Improving outcomes for patients undergoing major lower limb amputation for complications of peripheral vascular disease

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Abstract

Background: Around 5000 patients undergo major lower limb amputation in the UK each year, commonly as a result of peripheral vascular disease. Around 10% of these patients die before hospital discharge, and 30% die within a year of surgery. Despite this, evidence for optimal management of these patients is weak. The aim of this thesis is to develop tools which will direct future research and quality-improvement towards key interventions and outcomes for these patients.

Methods: I used data from the UK National Registry to identify risk-factors for poor mortality and morbidity outcomes using rigorous statistical tools and developed a prognostic model for in-hospital mortality.
I identified important outcomes for patients undergoing major lower limb amputation through systematic review of the literature and focus groups. I then established consensus on core outcome sets for short- and medium-term studies recruiting these patients using a multi-round consensus survey followed by a face-to-face consensus meeting.

Results: Independent risk-factors for in-hospital mortality were identified as emergency admission, bilateral operation, trans-femoral operation, age, American Society of Anesthesiologists grade, abnormal electrocardiogram and increased white cell count or creatinine, decreased albumin or patient weight. Previous revascularisation procedures were protective.
I established consensus on 11 core outcomes for short-term studies and 11 core outcomes for medium-term studies. Stump wound infection or healing, problems with the other leg and psychological morbidity were present in both sets. Outcomes related to death, additional healthcare, communication and pain relief were core for short-term studies. Outcomes related to mobility, social re-integration, independence and quality of life were core for medium-term studies.

Conclusions: I have identified contemporary risk-factors for peri-operative outcomes and defined core outcome sets for patients undergoing major lower limb amputation. Future work should adopt these in order to design interventions which modify key risk-factors and use core outcomes as their key endpoints.

Author’s declarations

This thesis is being submitted in partial fulfilment of the requirements for the degree of Doctor of Medicine.

This work has not been submitted in substance for any other degree or award at this or any other university or place of learning, nor is it being submitted concurrently for any other degree or award (outside of any formal collaboration agreement between the University and a partner organisation).

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I declare that this thesis is the result of my own independent work, except where otherwise stated, and the views expressed are my own. Other sources are acknowledged by explicit references. The thesis has not been edited by a third party beyond what is permitted by Cardiff University's Use of Third Party Editors by Research Degree Students Procedure.

Signed . . . . .  . . . . . Date . . 18/05/2020 . . . . . .

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1 Introduction

1.1 Background

The prevalence of lower extremity peripheral arterial disease (PAD) is rising globally, with rates exceeding 10% of the population in people aged 65-69 years.[1] The most significant risk factors for PAD are smoking and diabetes (of any type), so although rates of smoking are now gradually falling in many countries, high historical rates of smoking together with the rising prevalence of diabetes mellitus mean that this trend is likely to continue for the foreseeable future.[2] The global increasing prevalence of diabetes, which has almost quadrupled over 34 years from 108 million people worldwide in 1980 to 422 million in 2014,[2] has been described as 'the biggest epidemic in human history.' [3]

Despite advances in techniques for revascularisation, a small but significant proportion (1-2%) of patients with PAD will progress to non-reconstructable or non-salvageable disease, and be faced with major lower limb amputation (MLLA).[4] This risk is about 50% higher in patients who have diabetes-related PAD.[5] This has led to approximately 5000 MLLAs being performed each year in the United Kingdom alone.[6]

Poor outcomes after MLLA in the UK have been highlighted by a report from the National Confidential Enquiry into Patient Outcome and Death (NCEPOD).[4] This showed a 12.4% 30-day mortality rate, with more than 30% of patients dying in hospital within 90 days. This was worse than the 30-day mortality rate from a large study from the USA (9.1%).[7] It was also significantly worse than the target of 5% 30-day mortality which was set by the original Vascular Society of Great Britain and Ireland Quality Improvement Framework (QIF) in 2010, which was revised to a target of less than 10% at 90 days in 2016.[8] Major problems highlighted by the NCEPOD report included poor perioperative pain control and high short-term mortality.

In this context, the need for rigorous research is paramount. There is a need to both gain a clearer understanding of the factors driving these poor outcomes, and to identify interventions which might improve matters.

A recent systematic review and meta-regression of factors predictive of peri-operative mortality in patients undergoing MLLA for complications of PAD found 64 cohort studies with a total of 321,805 patients which examined this question.[9] There were no randomised controlled trials which published either 30-day or in-hospital mortality rates. The majority of these studies were small and performed only simple univariate analyses, though five studies did use multivariate techniques to look for independent predictive factors.[10-14] Only one of these studies went on to develop a prognostic model for peri-operative mortality for use in clinical practice.[12] Three other prognostic models of peri-operative risk have been published.[7,15,16] These were excluded from the above systematic review as they used slightly different definitions of peri-operative mortality. These models use factors such as 'impaired sensorium' and 'steroid use for a chronic condition' which are not collected in routine health records in the UK,[17] have poor discrimination, and there is no published evidence that any of the existing models have external validity. There is therefore a need for further work to explore risk factors for peri-operative mortality in patients undergoing MLLA.

Once risk factors are identified, multivariate statistical techniques may be employed to develop prognostic models. The development of prognostic models would also help with counselling of patients about the likely outcomes of surgery, informing the consent process and improving communication between the healthcare team and patients or carers. Researchers must then identify interventions which may be beneficial and run interventional trials to assess their efficacy, effectiveness and implementation.

These are well-trodden paths, which may result in improvements in a narrow set of outcomes. However this approach has been challenged recently by organisations such as the Core Outcome Measures in Effectiveness Trials (COMET) initiative and the James Lind Alliance (a non-profit organisation which aims to identify the most important unanswered

questions in different areas of health or healthcare), who have highlighted the fact that it is both necessary to gain consensus on what is important and to engage fully with patients to gain a full understanding of their perspective.[18,19] For example, while it may be clear to some that pain and perioperative mortality are important outcomes for patients undergoing MLLA for complications of PAD, this has not been formally assessed. It is entirely possible that these are not the most important outcomes from the patient's perspective and that there are other key outcomes which deserve consideration. Investing time and resources on studies which focus on outcomes which may not be considered important by the majority of patients or healthcare professionals is both wasteful and unethical, as interventional trials potentially expose patients to the risks associated with interventions which have not previously been fully tested. This is especially important in conditions such as MLLA, where there are large numbers of stakeholder groups. For example surgeons, physicians, anaesthetists, nurses, physiotherapists, occupational therapists, prosthetists and clinical psychologists all care for individuals having MLLA, so it is important to gain a broad perspective on the important outcomes.

In response to the need to both gain an appreciation of patients' perspectives and gain consensus on what the most important outcomes are, a growing number of "core outcome sets" have been developed.[20] Core outcome sets aim to find consensus on which key outcomes should be reported for all studies involving a particular group of patients, presenting a minimum standard. They aim to reduce research waste by directing research towards the most important outcomes and reduce the under-reporting of harms by listing the important harms which should be reported in clinical studies. Under-reporting of harms is an established problem in routinely collected health data,[21] and cherry-picking of outcomes to show a positive result is a known problem in both interventional trials and meta-analysis.[22] The drive towards publication of core outcome sets has been led recently by the COMET initiative,[18] which was launched in 2010, and core outcome sets have now been published for conditions as diverse as rheumatoid arthritis and head and neck cancer,[23,24] with 1330 projects registered with the initiative as of December 2019. With a rigorously developed core outcome set in place this should

enable researchers to do the right epidemiological studies to identify key drivers of these core outcomes and thus run the right interventional trials, which will make the biggest difference to our patients.

