenosis’ column (100%). As previously mentioned, the ’no stenosis’ column was so statistically strong and that it could be influencing the result. Another Chi Squared test was done with the ’no stenosis’ column omitted from the test and $p$ was 0.559. The result can be seen in table 15 overleaf.
Table 15: The table shows the Chi squared test result of classification one against classification two (without the no stenosis column)

Table 15 shows that there is no association between the non-significant and significant stenosis as p was more than 0.05. The results of both table 14 and table 15 show that classification one and classification three agree only on the "no stenosis" criteria but differ on the "non-significant stenosis" and "significant stenosis".

The statistical tests for all three classifications used by National Kidney Foundation, (2006), Chandra et al., (2010) and Stolic, (2013) show some association in this study. Classification 1 was the most commonly used classification system in the published studies which is the reason why classification one was used in this study.
4.5.5 Stenosis discussion

Classification one shows that out of the 89 patients assessed, 32 patients had a stenosis in their fistula. This means that 36% of the patients assessed had an undetected, asymptomatic stenosis. This is 28% lower than the published results obtained in a similar study by Pietura et al., (2005). In their study, Pietura et al., (2005) used duplex ultrasound to assess for stenosis in 139 asymptomatic fistula and found that 64% of the patients had an asymptomatic stenosis. This study showed that the majority of the stenoses are present at either the anastamotic segments or the venous segment. For the purposes of this study, the venous segment was defined as the vessel between the anastamosis and the confluence, where the superficial venous system joins the deep venous system. No stenoses were found in the inflow arterial segment in any of the patients. Furthermore, no patient was found to have more than one stenosis. Table 16 shows the comparative results of both studies.

<table>
<thead>
<tr>
<th></th>
<th>This study</th>
<th>Pietura et al (2005)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous stenosis</td>
<td>12.4%</td>
<td>22%</td>
</tr>
<tr>
<td>Arterial Stenosis</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>Anastamosis level</td>
<td>23.6%</td>
<td>57%</td>
</tr>
</tbody>
</table>

Table 16: The table compares the percentage stenosis within each segment for both studies.
4.6 Co-morbidity

Table 4 shows the various aetiologies for the end stage renal failure and the two leading causes were diabetes (28.2%) and hypertension (42.7%).

Johansson, Myredal, Friberg, and Gan (2010) explain that diabetes and hypertension are causes of atherosclerosis which can contribute to intimal hyperplasia which is one of the main causes that may lead to stenosis (Stolic, 2013). Bahadi et al., (2012) reported that diabetes (p = 0.02) is one of the risk factors for primary fistula failure in autogenous arteriovenous fistulae as atherosclerosis with calcific deposits playing a role in the fistula’s failure. Dixon (2006) reported that diabetes and hypertension can be contributors to fistula failure but the author also explains that other factors and not just a co-morbidity may have a decisive role in a fistula failure. These factors include the angle of the anastamosis, vein mobility and also possible ‘hinge’ issues when the fistula is fashioned (Dixon, 2006). Scaffaro et al., (2009) analysed if screening of autogenous arteriovenous fistula with duplex ultrasound and angiography and when necessary angioplasty could reduce the incidence of thrombosis and found that co-morbidities, such as diabetes and hypertension did not increase the risks of fistula stenosis and subsequent failure. When comparing this study’s results on co-morbidities with the ones of Scaffaro et al. (2009) the results are similar indicating that co-morbidities do no increase the risk of fistula stenosis and subsequent failure. Table 17 overleaf illustrates the multinomial statistical resemblance.
### Chapter 4

#### Results and Discussion

<table>
<thead>
<tr>
<th>Condition</th>
<th>Study 1</th>
<th>Study 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>0.743</td>
<td>0.999</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.621</td>
<td>0.460</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>0.376</td>
<td>N/A</td>
</tr>
<tr>
<td>Polycystic kidney disease</td>
<td>0.318</td>
<td>0.308</td>
</tr>
<tr>
<td>Genetic disorder</td>
<td>0.410</td>
<td>N/A</td>
</tr>
<tr>
<td>Other</td>
<td>0.743</td>
<td>0.940</td>
</tr>
</tbody>
</table>

**Table 17:** The table shows the P value of both studies where the incidence of stenosis was tested against the co-morbidity which led to the end stage kidney disease.

#### 4.7 Screening

The aim of this study was to assess the feasibility of introducing a screening programme for the Maltese patients with an autogenous arteriovenous fistula. Regardless of what imaging modality is used to screen the patients, the purpose of screening programmes is to identify any illnesses in healthy people. For this study the purpose of screening is to identify stenosis and allow intervention before thrombotic events can compromise the fistula and subsequently the patients' dialysis access.

The National Kidney Foundation (2006) has established that mature autogenous fistulas have fewer thrombotic episodes when compared to graft fistulas, but stenosis and thrombosis are still the most common type of autogenous fistula complications. The National Kidney Foundation (2006) also state that screening of arteriovenous fistulas with proper treatment may reduce thrombosis rates and even prolong the fistula survival rates. Tonelli et al., (2008) also deduced that arteriovenous fistula screening has its benefits and it was shown that screening has a positive impact on access survival through the reduction of thrombotic episodes. However, screening
did not prolong the overall fistula patency rate. In a longitudinal study, Shahin et al., (2005) concluded that access monitoring detected more fistula problems than with regular monitoring and as a result the number of angioplasty procedures increased in their experimental group. However, although the detection rate and treatments increased when compared to the control group, the thrombosis rates and cumulative access patency rates were not statistically significantly better. Shahin et al., (2005) were unable to establish why this was the case and the authors deduced that there is a limit as to how many sequential angioplasties may be performed and still obtain a successful outcome. The authors were of the opinion that angioplasties cause injury to the intima which probably leads to higher stenosis rates (Shahin et al., 2005).

Currently, there is no screening programme in place for patients undergoing haemodialysis in Malta. Patients are only referred for assessment which usually includes a duplex ultrasound scan when there is clinical evidence that the fistula is not performing adequately. This may be followed by fistulography with or without angioplasty depending on the findings. A drop in fistula performance is detected by an absent or a change in the thrill felt over the fistula, limb swelling and/or redness, difficulty in cannulation, increased pump pressures, ineffective dialysis and recirculation issues. Since patients are referred for additional investigations only when a problem is detected, the probability exists that the fistula may have a significant stenosis by this time which may threaten the fistula’s patency. The results of this study show that 36% of the patients undergoing haemodialysis with a native fistula have a form of undetected stenosis (non-significant or
significant). According to classification one, 14.6% of these patients have a significant stenosis which according to the National Kidney Foundation, (2006) should undergo some form of treatment.

4.7.1 Pre-emptive treatment

Pre-emptive treatment for fistulas means prophylactic endovascular intervention (angioplasty +/- stenting) or surgical intervention for non-significant stenosis. The rationale behind pre-emptive treatment is that the patency rates of autogenous fistulae is improved when compared to fistulas that are not treated (Work, 2011). Published literature such as Mccarley et al., (2001); Shahin et al., (2005); Tessitore et al., (2003, & 2004) provides conflicting evidence and there is no clear answer as to whether screening strategies followed by prophylactic treatment is beneficial. While several studies about pre-emptive treatment of graft fistulas by Dossabhoy et al., (2005) and Dember, Holmberg, & Kaufman, (2004) have been published, there are limited publications on autogenous fistulas. Four publications have tested the theory that screening monitoring with pre-emptive treatment is beneficial for autogenous arteriovenous fistulae (Mccarley et al., 2001; Shahin et al., 2005; Tessitore et al., 2003, 2004). Two studies (Mccarley et al., 2001; Shahin et al., 2005) were observational studies and the other two were prospective studies (Tessitore et al., 2003, 2004). Only one study Shahin et al., (2005) concluded that screening with pre-emptive treatments failed to reduce thrombosis rates and did not even increase the fistula access survival rates. Contrary to the study by Shahin et al., (2005) the other three studies demonstrated an overall decrease in thrombosis rates.
within the autogenous fistulas and these studies favoured screening and pre-emptive treatment. Still, the authors urge caution and suggest that a large scale multicentre study is needed to obtain stronger evidence. It should be noted that the above studies did not use duplex ultrasound for screening but used blood flow monitoring techniques. Although the instrument is different, the scope of the study was to collect the data in order to test if screening and monitoring strategies will increase the patency rate of autogenous fistulas and reduce thrombotic episodes. The National Kidney Foundation, (2006) deems duplex ultrasound as a reliable and accurate way of obtaining sequential flow rate measurements. Duplex ultrasound has not been used as much as flow monitoring techniques because it may not be readily available, is more expensive and requires trained professionals (Kumbar et al., 2012). This study used duplex ultrasound to assess the arteriovenous fistulae as ultrasound is capable of collecting far more data points than just blood flow measurements as in ultrasound dilution technique.

The main concern with pre-emptive treatment is that angioplasty tends to initiate an aggravated intimal hyperplasia response due to the mechanical stress and injury that the intima incurs during the angioplasty procedure (Allon & Robbin, 2009). Furthermore, re-stenosis is a common occurrence post angioplasty of fistulas with significant or non-significant stenosis (Allon & Robbin, 2009). A better understanding of the rate of progression of neointimal hyperplasia would assist better clinical decision making with regards to timing of treatments and the avoidance of unnecessary intervention (Kumbar et al., 2012).
4.8 Justification for the use of hospital resources

Possibly the biggest hurdle to set up a screening or monitoring programme is the justification of using hospital resources such as physician and nursing time and use of hospital equipment to carry out procedures (Tonelli, Klarenbach, Jindal, & Manns, 2006). Hospital resources are limited with significant demands on services and the additional burden of several screening programmes can have a detrimental effect on the hospital’s efficiency and performance (National Kidney Foundation, 2006). There must be clear evidence of the benefits of a screening programme in order to justify the extra expense and resources required (Tonelli et al., 2008). The rationale for screening and monitoring should be improving the patency of the fistula through a reduction in the thrombosis rates and a concomitant reduction in the use of temporary catheters and therefore the reduction in patient morbidity and mortality associated with such catheters (Kumbar et al., 2012).

A study by Tonelli et al., (2006) attempted to calculate the cost of a screening programme for autogenous arteriovenous fistula. Tonelli et al., (2006), deduced that a screening programme to detect a subclinical stenosis at the time of undertaking the study would cost the institution $9000 (Canadian dollars) per patient over a five year period. The data showed that the screening programme was effective in reducing fistula failure and estimated that the cost of the programme was justified. However, the authors explained that the screening programme does not reduce access related costs such as radiological examinations and hospitalisations. Still,
Tonelli et al., (2006) agree that although this additional economic burden might seem expensive, the aim is to prevent or prolong as much as possible terminal arteriovenous fistula loss as this is life threatening to the patient. The National Kidney Foundation, (2006) takes a broader stand on the cost implications of a screening programme. The National Kidney Foundation, (2006) is in favour of implementing a screening programme, however, it does not consider in detail the economic implications and only acknowledges that this will increase the demand for valuable hospital resources and costs related to the treatment. However, the National Kidney Foundation (2006) recommends that feasibility studies should be carried out with the intention of clarifying as much as possible the actual benefit of a screening programme that accompanies regular monitoring techniques. The authors also state that implementation of a screening programme would enable subclinical stenoses to be detected earlier and treated accordingly with the result of improved fistula patency. Furthermore, it is not clear which instrument (ultrasound dilution technique or duplex ultrasound) is best suited for the screening programme (Kumbar et al., 2012; National Kidney Foundation, 2006). Kumbar et al., (2012) explain that periodic evaluation through a screening programme is mandated and feasible as long as the tests are specifically designed and carried out by specific instrumentation. The most widely used tests are pressure monitoring, flow monitoring and duplex ultrasound.
4.9 Criteria for a screening programme

Wilson & Jungner, (1968) set up four basic criteria specifically for the world health organisation (WHO) that are needed to be satisfied in order for a screening programme to be set up and these criteria are still applicable today (Tidy, 2014).

These criteria are:

- **Knowledge of the disease**: The condition of the disease should be important to warrant the need of a screening programme. The disease aetiology must be understood and should be diagnosed early in the asymptomatic stage through screening and monitoring techniques.

- **Knowledge of the test**: An adequate test or examination needs to be set up in order to adequately identify the disease. This test must be easily repeatable and is relatively acceptable by the target population. For this study, duplex ultrasound was used and duplex ultrasound fulfils the criteria.

- **Treatment for the disease**: The disease must be treated by using an acceptable treatment that is readily available. The hospital where this study was conducted offers all the necessary treatments such as angioplasty and surgical interventions.

- **Cost considerations**: The screening costs and treatment are acceptable and economically balanced. This study did not take into consideration the screening costs as this was beyond the scope of the study.
4.10 Conclusions based on the findings

This study shows that the proportion of patients with undetected stenosis in an autogenous fistula in this cohort was 36%. Fourteen (14.6%) percent of the patients in this cohort had a significant stenosis which according to the present guidelines should undergo treatment.