The development of core outcome sets is therefore important for several reasons. Firstly, consensus about the most important outcomes for these patients should direct research towards the key areas for improvement. In a climate where research funding is in short supply, targeting research towards the most important outcomes becomes increasingly important. Secondly, adoption of core outcome sets improves the efficiency of research. Systematic review with meta-analysis is the optimal strategy for pooling results from multiple studies, but many studies involving similar patient cohorts report similar but subtly different outcomes.[25] This heterogeneity makes meta-analysis difficult, so that it is often impossible to generate pooled effect estimates.[26] This can result in studies being excluded from analysis simply because their outcomes are not directly comparable.

During the period where I was working on the projects in this thesis I was also a member of the trial management group for a randomised controlled feasibility study looking at an intervention designed to reduce post-operative pain following MLLA (the PLACEMENT trial).[27] Though this is not covered in this thesis, the ethical approval for and the management of the projects in this thesis were undertaken in collaboration with the PLACEMENT trial management group. The work described in this thesis came about because while we (I and several others on the trial management group) were setting up the PLACEMENT trial we realised that there was a real need for high-quality tools to direct research and quality-improvement towards key interventions and outcomes for patients undergoing MLLA for complications of peripheral vascular disease. This group is therefore referred to multiple times throughout the thesis.

1.2 Assessment of peri-operative mortality risk factors

The NCEPOD report highlighted the high perioperative mortality rate of patients undergoing MLLA, which was found to be 12.4% at 30 days.[4] This makes MLLA the highest risk commonly performed Vascular Surgery operation other than ruptured abdominal aortic aneurysm (AAA) repair: higher than elective open AAA repair (3.0%) or lower limb bypass (3.0%).[6] Despite this, it has historically been relatively overlooked by Vascular Surgeons, and the NCEPOD report found that around a third of cases were performed by unsupervised non-consultant grade surgeons.[4] This is changing, with the 2016 Quality Improvement Framework recommending that a consultant vascular surgeon should be present in theatre for all major lower limb amputation cases.

In the context of high-risk operations, quantification of risk is important for several reasons. Firstly, it is important when counselling patients about the benefits and hazards of conservative management or surgical intervention. Recent UK court rulings about patient consent have brought this to the fore for both patients and surgeons alike.[28] This is an evolving area, but current advice is now that 'surgeons are required to engage in a consenting process tailored to the individual patient with detailed, accurate and realistic explanations of the pros and cons of surgery.'[29] In procedures such as MLLA where individual risk varies widely between patients, it is important to be able to quantify risks as accurately as possible.

Secondly, the past few years have seen increasing publication of surgeon-specific or unit-specific outcomes. Some level of monitoring is important from a clinical governance point of view. This potentially carries the benefit of improving outcomes via effects similar to the Hawthorne effect,[30] which describes the now well-established research study effect where productivity or outcomes improve simply as a result of being monitored. It does, however, carry the risk of leading to risk-averse behaviour from surgeons if there is inadequate or inaccurate risk adjustment of these outcomes.[31] Use of accurate, validated risk adjustment tools also helps to identify high-risk patients to clinicians, enabling them to target more intensive pre-operative work-up and

optimisation and higher post-operative levels of care to the appropriate patients. There is increasing interest into the putative benefits of 'prehabilitation', with multiple on-going studies,[32] though with little evidence of benefit at this time.[33] This targeted care does, however, have the potential to lead to improvements in outcomes, and has been proposed as the major reason why outcomes in Cardiac Surgery improved dramatically after routine adoption of the European System for Cardiac Operative Risk Evaluation (EuroSCORE) into clinical practice.[34] These factors have led to an explosion of published risk models in surgery, including an updated EuroSCORE II for cardiac surgery,[35] and those used for laparotomy and abdominal aortic aneurysm repair,[36,37] to name but a few.

1.2.1 The UK National Vascular Registry

The National Vascular Registry (NVR) is an audit database which is used for reporting short-term surgeon-specific outcomes for the two compulsory vascular index procedures (elective AAA repair and carotid endarterectomy). In addition, data are collected for lower limb angioplasty, lower limb bypass and lower limb amputation, though data entry for these is voluntary rather than mandatory for surgeons practising within the UK National Health Services. Due to the voluntary nature of reporting for the amputation dataset, case completion rates have historically been low, with only about 30% of cases recorded in 2009. With talk of increasing the scope of compulsory reporting, this doubled to around 60% by the end of 2016.[38]

With this improved case ascertainment, it is now appropriate to look again at the factors which predict peri-operative mortality in patients undergoing MLLA for complications of PAD in the UK. While the missing 40% of cases may be systematically different from the remaining 60%, thus introducing an element of bias into any resulting analysis, with approximately 3,000 cases reported per year, I feel that analysis of this large number of cases will nonetheless provide useful insight into the risk factors for the majority of patients. Given the improvements in outcome seen in other fields following the development of high-quality prognostic models of risk, it is also therefore appropriate to

generate new prognostic risk prediction tools based on improved (larger) datasets, to see if it is possible to improve upon existing models.

Ideally, we would then move on to look at medium-term mortality as well as short- and medium-term morbidity. Unfortunately, while it will be possible to briefly examine short-term morbidity outcomes using data from the National Vascular Registry, as certain morbidity outcomes are reported, the data set has never been externally validated, so it is unclear how accurate the reporting of these outcomes will be. It is well known that morbidity outcomes are under-reported in routinely collected data,[21] so it is likely that morbidity outcomes in the National Vascular Registry are also under-reported. It will therefore not be possible to quantify the risks of these outcomes with any degree of certainty from the National Vascular Registry. Medium-term outcomes are not collected in the National Vascular Registry, so it will not be possible to examine these outcomes using this data source.

1.3 Core outcome sets

No core outcome set exists for major lower limb amputation. Some more tightly focussed work has been done on factors influencing mobility in established amputee patients,[39] but there is no consensus about which outcomes are important to report for patients undergoing major lower limb amputation. In this respect, vascular surgery in general is lagging behind many other specialties, such as oesophageal,[40] colorectal[41] and head and neck cancer surgery,[24] where core outcome sets already exist. In contrast, no core outcome set has been defined for any condition treated by or intervention delivered by vascular surgeons.