The Maltese population has the highest rates of diabetes and hypertension when compared to the other EU-27 countries. The results of this study did not show any significant increased risk of stenosis in patients with diabetes or hypertension. Furthermore the higher proportion of hypertension and diabetes in this cohort did not result in a higher prevalence of stenosis.

It is still not clear as to how and when a stenosis will eventually lead to fistula dysfunction. Screening programmes with pre-emptive treatment strategies have been implemented in some centres that claim to be of considerable benefit for the patient. As seen in section 4.7.1, the literature is still not clear as to whether pre-emptive treatment is beneficial. Unless there is clear evidence of the benefits of screening it would be difficult to justify the cost implications for introducing a screening programme.

The results have shown that a third of the current population being dialysed through an autogenous arteriovenous fistula have an asymptomatic stenosis which may cause thrombosis and ultimately fistula failure. The fistula is the lifeline of the patient and preventing thrombosis should be enough to warrant a screening programme. This study did not analyse the
cost implications associated with the implementation of a screening programme but other factors such as the duplex ultrasound scan and the availability of recourses for interventional procedures such as angioplasty have shown that it is feasible. Since no screening programme is available for the Maltese population and more than a third of these patients are unaware of their undetected stenosis, implementation of a screening programme is suggested.

The use of duplex ultrasound is more expensive when directly compared to ultrasound dilution techniques. As seen in chapter two, studies have shown that the specificity and sensitivity of both modalities are highly comparable with the gold standard angiography. Duplex ultrasound has several advantages which include the potential to assess both anatomical and physiological aspects of the fistula through measurement of diameters, velocities and flow rates. As seen in this study, lumen diameter measurements detected a higher percentage of patients with stenosis (non-significant) when compared to the velocity measurements.

4.11 Limitations of this study

This study’s design was cross-sectional due to the time limitations in the data collection period. This meant that only a snapshot of the current state of the autogenous arteriovenous fistulas within the Maltese populations was obtained. The ideal study to accurately determine the incidence of stenosis and the natural history of such stenoses would be from a
longitudinal study whereby the primary endpoint would be fistula patency rates with or without intervention from screening detected stenoses.

This study only included autogenous arteriovenous fistula for the presence of asymptomatic stenosis. Graft fistulas were omitted from this study as the working dynamics are different since they are made of prosthetic material.

The monetary cost of implementing a screening programme for autogenous arteriovenous fistula in Malta was not evaluated as the cost of duplex scanning and other screening related costs were not available at the time of initiation of this study.

4.12 Conclusion

In this chapter the findings that have emerged from the analysis of the data have been presented and discussed.

Thirty six (36%) percent of the population with an autogenous fistula had an undetected stenosis. This compares favourably with the prevalence of stenosis in autogenous fistulae published in the literature. The mean follow up period was of twenty seven (27) months and the mean flow rate was 1586 ml/min. The flow rates are slightly higher than what is reported in the literature. The higher proportion of hypertension and diabetes in this cohort did not result in a higher prevalence of stenosis. These initial results indicate that a screening programme is likely to identify a significant proportion of autologous arteriovenous fistulae with stenosis.
Chapter 5
Conclusions and Recommendations
Chapter 5

5.1 Introduction

In this chapter conclusions drawn up from the data and recommendations made on the findings are presented.

5.2 Conclusions based on the results

The aim of this study was to assess the feasibility of implementing a screening programme for patients suffering from end stage renal failure being dialysed using an autogenous arteriovenous fistula. In this case a screening programme is intended to detect problems with the arteriovenous fistula that are not detected clinically so that treatment of such stenosis by angioplasty to prevent access thrombus and ultimately access failure may commence at an early stage prior to any complications. Currently there is no screening programme for dialysis access for patients undergoing haemodialysis for end stage kidney failure. Three objectives, as outlined in section 3.1, were drawn up so that the aim of this study could be achieved.

One objective was to create a data collection tool. The proforma was developed after studying the current literature and then tested accordingly. The objective was completed successfully and all the data that was collected was subsequently analysed in order to obtain the required results.
Another objective was to assess the target population for asymptomatic stenosis. Patients undergoing dialysis were scanned by a duplex ultrasound examination. The results showed that 36% of the target population had an asymptomatic stenosis. Twenty one (21.4%) percent of these asymptomatic stenoses were non-significant and 14.6% were significant in nature. Significant stenoses are of great concern due to their increased risk of compromising the fistula's function. Non-significant stenoses do not pose an immediate threat to the fistula's function but these types of stenosis may progress into a significant stenosis.

The fistula functions as a vessel which is capable of sustaining blood flows that are higher than 400ml/min. The results for this study showed that even though there is a large range of blood flow velocities, the mean blood flow rate is approximately 1500ml/min. This is moderately higher than the ranges found by Alamdaran, (2008) and San Miguel & Chow, (2009). There is no specific reason as to why the blood flow rate is higher than the ranges found in the literature since the blood flow rate depends on a variety of factors such as, the type of fistula present and the fistula diameter. These factors were found to be statistically significant in determining blood flow rate and data gathered also showed that radiocephalic fistulas have smaller lumen diameters and lower blood flow volume when compared to brachiocephalic fistulae.

The mean follow up period of the fistulas examined was 27 months with nearly twenty five (24.7%) percent of these patients having had some form of treatment for stenosis and/or thrombosis prior to the scan.
An objective of this study was to identify any co-morbidity that may increase the risk of stenosis. In the study all co-morbidities that were likely to be responsible for the end stage renal disease cases were documented. The two main co-morbidities in the target population were diabetes (41.6%) and hypertension (34.8%). The results of this study did not show any statistically significant increased risk of stenosis for the patient undergoing dialysis.

The results have shown that a third of the target population undergoing dialysis through an autogenous arteriovenous fistula have an undetected, asymptomatic stenosis and these patients are at an increased risk for thrombosis and access failure. The fistula is the lifeline of the patient and since no screening programme is available for these patients, these stenoses would have remained undetected until problems are encountered during dialysis sessions. Therefore, the implementation of a screening programme is suggested.

5.3 Recommendations

One of the limitations of this study is the relatively small size which may be responsible for a failure to identify any significant differences in the prevalence of stenosis amongst patients with diabetes and hypertension. Therefore, it is being recommended that a larger scale study would be better powered to identify difference between groups of patients with different co-morbidities amongst those behind dialysed using an arteriovenous fistula within the Maltese population.
This study only assessed patients with autogenous arteriovenous fistula and did not assess arteriovenous grafts. Arteriovenous graft fistulas are physically different from autogenous arteriovenous fistulas as prosthetic graft is used to create the fistula instead of a native vessel. These prosthetic grafts do not usually develop intimal hyperplasia but studies have shown that intimal hyperplasia develops at around the anastamosis with native vessels. Currently, there is no published data on the state of arteriovenous grafts fistulas for the Maltese population and it is suggested that a future study would include both types of arteriovenous fistulas.

This study did not take into consideration the cost implications required for a screening programme. It is recommended that a costing exercise is undertaken in order to assess that screening costs, treatments costs and the additional burden of hospital recourses are justifiable.

A large longitudinal study with long follow up periods would provide important information as to the natural history of asymptomatic stenoses in autogenous arteriovenous fistulae. Such a study would provide useful information as to whether and which asymptomatic stenoses are likely to lead to thrombosis or compromise of dialysis access. This type of study is recommended because if such a study did show that particular asymptomatic stenoses frequently lead to dialysis problems then it would be justified to recommend a randomised controlled trial.

A randomised control trial is suggested as it would be the best way to assess whether a screening programme would be of any clinical benefit for a patient undergoing haemodialysis. A randomised control trial would
determine whether the study group would have better patency rates when compared to a control group. The study group would also undergo preemptive treatment of any stenoses that are detected by the duplex scans. The results could also accurately determine the feasibility of a screening programme of all or a section of the patients suffering from end stage renal disease.

5.4 Final Comments

This study has shown that the incidence of stenosis in autogenous arteriovenous fistula in the Maltese population is 36% and that the implementation of a screening programme for patients suffering from end stage renal failure being dialysed using an autogenous arteriovenous fistula is feasible.

Total word count approximately 22,550 words without tables and figures


References


Appendix A

Permissions
Dear Eng Caruana,

I am presently reading for a Masters in Radiography, Vascular Ultrasound and as part of my studies I am required to undertake a research project. My study is entitled: "Screening for non-significant stenosis in native arteriovenous fistulae within the Maltese population".

The research proposal will be submitted to the Research Ethics Committee for consideration and approval. The aim of the study is to screen all the non-symptomatic patients undergoing haemodialysis through the use of a native arteriovenous fistula and assess if these patients have a non-significant stenosis. I am being supervised by Dr. Paul Bezzina.

I would be grateful if you would give me permission to scan these patients after having obtained their signed consent. Your support for this project is greatly appreciated.

Should you require further information, I can be contacted on or else at the Accident and Emergency department on .

I look forward for a favourable reply.

Thanking you in advance

Yours sincerely,

Christopher Gauci
B.Sc (Hons) Diagnostic Radiography
Data protection officer Mr M. Gonzi

Study: Screening for non-significant stenosis in native arteriovenous fistula within the Maltese population

From: Data Protection at MDH
Subject: Study Screening for non-significant stenosis in native arteriovenous fistula within the Maltese population
Date: 13 May 2013 at 22:09
To: Chris Gauci

13th May 2013
Dear Mr. Gauci,

With reference to the above-named study, this is to confirm that, on the basis of the documentation you submitted, from the data protection point of view you have been cleared to proceed with your study.

You are requested to submit a copy of your findings to this office at the end of your study. You are also kindly requested to call Ms. Nadine Buhagiar to fill in the appropriate Data Protection Form prior to your commencement of the study.

Please remember that in no way should you retain any personal details you obtain from your research and this should be destroyed at the end of your study and you should abide to the provisions of the Data Protection Act at all times.

Good luck with your study.

Kind regards,

Michael Gonzi
Data Protection Officer,
Consultant Nephrologist Dr. E. Farrugia

Dear Dr Farrugia,

I am presently reading for a Masters in Radiography, Vascular Ultrasound and as part of my studies I am required to undertake a research project. My study is entitled: "Screening for non-significant stenosis in native arteriovenous fistulae within the Maltese population".

The research proposal will be submitted to the Research Ethics Committee for consideration and approval. The aim of the study is to screen all the non-symptomatic patients undergoing haemodialysis through the use of a native arteriovenous fistula and assess if these patients have a non-significant stenosis. I am being supervised by Dr. Paul Bezzina.

I would be grateful if you would give me permission to contact you should any issues arise with the patients found under your care. Your help and support for this project is greatly appreciated. Should you require further information, I can be contacted on or else at the Accident and Emergency department on

I look forward for a favourable reply.
Thanking you in advance

Yours sincerely,

Christopher Gauci
B.Sc (Hons) Diagnostic Radiography

Dr Emanuel Farrugia
MD, MRCP, Dip Neph, FACP,
FRCP (Lond), FRCP (Edin), FEFIM
Consultant Physician and Nephrologist
Dear Dr Farrugia Agius,

I am presently reading for a Masters in Radiography, Vascular Ultrasound and as part of my studies I am required to undertake a research project. My study is entitled: "Screening for non-significant stenosis in native arteriovenous fistulae within the Maltese population".

The research proposal will be submitted to the Faculty of Health Sciences Research Ethics Committee for consideration and approval. The aim of the study is to screen all the non-symptomatic patients undergoing haemodialysis through the use of a native arteriovenous fistula and assess if these patients have a non-significant stenosis. I am being supervised by Dr. Paul Bezzina.

I would be grateful if you would give me permission to contact you should any issues arise with the patients found under your care. Your help and support for this project is greatly appreciated. Should you require further information, I can be contacted on [contact details], or else at the Accident and Emergency department on [contact details].

I look forward for a favourable reply.

Thanking you in advance

Yours sincerely,

Christopher Gauci
B.Sc (Hons) Diagnostic Radiography

[Signature]

Dr. Joseph Farrugia Agius
MD, MRCP, FRCP (Edin)
Consultant Physician and Nephrologist
Dear Dr Buhagiar,

I am presently reading for a Masters in Radiography, Vascular Ultrasound and as part of my studies I am required to undertake a research project. My study is entitled: “Screening for non-significant stenosis in native arteriovenous fistulae within the Maltese population”.

The research proposal will be submitted to the Faculty of Health Sciences Research Ethics Committee for consideration and approval. The aim of the study is to screen all the non-symptomatic patients undergoing haemodialysis through the use of a native arteriovenous fistula and assess if these patients have a non-significant stenosis.

I am being supervised by Dr. Paul Bezzina.

I would be grateful if you would give me permission to contact you should any issues arise with the patients found under your care. Your help and support for this project is greatly appreciated. Should you require further information, I can be contacted on or else at the Accident and Emergency department on .