Some additional complexity arises from the fact that recovery and rehabilitation after MLLA is a lengthy process, taking many months. This means that there is a reasonable chance that the core outcomes for studies with short-term primary outcomes (where peri-operative complications, acute pain management, etc. may be key) may be different

from the core outcomes for studies with medium-term primary outcomes (where mobility and independence may be most important). There is no agreed definition of what, precisely, is meant by 'short-term' or 'medium-term' in patients undergoing MLLA. Surgical audits often define short-term variously as within 30 days (as in the USA[7]), during the primary hospital admission (as in the National Vascular Registry[17]), or sometimes within 90 days (as in the UK national oesophago-gastric cancer audit).[42] Medium-term is again a poorly defined term. Reporting standards for abdominal aortic aneurysm repair define it as 'up to 5 years after graft implantation'.[43]

Given the poor outcomes highlighted by the NCEPOD report, it is imperative that we move forward in developing interventions to improve the care of patients undergoing MLLA. However, as described above, to maximise the efficiency of this work it is vitally important that core outcome sets are developed. Development of core outcome sets will aid the chain of research at multiple levels. Firstly, core sets will guide epidemiological studies to consider which risk factors impact the core outcomes, leading to the development of risk models for those outcomes. Secondly, they will guide researchers to investigate interventions designed to improve core outcomes, rather than investing valuable time and money pursuing interventions which are targeted at improving outcomes, but which might not be of central importance. The efficacy and effectiveness of these interventions should then be assessed by measurement of core rather than non-core outcomes in clinical trials, and by harmonising outcomes, data from multiple trials can better be subjected to meta-analysis in order to provide pooled estimates of treatment effects.

1.4 Thesis aims and objectives

1.4.1 Aim

The aim of this thesis is to develop tools which will direct future research and quality-improvement towards key interventions and outcomes for patients undergoing MLLA for complications of peripheral vascular disease.

1.4.2 Objectives

I will do this in two major ways.

1.
    a. I will identify the principal risk factors for peri-operative mortality and morbidity in patients undergoing MLLA using routinely collected national data.
    b. Following on from this, I will use these risk factors to develop a prognostic model for peri-operative mortality, again using routinely collected national data.

This work is presented in Chapter 2 of this thesis.

2.
    a. I will develop an exhaustive list of outcomes for research and service evaluation involving patients undergoing major lower limb amputation as a result of complications of peripheral vascular disease.
    b. Following on from this, I will establish consensus on core outcome sets for both short-term and medium-term research and service evaluation involving patients undergoing MLLA for complications of peripheral vascular disease, using the list developed in 2.a. above as a starting point.

The development of core outcome sets for patients undergoing MLLA for complications of PAD is described in Chapters 3 and 4.

The thesis concludes in Chapter 5 by giving an overview of the work, discussing the ways in which I have achieved the objectives I set out at the beginning of the project and including discussion of limitations and areas where further work is needed.

Some of the work described in this thesis has been published in peer-review journals, and I have also presented much of the work at national and international conferences. Details of these publications and presentations are given in Appendix B.

2 Assessment of peri-operative risk for people undergoing major lower limb amputation for complications of peripheral vascular disease: analysis of a three-year cohort from the UK National Vascular Registry

2.1 Introduction

Risk prediction for high-risk surgical procedures is of increasing importance internationally but has gained particular prominence within the United Kingdom as a result of three principal factors. Firstly, population aging has resulted in an increasingly frail patient population, with multiple co-morbidities as well as functional decline.[44,45] Secondly, recent UK court rulings about patient consent have brought the issue of appropriate patient counselling prior to surgery to the fore for both patients and surgeons alike.[28] Finally, the advent of surgeon-specific outcome publication in the United Kingdom has made the importance of appropriate risk adjustment a high priority for national audit.

There is widespread concern that the publication of these data will lead to high risk patients being denied procedures which they might otherwise have chosen to undergo as a result of surgeons being more concerned about having an unfavourable statistic recorded next to their name than patients might be about experiencing those negative outcomes. [31] Appropriate risk adjustment reduces this issue by modifying the expected

number of adverse outcomes according to patients' fitness for surgery and thus comparing a surgeon's performance with a more appropriate standard.

Major lower limb amputation is a high risk surgical procedure, with an in-hospital mortality rate in the UK of approximately 6% for below knee amputation and 12% for above knee amputation.[6] These mortality rates make it the highest-risk lower limb procedure in Vascular Surgery in this country. It is important, therefore, to identify the factors which contribute to these high mortality rates. While it was appropriate in the last century to do this in a simple univariate manner from small single-centre studies, the adoption of national registries over the past two decades mean that there is an opportunity to use much more rigorous methodology, such as using multivariate techniques to identify whether predictors are independent or highly correlated.

The earliest work of this type came from a Scottish study, published in 1999, and identified only age and sex as significant independent risk factors for mortality at 30 days.[10] More recently, work by Easterlin et al. from the USA using data from the National Surgical Quality Improvement Program database found several other predictors of mortality, going on to develop a predictive model to allow assessment of perioperative risk for an individual patient.[12] Application of this work to data from UK audit is unfortunately hampered by the fact that several of the included variables, such as 'steroid use for a chronic condition', are not routinely collected in this country. Work from Japan identified similar factors, but no risk model was developed to aid in presenting an accurate picture of the likely outcomes of surgery to patients, or in risk adjustment.[14] Table 2.1 lists the independent risk factors for peri-operative mortality identified in these studies. In addition to the work of Easterlin et al. three other risk models exist for patients undergoing major lower limb amputation. These are two versions of the Vascular Biochemistry and Haematology Outcome Model (VBHOM), as well as the Veterans Affairs model (VAM).[15,16,46] These latter models were developed using quite small databases and do not report high levels of accuracy, even internally within the datasets used to generate the models. The second VBHOM model was developed in response to work attempting to externally validate the first VBHOM model, which found

it to have poor predictive power in terms of both discrimination and calibration. There is no work which externally validated the second VBHOM model, the VAM or the model of Easterlin et al.

Study	**Country**	**Patients**	**Independent Risk Factors**
Tang et al. 2009 [46]	UK	269	Age, sex, emergency admission, urea, sodium, potassium, haemoglobin, white cell count, creatinine, urea/creatinine ratio
Patterson et al. 2012[15]	UK	306	Age, sodium, creatinine, albumin, potassium
Pell et al. 1999[10]	UK	2759	Age, sex
Easterlin et al. 2013[12]	USA	9244	Age, dependent functional status, dialysis, steroid use for a chronic condition, dyspnoea, history of CHF, history of COPD, impaired sensorium, preoperative systemic sepsis, previous major cardiac surgery
Yamada et al. 2016[14]	Japan	8565	Age, sex, dependent functional status, malignancy, CRF, history of cardiac disease, level of amputation, emergency admission
Feinglass et al. 2001[16]	USA	4061	Age, smoking history, dyspnoea at rest, DNR status, dependent functional status, current pneumonia, ventilator dependent, COPD, previous revascularisation or amputation,

			gangrene, hepatomegaly, hypertension requiring medications, current dialysis, cerebrovascular accident without neurological deficit, impaired sensorium, disseminated cancer, albumin, bilirubin > 1mg/dL, potassium < 3.5mmol/L, BUN > 40mg/dL, WBC > 11, emergency operation, ASA grade

Table 2.1: Risk factors for peri-operative mortality from previous multicentre studies employing multivariate modelling to identify independent risk factors. All listed factors were significant at the 5% level. CHF: congestive heart failure. COPD: chronic obstructive pulmonary disease, CRF: chronic renal failure, DNR: do not resuscitate, BUN: blood urea nitrogen, WBC: white blood-cell count, ASA: American Society of Anesthesiology.