I look forward for a favourable reply.
Thanking you in advance

Yours sincerely,

Christopher Gauci
B.Sc (Hons) Diagnostic Radiography
Dear Dr Vella,

I am presently reading for a Masters in Radiography, Vascular Ultrasound and as part of my studies I am required to undertake a research project. My study is entitled: “Screening for non-significant stenosis in native arteriovenous fistulae within the Maltese population”.

The research proposal will be submitted to the Faculty of Health Sciences Research Ethics Committee for consideration and approval. The aim of the study is to screen all the non-symptomatic patients undergoing haemodialysis through the use of a native arteriovenous fistula and assess if these patients have a non-significant stenosis. I am being supervised by Dr. Paul Bezzina.

I would be grateful if you would give me permission to contact you should any issues arise with the patients found under your care. Your help and support for this project is greatly appreciated. Should you require further information, I can be contacted on or else at the Accident and Emergency department on

I look forward for a favourable reply.
Thanking you in advance

Yours sincerely,

Christopher Gauci
B.Sc (Hons) Diagnostic Radiography

Dr. M.P. Vella
Consultant Physician & Nephrologist
Dear Professor Cassar,

Presently, I am reading for my Masters in Vascular Ultrasound and as part of my Final Comprehensive Examination I have to undertake a research project. My study is entitled: “Screening for non-significant stenosis in native arteriovenous fistulae within the Maltese population”.

The research proposal has been approved by the Faculty of Health Sciences and I am currently seeking ethical approval. I am aware that I have to strictly adhere to ethical issues especially those involving informed consent and confidentiality. The main aim of the study is to screen using ultrasound all the non-symptomatic patients undergoing haemodialysis through the use of a native arteriovenous fistula and assess if these patients have a non-significant stenosis. I am being supervised by Dr Paul Bezzina.

I would be grateful if you would give me permission to contact you should any issues arise with the patients found under your care. Your help and support for this project is greatly appreciated. Should you require further information, I can be contacted on [insert contact details] or else at the Accident and Emergency department on [insert contact details].

I look forward for a favourable reply.

Thanking you in advance

Yours sincerely,

Christopher Gauci
B.Sc (Hons) Diagnostic Radiography

[Signature]

Prof. Kevin Cassar
Consultant Vascular Surgeon
Dear Dr. Zrinzo,

Presently, I am reading for my Masters in Vascular Ultrasound and as part of my Final Comprehensive Examination I have to undertake a research project. My study is entitled: “Screening for non-significant stenosis in native arteriovenous fistulae within the Maltese population”.

The research proposal has been approved by the Faculty of Health Sciences and I am currently seeking ethical approval. I am aware that I have to strictly adhere to ethical issues especially those involving informed consent and confidentiality. The main aim of the study is to screen using ultrasound all the non-symptomatic patients undergoing haemodialysis through the use of a native arteriovenous fistula and assess if these patients have a non-significant stenosis. I am being supervised by Dr. Paul Bezzina.

I would be grateful if you would give me permission to scan these patients after having obtained their signed consent. I shall be using a checklist to document all the required data. Your support for this project is greatly appreciated.

Should you require further information, I can be contacted on or else at the Accident and Emergency department on

I look forward for a favourable reply.
Thanking you in advance

Yours sincerely,

Christopher Gauci
B.Sc (Hons) Diagnostic Radiography

Dr. Salvina Zrinzo
Consultant Radiologist
Dear Mr Castillo,

I am presently reading for a Masters in Radiography, Vascular Ultrasound and as part of my studies I am required to undertake a research project. My study is entitled: “Screening for non-significant stenosis in native arteriovenous fistulae within the Maltese population”.

The research proposal will be submitted to the Faculty of Health Sciences Research Ethics Committee for consideration and approval. The aim of the study is to screen all the non-symptomatic patients undergoing haemodialysis through the use of a native arteriovenous fistula and assess if these patients have a non-significant stenosis. I am being supervised by Dr. Paul Bezzina.

I would be grateful if you would give me permission to scan these patients after having obtained their signed consent. I shall be using a checklist to document all the required data. Your support for this project is greatly appreciated.

Should you require further information, I can be contacted on or else at the Accident and Emergency department on

I look forward for a favourable reply.
Thanking you in advance

Yours sincerely,

Christopher Gauci
B.Sc (Hons) Diagnostic Radiography
Dear Dr Bezzina,

I am presently reading for a Masters in Radiography, Vascular Ultrasound and as part of my studies I am required to undertake a research project. My study is entitled: “Screening for non-significant stenosis in native arteriovenous fistulae within the Maltese population”.

The research proposal will be submitted to the Faculty of Health Sciences Research Ethics Committee for consideration and approval. The aim of the study is to screen all the non-symptomatic patients undergoing haemodialysis through the use of a native arteriovenous fistula and assess if these patients have a non-significant stenosis.

I would be grateful if you would give me permission to use the ultrasound machine to scan these patients. Your support for this project is greatly appreciated. Should you require further information, I can be contacted on or e/s at the Accident and Emergency department on

I look forward for a favourable reply.
Thanking you in advance

Yours sincerely,

Christopher Gauci
B.Sc (Hons) Diagnostic Radiography
Head of department of Renal Unit Mr P Calleja

Dear Mr Calleja,

Presently, I am reading for my Masters in Vascular Ultrasound and as part of my Final Comprehensive Examination I have to undertake a research project. My study is entitled: “Screening for non-significant stenosis in native arteriovenous fistulae within the Maltese population”.

The research proposal has been approved by the Faculty of Health Sciences and I am currently seeking ethical approval. I am aware that I have to strictly adhere to ethical issues especially those involving informed consent and confidentiality. The main aim of the study is to screen using ultrasound all the non-symptomatic patients undergoing haemodialysis through the use of a native arteriovenous fistula and assess if these patients have a non-significant stenosis. I am being supervised by Dr. Paul Bezzina.

I would be grateful if you would give me permission to use a room within the Renal unit in order to be able to scan these patients. Your support for this project is greatly appreciated.

Should you require further information, I can be contacted on or else at the Accident and Emergency department on

I look forward for a favourable reply.
Thanking you in advance

Yours sincerely,

Christopher Gauci
B.Sc (Hons) Diagnostic Radiography
**UNIVERSITY OF MALTA**

**UNIVERSITY RESEARCH ETHICS COMMITTEE**

*Check list to be included with UREC proposal form*

Please make sure to tick ALL the items. Incomplete forms will not be accepted.

<table>
<thead>
<tr>
<th></th>
<th>YES</th>
<th>NOT APP.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Recruitment letter / Information sheet for subjects, in English</td>
<td>✓</td>
</tr>
<tr>
<td>1b</td>
<td>Recruitment letter / Information sheet for subjects, in Maltese</td>
<td>✓</td>
</tr>
<tr>
<td>2a</td>
<td>Consent form, in English, signed by supervisor, and including your contact details</td>
<td>✓</td>
</tr>
<tr>
<td>2b</td>
<td>Consent form, in Maltese, signed by supervisor, and including your contact details</td>
<td>✓</td>
</tr>
<tr>
<td>3a</td>
<td>In the case of children or other vulnerable groups, consent forms for parents/guardians, in English</td>
<td>✓</td>
</tr>
<tr>
<td>3b</td>
<td>In the case of children or other vulnerable groups, consent forms for parents/guardians, in Maltese</td>
<td>✓</td>
</tr>
<tr>
<td>4a</td>
<td>Tests, questionnaires, interview or focus group questions, etc, in English</td>
<td>✓</td>
</tr>
<tr>
<td>4b</td>
<td>Tests, questionnaires, interview or focus group questions, etc, in Maltese</td>
<td>✓</td>
</tr>
<tr>
<td>5a</td>
<td>Other institutional approval for access to subjects: Health Division, Directorate for Quality and Standards in Education, Department of Public Health, Curia...</td>
<td>✓</td>
</tr>
<tr>
<td>5b</td>
<td>Other institutional approval for access to data: Registrar, Data Protection Officer Health Division/Hospital, Directorate for Quality and Standards in Education, Department of Public Health...</td>
<td>✓</td>
</tr>
<tr>
<td>6a</td>
<td>Approval from person directly responsible for subjects: Medical Consultants, Nursing Officers, Head of School...</td>
<td>✓</td>
</tr>
</tbody>
</table>

**Received by Faculty office on**  
01.07.13

**Discussed by Faculty Research Ethics Committee on**  
23.07.13

**Discussed by university Research Ethics Committee on**  

UNIVERSITY OF MALTA

Request for Approval of Human Subjects Research

PROJECT TITLE:
Screening for non-significant stenosis in native arteriovenous fistulae within the Maltese population

TELEPHONE:

F-MAIL:

DURATION OF ENTIRE PROJECT:
from 01/02/2012 to 31/01/2015

FACULTY SUPERVISOR'S NAME:
Dr Paul Bezzina

ANTICIPATED FUNDING SOURCE: N/A
(include grant or contract number if known)

1. Please give a brief summary of the purpose of the research, in non-technical language.
The purpose of the research is to screen by using ultrasound the arteriovenous fistula of Maltese patients attending a renal unit for dialysis in a local hospital. This fistula is used approximately once every three days for dialysis. Like with any treatment, the fistula suffers from certain complications. The main complications is narrowing (stenosis) of the fistula. At present there is no screening/monitoring program of the fistula for these patients and only once a problem is encountered during dialysis are they then referred for the necessary investigations. During this time the patient will not be able to undergo dialysis from the fistula. The aim of the study is to assess the feasibility of introducing such a screening program in Malta where by the stenosis can be detected early on in its progression. This means that the patient can be offered planned less invasive treatment whilst preventing any other complications through missed dialysis.

2. Give details of procedures that relate to subjects' participation
(a) How are subjects recruited? What inducement is offered? (Append copy of letter or advertisement or poster, if any.)
For recruitment of patients: The first approach is by a dialysis nurse who works in the renal unit. The patient is then handed an information sheet which explains the purpose of the study. If the patient agrees to take part in the study, then the nurse would eventually inform the researcher. The researcher will then approach the patient and also answer any questions that the patient might have. It will be made clear to the patient that the ultrasound scan is short, safe, painless and not harmful to the patient. If the patient is happy to proceed, then the patient would be handed the consent letter and sign it if he/she agrees to the terms. Scanning would take place after the signing of the consent.

For what inducement is offered: it will be explained that if eventually a screening programme is introduced, the participant would directly benefit from this and also any future individuals that would require dialysis.
(b) Salient characteristics of subjects—number who will participate, age range, sex, institutional affiliation, other special criteria:
All patients who have a native arteriovenous fistula = approximately 100 people.
Both men and female.
Have to be of legal age and Maltese
No symptoms or recent interventions.

(c) Describe how permission has been obtained from cooperating institution(s)—school, hospital, organization, prison, or other relevant organization. (Append letters.) Is the approval of another Research Ethics Committee required?
Approval was sought from:
CEO of a general hospital in Malta
Four (4) consultant nephrologists
Vascular surgeon
Data protection officer

(d) What do subjects do, or what is done to them, or what information is gathered? (Append copies of instructions or tests or questionnaires.) How many times will observations, tests, etc., be conducted? How long will their participation take?

The patient would undergo a one time ultrasound scan of not more than ten (10) minutes. The scan would take place before the dialysis session. The data gathered would be demographic (sex and age) as well as numerical. The numerical data will be documented on a check list. All the data will be password protected and kept in a secure location. Confidentiality will always be adhered to.
(e) Which of the following data categories are collected? Please indicate 'Yes' or 'No'.

Data that reveals – race or ethnic origin  No  
  political opinions  No  
  religious or philosophical beliefs  No  
  trade union memberships  No  
  health  Yes  
  sex life  No  
  genetic information  Yes  

3. How do you explain the research to subjects and obtain their informed consent to participate? (If in writing, append a copy of consent form.) If subjects are minors, mentally infirm, or otherwise not legally competent to consent to participation, how is their assent obtained and from whom is proxy consent obtained? How is it made clear to subjects that they can quit the study at any time?

The research will be explained through the use of an information sheet. If the patient accepts, then a consent letter would be presented. The patient is able to ask any questions before signing the consent. It is made clear on the consent letter that the patient can quit from the study at any time.

4. Do subjects risk any harm—physical, psychological, legal, social—by participating in the research? Are the risks necessary? What safeguards do you take to minimize the risks?

The patient will suffer no harm. Ultrasound is safe and painless.
5. Are subjects deliberately deceived in any way? If so, what is the nature of the deception? Is it likely to be significant to subjects? Is there any other way to conduct the research that would not involve deception, and, if so, why have you not chosen that alternative? What explanation for the deception do you give to subjects following their participation?

No the patients are not deceived in any way.