Part of the reason for there being little work examining risk prediction in these patients may be a historical lack of availability of large clinical databases including patients undergoing major lower limb amputation. As recently as 2009 for example, case ascertainment rates from the UK National Vascular Database were as low as 30%. While this is not likely to improve dramatically until such a time as major amputation becomes subject to mandatory outcome reporting, many Vascular Surgeons in the UK believe that it is only a matter of time before the scope of mandatory reporting is widened to include these patients. As a result, increasing numbers of amputations are being reported in national audit databases. Case ascertainment estimates in the re-titled UK National Vascular Registry (NVR) rose to almost 60% in 2015.[6] With well over 50% case ascertainment, it is now appropriate to begin thinking about the generation of risk prediction tools analogous to those already widely available for other high risk procedures such as cardiac surgery and abdominal aortic aneurysm repair.[37,47]

The objectives of this chapter are

c. To identify the principal risk factors for peri-operative mortality and morbidity in patients undergoing MLLA using routinely collected national data.
d. To use these risk factors to develop a prognostic model for peri-operative mortality, again using routinely collected national data.

I will also compare the efficacy of the prognostic model to existing risk models and assess the model's ability to predict morbidity outcomes such as length of stay and systemic peri-operative complications.

Work from this chapter has been published in the European Journal of Vascular and Endovascular Therapy.

2.2 Methods

2.2.1 Data

All patients recorded in the NVR as undergoing major lower limb amputation (below knee, through knee, above knee, hip disarticulation and hind quarter amputation) from January 2014 until December 2016 were included in the study. Data were formally requested through and approved by the UK Healthcare Quality Improvement Partnership, who are the data controllers for English and Welsh data within the NVR; and through the Audit and Quality Improvement Committee of the Vascular Society of Great Britain and Ireland, who are the data controllers for Scottish and Northern Irish data within the NVR. Unfortunately, there was some delay in receiving the data, as there were some database issues which the data controllers needed to resolve prior to handing over the data.

Data applications from the NVR are tightly controlled, and applicants are given only data which they can justify as important for the purpose of the project. As one of the purposes of the project was to determine which factors were important for predicting outcome, I therefore applied for a reasonable number of parameters. I also applied for a number of

outcome variables. A list of the variables applied for and their type is given in Table 2.2. A full description of each of the data fields can be found in the NVR data dictionary, available from the NVR website.

2.2.2 Outcomes

As shown in Table 2.2, I requested several different outcome data fields. It is therefore necessary to define, a priori, the primary outcome of interest, with the remainder being defined as secondary outcomes, in order to avoid being accused of selective reporting bias. While all the outcomes requested are important in their own contexts, I chose *in-hospital mortality as the primary outcome*. This is coded in the NVR as 'Discharge status', with two possible values: alive or dead. I have done this for two main reasons. Firstly, it is a clear, categorical outcome which is not subject to significant recall bias. This is important in work which relies on observational data, as it adds strength to any findings. Secondly, as it is not possible to submit records to the NVR without completing these data, it is unlikely that there will be significant missing data for this outcome.

Other (secondary) outcomes available are return to theatre during admission, re-admission to a higher level of care, length of stay (both post-operative and total), length of time from operation to last date of follow-up and last follow-up status (alive/dead – different from the primary outcome, which was in-hospital death as some patients do have later follow-up entered and whether this was 'death' or further clinical interaction), and post-operative complications, which are subdivided into several different categories: cardiac, respiratory, cerebral (stroke), renal failure, haemorrhage and limb ischaemia.

Data field	Type	Justification
Age	Predictor	In order to take patient age into account in modelling
Sex	Predictor	In order to take patient sex into account in modelling
Deprivation index	Predictor	In order to look at whether social deprivation effects outcome
Country of residence	Predictor	Required for Deprivation index analysis as these are country-specific
Operation date	Predictor	In order to look at whether outcomes have changed over time, or with seasonal fluctuations
Mode of admission	Predictor	In order to examine whether emergent or unplanned admissions are associated with worse outcomes compared with patients admitted electively
Hospital status	Predictor	To examine whether there are differences between patients treated at major vascular centres and those who are not
Side of indication	Predictor	To check for any difference in frequency between operative side, and the difference in outcome if bilateral amputation is performed in a single operation.
Presenting problem	Predictor	To determine the effect that the underlying pathology leading to amputation has on outcomes.
Previous ipsilateral treatment	Predictor	To determine the effect previous ipsilateral treatment has on outcome.

Comorbidities	Predictor	To look at the effect of comorbidities on outcome
Smoking status	Predictor	To look at the effect of smoking status on outcome
White cell count	Predictor	To look at the effect of blood parameters on outcome
Sodium	Predictor	To look at the effect of blood parameters on outcome
Potassium	Predictor	To look at the effect of blood parameters on outcome
Creatinine	Predictor	To look at the effect of blood parameters on outcome
Albumin	Predictor	To look at the effect of blood parameters on outcome
Haemoglobin	Predictor	To look at the effect of blood parameters on outcome
Glucose	Predictor	To look at the effect of blood parameters on outcome
HbA1C	Predictor	To look at the effect of blood parameters on outcome
Abnormal ECG?	Predictor	To look at the effect of cardiac conduction abnormalities on outcome
ASA grade	Predictor	To look at the effect of ASA grade on outcome
Ankle-brachial pressure index	Predictor	To look at the effect of degree of ischaemia at the ankle on outcome
Medication	Predictor	To look at the effect of various medications (statins, ACE inhibitors/ARBs, beta blockers, antiplatelet agents, antibiotic prophylaxis, DVT prophylaxis) on outcome
Weight	Predictor	To look at the effect of nutritional status on outcome

Height	Predictor	To enable us to calculate BMI and look at the effect of nutritional status on outcome
Operation type	Predictor	To look at the effect of amputation level on outcome, and to make sure that all included cases were major amputations
Method of wound closure	Predictor	To look at the effect of method of wound closure on outcome
Destination after theatre	Predictor	To look at whether critical care admission after theatre is associated with outcome
Critical care stay	Predictor	To look at whether duration of critical care admission after theatre is associated with outcome
Return to theatre during admission	Outcome	To look both at whether return to theatre effects other outcomes and also whether other factors affect the likelihood of return to theatre during admission
Re-admission to higher level of care	Outcome	To look both at whether re-admission to higher level of care effects other outcomes and also whether other factors affect the likelihood of re-admission to higher level of care
Post-operative complications	Outcome	To look at the frequency of post-operative complications and what factors predict post-operative complications
Discharge status (alive/dead)	Outcome	To look at what factors affect in-hospital mortality

Length of stay	Outcome	To look at what factors affect length of post-operative stay in hospital.
Post-op length of stay	Outcome	To look at what factors affect length of post-operative stay in hospital.
Length of time from operation to last date of follow-up	Outcome	To work out survival or censoring dates for the purposes of looking at what factors affect post-operative survival.
Last follow-up status (alive/dead)	Outcome	To indicate whether length of time from operation to last date of follow-up is a time to death or a time to censoring event.