6. How will participation in this research benefit subjects? If subjects will be “debriefed” or receive information about the research project following its conclusion, how do you ensure the educational value of the process? (Include copies of any debriefing or educational materials)

If the research suggests that a screening program is feasible and eventually introduced into the hospital system, then the patient would directly benefit from the screening program.
TERMS AND CONDITIONS FOR APPROVAL IN TERMS OF THE DATA PROTECTION ACT

- Personal data shall only be collected and processed for the specific research purpose.
- The data shall be adequate, relevant and not excessive in relation to the processing purpose.
- All reasonable measures shall be taken to ensure the correctness of personal data.
- Personal data shall not be disclosed to third parties and may only be required by the University or the supervisor for verification purposes. All necessary measures shall be implemented to ensure confidentiality and, where possible, data shall be anonymized.
- Unless otherwise authorised by the University Research Ethics Committee, the researcher shall obtain the consent from the data subject (respondent) and provide him with the following information: The researcher’s identity and habitual residence, the purpose of processing and the recipients to whom personal data may be disclosed. The data subject shall also be informed about his rights to access, rectify, and where applicable erase the data concerning him.

I, the undersigned hereby undertake to abide by the terms and conditions for approval as attached to this application.

I, the undersigned, also give my consent to the University of Malta’s Research Ethics Committee to process my personal data for the purpose of evaluating my request and other matters related to this application. I also understand that, I can request in writing a copy of my personal information. I shall also request rectification, blocking or erasure of such personal data that has not been processed in accordance with the Act.

Signature:

APPLICANT’S SIGNATURE:
I hereby declare that I will not start my research on human subjects before UREC approval

DATE 28/6/13

FACULTY SUPERVISOR’S SIGNATURE
I have reviewed this completed application and I am satisfied with the adequacy of the proposed research design and the measures proposed for the protection of human subjects.

DATE 28/6/2013

Return the completed application to your faculty Research Ethics Committee
To be completed by Faculty Research Ethics Committee

We have examined the above proposal and advise

 acceptance  refusal  conditional acceptance

For the following reason/s:

Signature

Date 6/8/2013

To be completed by University Research Ethics Committee

We have examined the above proposal and grant

 acceptance  refusal  conditional acceptance

For the following reason/s:

Signature

Date 14/9/2013
Appendix B

Information Sheets and Consent form
Consent Form: English

Consent for participation:

Study Title: Screening for non-significant stenosis in native arteriovenous fistula within the Maltese population.

The purpose and details of this study have been explained to me by Mr Christopher Gauci and any difficulties which I raised have been adequately clarified.

I hereby, give my consent to participate in the study which is being carried out by Mr Christopher Gauci.

I am aware that:

- It is my right to refuse participation at any time without the need for an explanation.
- I am under no obligation to participate in this study and I am doing this so voluntary.
- I can stop the scan at any time I want.
- I am aware that my hospital file can be reviewed for information only relevant to the study and that all the data collected will be kept confidential.
- I understand that the results of this study may be used for medical or scientific purposes and that the results achieved from this study may be reported or published.
- My name and identity will remain safe, strictly confidential and will never appear in any report or publication.
- I will not receive any remuneration.

In case of any queries I may contact Mr Christopher Gauci on or else call Dr Paul Bezzina who is supervising my study on

____________________  __________________  __________________  
Signature of participant  Name

____________________  __________________  __________________  
Signature of researcher  Name

____________________  __________________  __________________  
Signature of supervisor  Name
Consent Form: Maltese

**Formula tal-Kunsens**

It-titlu tal-istudju: “Screening for non-significant stenosis in native arteriovenous fistula within the Maltese population.”

L-ġkan u d-det tal-istudju ġew spjegati lili mis-Sur Christopher Gauci li wkoll ġi ġarali xi mistoqsijiet li ġkamilt.

Jiena nagkti l-kunsens tiegki biex nipparte ŵapa fl-istudju msemmi u li qiegked isir mis- Sur Christopher Gauci.

Ħbe spjegat lili li:

- Huwa dritt tiegki li nirrifjuta li nipparte ŵapa meta rrid mingkajr ma nagkti raâni.
- Jiena mġkandi l-ebda obbligu nieku sehem f'dan l-istudju u dan qed nagkmlu minn rajja.
- Nistaônwaqqaf l-ultrasound meta rrid.
- Jiena naf li xi informzzjoni relevanti mal-istudju se tiâ miaâbura mill-fajl tal-isptar, però kull informazzjoni se tibqaĊ bunktunfienzjalità.
- Jiena nifhem li r-riûtati ta'dan l-istudju jistgku jintu ŵaw gkal skopijiet xjentifiâ u jistaĊ jiâ ppublikat rapport bil-miktub.
- Ismi u l-identità tiegki se jinûammu f'ost sikur, bunktunfienzjalità stretta u qatt mhuma se jidhru fl-ebda rapport jew pubblikazzjoni.
- Mâniex se nirûevi xi klas gkall-partuǷazzjoni tiegki.

FâaUtâdiffiktà nistaônikkuntattja lis-Sur Christopher Gauci fuq , inkella tistaôtellem lil Dr Paul Bezzina, li huwa t-tutur tal-istudju tiegki, fuq

_______________________
Firma tal-partiǭpant                                Isem

_______________________
Firma ta'nin qed jagkmel ir-riûrka                                 Isem

_______________________
Firma tat-tutur                                                        Isem
Information Sheet: English

Note for Patients undergoing haemodialysis

Dear Sir or Madam,

My name is Christopher Gauci and I am currently reading for a Masters in Vascular Ultrasound and as part of my degree, I am conducting a research study entitled: "Screening for non-significant stenosis in native arteriovenous fistula within the Maltese population."

The study aims are to assess the feasibility of introducing a screening programme for the Maltese patient with native arteriovenous fistula. You are invited to take part in this study which will involve a painless, harmless, ten minute ultrasound scan performed by myself. All the information will be kept safe, in strict confidentiality and your name and identity will not be published anywhere, nor will it be disclosed to any other person.

Participation in this study is totally voluntary and therefore you are free to choose whether to take part in the study. I would really be grateful if you do accept to take part as your collaboration will be very much appreciated and will serve a very important function because apart from helping me complete my studies, the data collected during the ultrasound scan will aid in the assessment for introducing a screening programme for patients with arteriovenous fistulae.

Should you require any additional information or would like to ask me something about this study, please do not hesitate to contact me on 21499524 or 99288222 or email to cgau0006@um.edu.mt, or else call Dr Paul Bezzina, who is supervising my study.

Whilst wishing you the best, I thank you in anticipation for your time and cooperation.

Yours faithfully,

_____________________

Christopher Gauci
Information Sheet: Maltese

Nota ġkall-pazjenti li qegḵdin jagkmlu l-haemodialysis

GkaŪūa Sinjur/a,

Jiena Christopher Gauci u bkalissa qiegked nagkmel Masters fl-Ultrasound Vaskulari. Bkala parti mill-kors tieği, qiegked nagkmel studju fuq il-vini li jkunu mqabbddin direttament mal-arterja. Dawn insejkulhom fistulae. It-titlu tal-istudju tieği jismu, ġ SCREENING for non-significant stenosis in native arteriovenous fistula within the Maltese population ġ

L-ġkan taĊ dan l-istudju huwa biex tieġ ġekkjata l-vijabbilità li jja ġ introdott programm taċsorveljanza ġkall-pazjent Malti bdin it-tip taĊvinas. Jiena nistiednek biex tkun parti minn dan l-istudju li kulma ġnvolvi huwa ultrasound li ma jikkawūa ġebda waġk jew ġsara liliek u ma jдумx iktar minn ġkaxar minuti. Dan l-ultrasound se nkun qiegked nagkmlu jiena stess u niξtieq na createTime ġ kull informazzjoni li tinĊabbar se tinĊamm sikura u kunfidenzjali, jiĊieri ismek u l-indentità tieġkek mhu se jiĊ ppublikati mkien u lanqas mhuma se jiĊ mgkoddija lil ġkaddiekor.

Il-parteĊpazzjoni ġĊadan l-istudju hija ġkalkollox voluntarja, u ġkalhekk tistaĊ tagĊĊel jekk tridx tieku sehem jew le. Jiena nkun ġrat lej jekk inti taĊetta li tieku sehem ġĊadan l-istudju u ġgkajnuna tieġkek tkun apprezzata ġafna u importanti ġkaliex minbarra li tkkinni ntemm l-istudji tieği, l-informazzjoni li tinĊabbar waqt l-ultrasound se tkkin fir-rìurka dwar il-vijabbilità li jja ġ introdott dan il-programm taċsorveljanza ġkall-pazjenti kollha bdin it-tip taĊvina.

Jekk ġkandek xi miΣtqissijew jeb ġbnn taĊ aktar informazzjoni dwar dan l-istudju, nitolbok tikkuntattjani fuq in-numru jew fuq l-indirizz elettroniku , inkella tistaĊtkellem lil Dr Paul Bezzina, li huwa t-tutur tal-istudju tieġk, fuq

Filwaqt li nixtieqlek l-akjar ġkal sakktkek, nirringrazzjak tal-kin u l-koperazzjoni tieġkek.

Dejjem tieġkek,

__________________________
Christopher Gauci
Appendix C

Proforma
Proforma

Patient Age: ____________ years

Gender: 

- Male
- Female

What is the type of fistula:

- Radiocephalic
- Brachiocephalic
- Transposed brachiobasilic
- Other ______________

When was the Fistula created: ________________

How long has the fistula been used:

- Month/s
- Year/s

Any previous problems with the fistula such as previous treated stenosis or thrombosis

- Yes
- No

If yes, what treatment?

- Angioplasty
- Thrombectomy
- On table Angioplasty
- On table Thrombectomy
- Other ______________

What was the predominant illness that led to the end stage kidney disease?

- Diabetes
- Hypertension
- Glomerulonephritis
- Polysystic kidney disease
- Genetic disorder
- Other ______________

B-mode measurements

- Axilla
- 1cm proximal
- Mid fistula

- mm

Colour flow disturbance

- Yes
- No
<table>
<thead>
<tr>
<th>Doppler measurement</th>
<th>Axilla</th>
<th>2cm proximal</th>
<th>Mid fistula</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>cm/s</td>
<td>cm/s</td>
<td>cm/s</td>
</tr>
</tbody>
</table>

| Stenosis present?         | Yes    | No           |

<table>
<thead>
<tr>
<th>Stenosis measurements B-mode</th>
<th>1cm proximal to stenosis</th>
<th>mm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At stenosis</td>
<td>mm</td>
</tr>
<tr>
<td></td>
<td>1cm distal to stenosis</td>
<td>mm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stenosis measurements Doppler</th>
<th>1cm proximal to stenosis</th>
<th>cm/s</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>At stenosis</td>
<td>cm/s</td>
</tr>
<tr>
<td></td>
<td>1cm distal to stenosis</td>
<td>cm/s</td>
</tr>
</tbody>
</table>
**Proforma**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient Age:</strong></td>
<td>__________</td>
<td>years</td>
</tr>
<tr>
<td><strong>Gender:</strong></td>
<td>□ Male</td>
<td>□ Female</td>
</tr>
<tr>
<td><strong>What is the type of fistula:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Radiocephalic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Brachiocephalic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Transposed brachiobasilic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Other</td>
<td>__________</td>
</tr>
<tr>
<td><strong>When was the Fistula created:</strong></td>
<td>__________</td>
<td></td>
</tr>
<tr>
<td><strong>How long has the fistula been used:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Month/s</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Year/s</td>
<td></td>
</tr>
<tr>
<td><strong>Any previous problems with the fistula such as previous treated stenosis or thrombosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ No</td>
<td></td>
</tr>
<tr>
<td><strong>If yes, what treatment?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Angioplasty</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Thrombectomy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ On table Angioplasty</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ On table Thrombectomy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Other</td>
<td>__________</td>
</tr>
<tr>
<td><strong>What was the predominant illness that led to the end stage kidney disease?</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Diabetes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Hypertension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Glomerulonephritis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Polysystic kidney disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Genetic disorder</td>
<td></td>
</tr>
<tr>
<td></td>
<td>□ Other</td>
<td>__________</td>
</tr>
<tr>
<td><strong>B-mode measurements</strong></td>
<td>Axilla</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1cm proximal</td>
<td>mm</td>
</tr>
<tr>
<td></td>
<td>Mid fistula</td>
<td>mm</td>
</tr>
<tr>
<td><strong>Colour flow disturbance</strong></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>
Proforma Version 2

Doppler measurement

Axilla
2cm proximal
Mid fistula

 cm/s
 cm/s
 cm/s

Stenosis present?
Yes
No

How many

Stenosis measurements B-mode
1cm proximal to stenosis
At stenosis
1cm distal to stenosis

 mm
 mm
 mm

Stenosis measurements Doppler
1cm proximal to stenosis
At stenosis
1cm distal to stenosis

 cm/s
 cm/s
 cm/s

Stenosis measurements B-mode
1cm proximal to stenosis
At stenosis
1cm distal to stenosis

 mm
 mm
 mm

Stenosis measurements Doppler
1cm proximal to stenosis
At stenosis
1cm distal to stenosis

 cm/s
 cm/s
 cm/s

Any vascular anomalies detected:

______________________________________
______________________________________