Table 2.2: Data requested from the NVR. A full description of each of the above data fields can be found in the NVR data dictionary, which is available on the NVR website.

2.2.3 Ethical approval and study registration

The Health Research Authority give guidance in the UK about whether studies involving patients or their data should be defined as audit, service evaluation or research. Retrospective observational studies often fall under the banner of 'service evaluation', and thus do not require formal ethical approval. The exception to this is when this work is designed to generate 'generalisable or transferable findings'.[48] The generation of a prognostic model for outcomes such as in-hospital mortality certainly falls into this category, and so the present work does require ethical approval. I therefore added a description of the project as a sub-project to an existing project recruiting patients undergoing major lower limb amputation: the PLACEMENT trial.[27] This was then

submitted as a substantial amendment to Wales Research Ethics Committee 3, and was approved (reference number 16/WA/0353).

There is also a strong argument that observational studies, like randomised controlled trials, should be registered on a WHO-compliant trial registry (though these are not trials) to guard against selective reporting bias.[49] This has been supported by multiple high-profile journals including the BMJ and The Lancet.[50] I therefore elected to register my project on one of the WHO-compliant registries which accept registration of observational studies. I chose the Australia and New Zealand Clinical Trial Registry (ANZCTR) as it is free to use, accepts observational studies, and allows individual users to submit study registrations. The project is registered as ACTRN12618000356268.

2.2.4 Statistical methodology

All statistical analysis was performed in the R statistical programming environment version 3.5.1.[51] Missing data are a problem within all large clinical databases, so it is important that these are correctly handled. Approaches which have been used in the past include 'complete case analysis', where only cases without any missing data items are included in analysis, single value imputation and multiple value imputation techniques. Complete case analysis is often the method adopted where statistical analysis is restricted to univariate testing, as it allows all of the directly available data to be used. The NVR includes many different parameters however, some of which have very poor completion rates, so a complete case analysis might inevitably result in exclusion of the vast majority of cases where multivariate analysis is performed. This is a hugely wasteful approach, making this approach unacceptable where multivariate analysis is performed on large databases. The situation is actually worse than this, however, as sometimes data may not be 'missing completely at random'. What this means is that data may be more likely to be missing in certain contexts. One example of this is that data may be more likely to be missing if a patient dies. This is known to be the case for patients operated on for abdominal aortic aneurysm who were entered into the UK

National Vascular Database, the precursor of the NVR.[52] This can lead to bias in the results which we would hope to avoid.[53]

Single value imputation methods (for example imputing the mean value where an item is missing) also lead to bias where data are not 'missing completely at random', so this is also an unacceptable option.[54] Instead, I chose to use multiple imputation methodology to account for missing data.[53] This has several key advantages. First of all, it avoids discarding cases and thus uses as many of the data as possible. Secondly, under quite weak conditions it is robust to cases where data are not 'missing completely at random'. To be more precise, missing values may be systematically different from observed values, but this can be predicted by one of the other measured parameters. This is referred to as data being 'missing at random' in the literature on missing data.[53] Returning to the example above where data were more likely to be missing if a patient had died, this would be an example of the missing data being 'missing at random', as the predictor (death of the patient) is measured.

Finally, multiple imputation is widely-available in the form of the 'mice' package version 3.3.0 for the R statistical programming environment, which uses a chained equations approach to perform multiple imputation.[55] Owing to its attractive properties and its wide availability, multiple imputation has also been recommended by prominent expert reviews for use in clinical studies where significant amounts of missing data are present.[53,56] No method of handling missing data, no matter how good, can cope with the situation where the majority of data is missing, so I excluded parameters where more than 50% of values were not recorded. Data were imputed using 45 replicates with 45 iterations of the chained equations algorithm for each replicate. This is both more replicates and more algorithm iterations than are recommended in order to be likely to remove significant bias due to initial values.[54] In order to explore any differences which there might be between the imputed data and the unimputed data, a sensitivity analysis was done by performing univariate analysis using both complete case analysis and also the multiply imputed data.

Univariate analysis was performed using univariate logistic regression, together with application of Rubin's rules to pool estimates for multiple imputation.[53] Continuous variables were kept as such rather than dichotomised into 'high' and 'low' values. Odds ratios are given in the results per unit change in value. Multivariate analysis was performed using multivariate logistic regression analysis to develop models using pre-operative predictors. Parameters were selected for inclusion in prognostic models using Information Criterion analysis in order to generate a parsimonious model which avoided over-fitting, by minimizing the Schwarz-Bayes Criterion.[57] The Schwarz-Bayes Criterion (SBC) is a quantity which trades off model complexity against model fit, and is calculated using the formula

$$\text{SBC} = k.\log_e(n) - 2.\log_e(L),$$

where k is the number of parameters in the model, n is the sample size and L is the likelihood of the model given the data, where the values of the parameters have been chosen to maximise L. In practice, I will have used a statistics package to estimate L. As I have a large number of possible parameters it is not practical to calculate the SBC for all possible models, so I use a stepwise iterative process starting from a minimal model and then calculating the SBC for models with either a parameter added, or a parameter removed. The model with the minimum SBC is then selected as the new model and the process repeats until the SBC is smaller for the current model than it is for any model with an additional parameter and any model with a parameter removed. This was done separately for each of the 45 replicates and terms which were present in at least half of the replicates were retained.

ROC curve analysis was used to assess model discrimination using the pROC package version 1.12.1.[58] This plots the sensitivity against one minus the specificity for all possible cut-off values of a binary prediction model. The area under this curve (also known as the C-statistic) is then used to assess the ability of the model to discriminate between cases where the outcome is positive and those where it is not. A prediction model which is no better than chance will have a ROC curve which is a straight line at a 45-degree angle

from (0,0) to (1,1), with a C-statistic of 0.5. Standard statistical texts suggest that a C-statistic of 0.6 implies average predictive power, 0.7 implies good predictive power and 0.8 (or above) implies excellent predictive power.[59] Another way of interpreting the meaning of the C-statistic is that it is the probability that the prediction model will give a higher score to a case where the outcome is positive than to one where the outcome is not. The Delong method was then used to calculate confidence intervals for the C-statistic and test whether performance was different to the estimated C-statistics of existing models.[60]

The Hosmer-Lemeshow goodness of fit test was used to assess calibration of the models.[59] This divides the data into several groups according to the predicted probability of the outcome, compares observed and expected counts and uses a χ^2 test to detect any significant mis-calibration.

2.3 Results

2.3.1 Demographics and outcomes

There were 12,593 amputations entered into the registry during the study period (January 2014 to December 2016), of which 9549 were above the ankle joint and so comprised the study population. Of these, 4516 (47%) were trans-tibial, 4369 (46%) trans-femoral, 442 (5%) through-knee, 32 (0.3%) hip disarticulation and 190 (2%) were simultaneous bilateral procedures. Table 2.3 summarises the baseline characteristics of the study population, together with the amount of missing data for each parameter. Some of the parameters requested were not available due to database issues, so there are some differences between the list presented in Table 2.3 and those requested in Table 2.2.

Overall, 865 patients (9.1%) died before leaving hospital. There was also a high rate of post-operative morbidity in the cohort, with 6.6%, 9.7% and 4.3% of patients suffering

cardiac, respiratory and renal complications respectively. Less than 1% of patients were recorded as having a post-operative stroke or bleeding complication, and 4.4% had a complication relating to limb ischaemia. Ten percent (966/9546) of patients had an unplanned return to theatre, while four percent (363/9545) were re-admitted to critical care. The median post-operative length of stay was 16 days (IQR 9—28 days, 1 missing value), with an overall median length of stay of 24 days (IQR 14—42 days, 1 missing value).

Parameter	**Value**	**Number missing (%)**
Age (median (IQR))	70.3 (60.3—78.5)	5 (<1)
Sex (Male : Female)	6729 : 2820	0 (0)
Hospital type (teaching : non-teaching)	4544 : 5005	0 (0)
Emergency admission (Y : N)	7489 : 2060	0 (0)
Country (Eng:Sco:Wal:NI)	5875:494:439:358	2383 (25)
Side (Left : Right : Bilateral)	4635 : 4724 : 190	0 (0)
Previous intervention on same side (Y : N)	5902 : 3628	19 (<1)
Comorbidities (Y : N) Diabetes Ischaemic heart disease Congestive heart failure	 5065 : 4467 3788 : 5744 1004 : 8528	

Chronic lung disease Chronic kidney disease Hypertension Stroke	1939 : 7593 1968 : 7564 5812 : 3720 1085 : 8447	17 (<1)
Smoking (Never : Ex : Current)	1948 : 4721 : 2850	30 (<1)
Pre-operative blood tests (median (IQR)) White cell count (10^9 cells/L) Haemoglobin (g/L) Sodium (mmol/L) Potassium (mmol/L) Creatinine (μmol/L) Albumin (g/L)	 11.7 (9.0—15.4) 112 (97—148) 136 (133—139) 4.5 (4.1—4.9) 81 (61—118) 30 (24—35)	 14 (<1) 3416 (36) 38 (<1) 18 (<1) 11 (<1) 2824 (30)
Abnormal ECG (Y : N)	3672 : 4889	988 (10)
ASA grade (1:2:3:4:5)	90:756:6164:2462:75	2 (<1)
Pre-operative medications Antiplatelet agent Statin Beta-blocker ACE-inhibitor / ARB	 6783 : 2763 6701 : 2845 2560 : 6986 3035 : 6511	 3 (<1)
Weight (median (IQR))	75 (63—87)	2607 (27)

Table 2.3: Baseline characteristics of patients. ACE – Angiotensin converting enzyme. ARB – Angiotensin II receptor blocker.

2.3.2 Risk factors for post-operative mortality

2.3.2.1 Univariate analysis

Univariate analysis revealed that increased patient age; a history of ischaemic heart disease, congestive heart failure, chronic lung disease, chronic kidney disease or stroke; a raised pre-operative white cell count, raised pre-operative serum creatinine or low pre-operative serum albumin; an abnormal ECG; increased American Society of Anesthesiologists (ASA) grade; emergency admission and pre-operative beta blocker therapy all increased the odds of in-hospital mortality. Male sex, previous intervention on the same side, below knee amputation, current smoking, statin or ACEi/ARB therapy (Angiotensin Converting Enzyme inhibitor/Angiotensin II receptor blocker – a class of anti-hypertensive medication), and increased weight all had protective effects, when using multiple imputation to handle challenges with missing data (Table 2.4).

Parameter	Multiple Imputation			Complete Case Analysis	
	O.R.	95% C.I.	P-value	O.R.	95% C.I.
Age (per 10 year ↑)	0.763	0.720—0.809	<0.0001	0.764	0.721—0.810
Sex (Male vs. Female)	1.241	1.070—1.439	0.004	1.241	1.070—1.439
Hospital type (teaching v. non-teaching)	1.034	0.899—1.190	0.637	1.034	0.899—1.190
Emergency admission	0.263	0.203—0.342	<0.0001	0.263	0.203—0.342
Previous intervention on same side	1.617	1.406—1.861	<0.0001	1.618	1.406—1.861
Below knee amputation vs. higher level	2.216	1.907—2.575	<0.0001	2.216	1.907—2.575

Comorbidities (Yes vs. No)					
Diabetes	1.069	0.930—1.230	0.349	1.069	0.930—1.230
Ischaemic heart disease	0.634	0.551—0.730	<0.0001	0.635	0.552—0.731
Congestive heart failure	0.478	0.397—0.576	<0.0001	0.479	0.398—0.577
Chronic lung disease	0.690	0.588—0.810	<0.0001	0.690	0.588—0.811
Chronic kidney disease	0.477	0.411—0.555	<0.0001	0.477	0.411—0.556
Hypertension	0.867	0.750—1.003	0.054	0.868	0.750—1.003
Stroke	0.785	0.640—0.963	0.021	0.785	0.640—0.963
Smoking – Current	1.208	1.031—1.415	0.019	1.206	1.030—1.413
Pre-operative blood tests					
White cell count (per 10^9 cells/L ↑)	0.968	0.961—0.975	<0.0001	0.968	0.961—0.975
Haemoglobin (per g/L ↑)	1.005	0.996—1.014	0.307	1.005	0.996—1.014
Sodium (per mmol/L ↑)	0.995	0.980—1.010	0.507	0.995	0.980—1.010
Potassium (per mmol/L ↑)	0.993	0.924—1.069	0.860	0.994	0.924—1.069
Creatinine (per 10 μmol/L ↑)	0.973	0.968—0.977	<0.0001	0.973	0.968—0.977
Albumin (per g/L ↑)	1.061	1.051—1.072	<0.0001	1.062	1.051—1.072
Abnormal ECG	0.411	0.353—0.478	<0.0001	0.400	0.343—0.467
ASA grade (per grade ↑)	0.248	0.219—0.282	<0.0001	0.248	0.219—0.282
Pre-operative medications					
Antiplatelet agent	1.113	0.957—1.295	0.166	1.113	0.957—1.295
Statin	1.258	1.086—1.459	0.002	1.259	1.086—1.459
Beta-blocker	0.718	0.619—0.834	<0.0001	0.719	0.619—0.834

ACE-inhibitor / ARB	1.169	1.002—1.363	0.047	1.169	1.002—1.364
Weight (per 10kg ↑)	1.085	1.042—1.129	<0.0001	1.088	1.043—1.134

Table 2.4: Univariate analysis showing odds ratios of being discharged alive according to different risk factors for patients undergoing major lower limb amputation in the UK National Vascular Registry. The last two columns present a sensitivity analysis using complete cases only. Numbers greater than one indicate greater odds of being discharged alive. O.R. – Odds Ratio. C.I. – Confidence Interval. ACE – Angiotensin converting enzyme. ARB – Angiotensin II receptor blocker. The ↑ symbol is used to indicate an increase in value, for example 'per 10 year ↑' indicates that the odds ratios are those associated with a ten-year increase in age.

Analysis was repeated using complete case analysis to assess sensitivity to the imputation methodology. Results were almost identical to the multiple imputation analysis, giving confidence that the imputation methodology had not introduced any unwanted bias (Table 2.4).

2.3.2.2 Multivariate modelling

Multivariate regression modelling revealed that independent factors associated with in-hospital mortality were emergency admission (Odds Ratio (OR) 2.47, 95% Confidence Interval (C.I.) 1.89-3.24), bilateral operation (OR 2.19, 95% C.I. 1.48-3.25), age (OR per 10 year increase 1.21, 95% C.I. 1.13-1.29), ASA grade (OR per unit increase 2.60, 95% C.I. 2.27-2.98), abnormal ECG (OR 1.52, 95% C.I. 1.28-1.79), and increased white blood cell count (OR per 10^9 cells/L increase 1.02, 95% C.I. 1.01-1.03) or serum creatinine (OR per 10 μmol/L increase 1.02, 95% C.I. 1.02-1.03).

Independent protective factors included trans-tibial operation (OR 0.61, 95% C.I. 0.52-0.72), increased serum albumin (OR per g/L increase 0.97, 95% C.I. 0.95-0.98), previous procedures to the amputated limb (OR 0.79, 95% C.I. 0.68-0.92), and increased patient weight (OR per 10kg increase 0.95, 95% C.I. 0.91-0.99).

2.3.3 Development of a prognostic model of post-operative mortality

One of the benefits of logistic regression analysis is that the model allows quantification of the probability of the specified outcome occurring (in-hospital mortality in this case). This model can be calculated using the formula

$$P = 1 / (1 + e^{A})$$

where

- A is the fitted model formula, in this case

A = 6.736 - 0.784 x (*Bilateral operation*) + 0.491 x (*Trans-tibial operation*) - 0.904 x (*Emergency admission*) - 0.019 x (*Patient Age*) - 0.410 (*ECG abnormal*) + 0.036 x (*Albumin*) - 0.958 x (*ASA grade*) - 0.002 (*Creatinine*) - 0.020 (*White Cell Count*) + 0.005 (*Patient Weight*) + 0.231 (*Previous Ipsilateral Intervention*)

- the logical variables (bilateral, trans-tibial, emergency, ECG abnormal, previous intervention) are replaced by one if they are true and zero if they are false; age is in years, albumin is measured in grams per litre, creatinine in micromoles per litre, white cell count in 10^9 per litre and patient weight in kilograms.

The parameters used in the prognostic model above are all of the predictors found to be significant independent risk factors for in-hospital mortality in the previous section. As described in the Methods in Section 2.2.4, we used the Schwarz-Bayes Criterion to determine whether the improved fit from retaining a parameter was sufficient to offset the increased complexity of adding the parameter to the model.

When developing a model to predict outcome, it is common to test whether the model successfully discriminates between patients, and whether it is well calibrated.

I subjected the multivariate model described above to ROC curve analysis to determine the power of the model to discriminate between patients who died in hospital and those discharged alive. As discussed above in the Methods, the area under the ROC curve gives a good summary of the discrimination of a prognostic model, with a value of 0.5 representing discrimination no better than chance, 0.6 regarded as average discrimination, 0.7 as good discrimination and 0.8 as excellent discrimination.[59] This showed that the model has good (bordering on excellent) discrimination (area under ROC curve 0.79, 95% C.I. 0.77-0.80). A plot of the ROC curve is shown in Figure 2.1.

I also performed the Hosmer-Lemeshov goodness of fit test to assess the calibration of the model. There was no evidence of model mis-calibration (P=0.348). Table 2.5 shows observed and expected outcomes with the data divided into 10 groups according to the predicted probability of in-hospital mortality from the model. This is shown graphically in Figure 2.2.

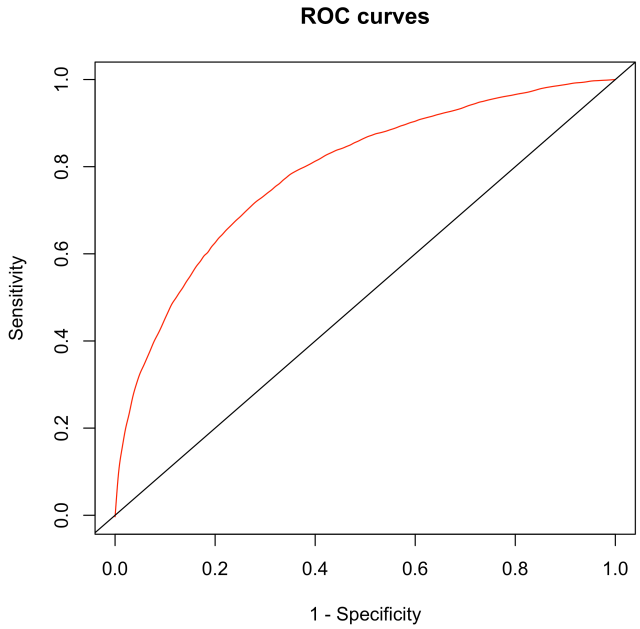

Figure 2.1: ROC curve for prognostic model.

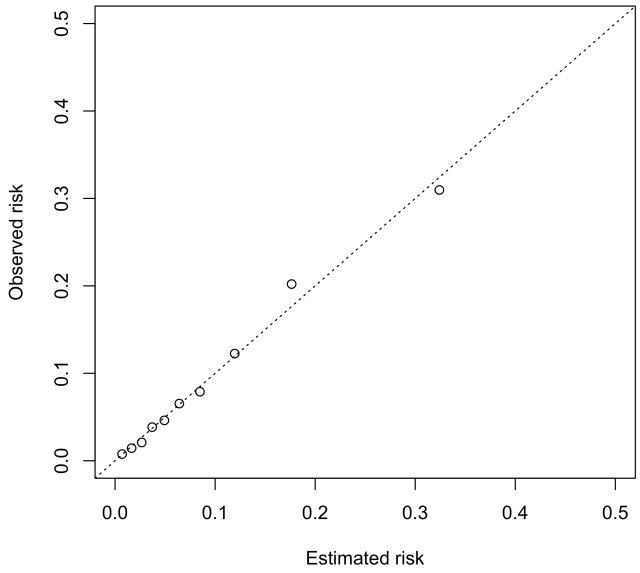

Figure 2.2: A comparison between the predicted proportion of patients not surviving until hospital discharge and the observed proportion according to the predictive model developed here. The cohort has been divided into 10 subsets according to predicted risk of mortality. These data are given in a tabular format in Table 2.5.

Observed deaths	Expected deaths	Number of patients	Probability range
7	7	954	0 – 1.2%
14	16	955	1.2 – 2.2%
20	25	955	2.2 – 3.2%
37	35	955	3.2 – 4.3%
44	47	955	4.3 – 5.6%
62	61	955	5.6 – 7.3%
75	81	955	7.3 – 9.9%
117	114	955	9.9 – 14%
193	169	955	14 – 22%
295	309	954	> 22%

Table 2.5: Model calibration table for the logistic regression model for in-hospital mortality. The 'number of patients' in each row is the number whose predicted probability of failing to survive to hospital discharge is in the range given in the final column.

2.3.3.1 Comparison to existing models

As mentioned above, there are several existing models for peri-operative mortality following major lower limb amputation.[12,15,16,46] Comparison with these models is hampered by the fact that three of the four models include terms which are not recorded in the National Vascular Registry, so any estimation of the discriminatory power of these

models will be hampered by the fact that I can only set these parameters to default values. This will clearly also affect the calibration of the models, as I can only guess at the correct 'average' values. The revised VBHOM model (which I will refer to as 'VBHOM2') does not suffer from this problem, so comparison with this model can be viewed as 'fair'.[15]

The calculated areas under the ROC curve for each of the four models were 0.59 (95% C.I. 0.56-0.61) for VBHOM, 0.65 (95% C.I. 0.63-0.67) for VBHOM2, 0.68 (95% C.I. 0.66-0.70) for VAM and 0.65 (95% C.I. 0.64-0.68) for the NSQIP model. All four models showed inferior discrimination to the model I have developed ($P<10^{-6}$ for all comparisons). Figure 2.3 shows all five ROC curves on the same graph for comparison. The NSQIP, VBHOM and VBHOM2 models all failed the Hosmer-Lemeshov goodness of fit test ($P<0.0001$ in all cases), suggesting that they are also poorly calibrated for this patient cohort. The intercept coefficient was not published for the VAM model, so it was not possible to assess discrimination for that model.

2.3.3.2 Performance of the model for predicting secondary outcomes

Although the primary purpose of the model is to predict peri-operative mortality, it is also of interest to determine whether it is predictive of other negative post-operative outcomes. I again used ROC curve analysis, this time with the secondary outcomes. The model was a good discriminator of cardiac, respiratory and renal complications (area under ROC curve 0.74, 0.69 and 0.74 respectively). It also had some ability to predict the need for return to critical care (area under ROC curve 0.62). However, it was a poor discriminator of the need to return to theatre (area under ROC curve 0.52). The model was also not a good discriminator of prolonged post-operative length of stay (area under ROC curve 0.57).

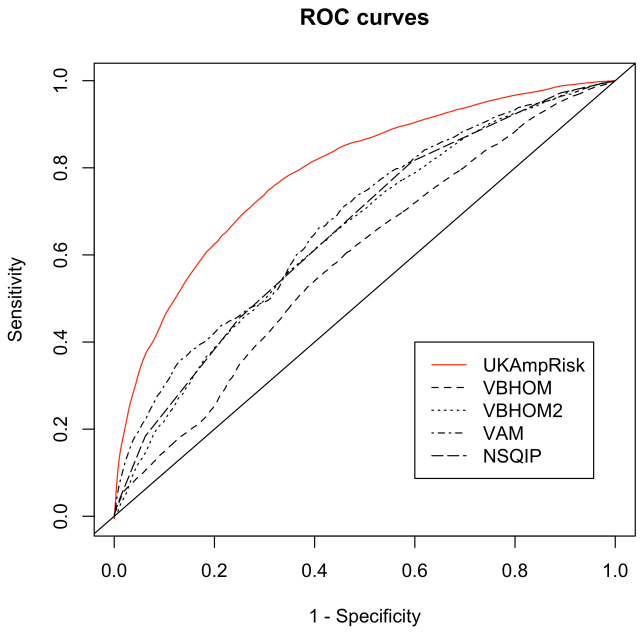

Figure 2.3: ROC curve for prognostic model, with best estimates of the VAM, VBHOM and NSQIP models. Some parameters from the other models were not available in the NVR dataset so these are conservative estimates of the true discrimination of these models.

2.3.4 Risk factors for secondary outcomes

In addition to examining risk factors for the primary outcome, I also looked at several secondary outcomes: return to theatre during admission, re-admission to a higher level of care, length of stay (both post-operative and total) and post-operative complications, which are subdivided into several different categories: cardiac, respiratory, cerebral (stroke), renal failure, haemorrhage and limb ischaemia. The length of time from operation to last date of follow-up and last follow-up status (alive/dead) were very poorly completed, with missing data rates of 60% and 76% respectively, so these were not analysed. Multivariate regression parameters for each of the secondary outcomes are presented in Table 2.6, and these analyses are discussed in some detail in the following subsections.

2.3.4.1 Return to theatre during admission

As stated above, 10% of patients had an unplanned return to theatre during their index admission. Multivariate regression modelling revealed that there were seven independent predictors of return to theatre: bilateral operation (OR 2.58, 95% C.I. 1.61—4.14), amputation below knee level (OR 0.673, 95% C.I. 0.544—0.832), history of diabetes (OR 1.44, 95% C.I. 1.16—1.78), emergency operation (OR 2.18, 95% C.I. 1.55—3.08), serum albumin (OR per g/l increase 0.951, 95% C.I. 0.936—0.965), increased patient age (OR per year increase 0.996, 95% C.I. 0.989—1.004) and increased white blood cell count (OR per unit increase 1.015, 95% C.I. 1.005—1.025).

A model using these factors to predict cardiac complications had only average discrimination (C-statistic 0.64), though this was significantly better than the ability of the mortality model described in Section 2.3.3 to predict unplanned return to theatre (C-statistic 0.52, P<0.0001).

2.3.4.2 Re-admission to a higher level of care

As stated in Section 2.3.1, 10% of patients had an unplanned return to theatre during their index admission. Multivariate regression modelling revealed that there were only three independent predictors of readmission to critical care: ASA grade (OR per level increase 2.40, 95% C.I. 2.02—2.87), increased serum creatinine (OR per micro g per l increase 1.0035, 95% C.I. 1.0029—1.0040) and serum albumin (OR per g/l increase 0.958, 95% C.I. 0.943—0.973).

A model using these factors to predict re-admission to a higher level of care had only average discrimination (C-statistic 0.63), which was not significantly better than the ability of the mortality model described in Section 2.3.3 to predict readmission to critical care (C-statistic 0.62, P=0.274).

	Complications								
Parameter	Return to theatre	Re-admission to critical care	Prolonged length of stay	Cardiac	Respiratory	Renal	Limb ischaemia	Stroke	Bleeding
Age	0.996 (0.989-1.004)				1.015 (1.010-1.022)				
Emergency	2.18 (1.55-3.08)		1.74 (1.57-1.93)	1.94 (1.47-2.57)	1.40 (1.14-1.71)	1.96 (1.38-2.77)	1.89 (1.39-2.58)		
Bilateral	2.58 (1.61-4.14)		1.65 (1.22-2.23)	2.09 (1.36-3.21)					
Trans-tibial	0.673 (0.544-0.832)		1.18 (1.08-1.29)	0.719 (0.602-0.858)	0.729 (0.629-0.846)		1.73 (1.40-2.13)		
Previous procedures					0.784 (0.680-0.903)	0.704 (0.573-0.864)			
White cell count	1.015 (1.005-1.025)				1.017 (1.010-1.025)				
Creatinine		1.0035 (1.0029-1.0040)	1.0009 (1.0005-1.0013)	1.0010 (1.0005-1.0016)		1.0026 (1.0019-1.0032)			
Sodium					1.029				

					(1.014-1.043)				
Albumin	0.951 (0.936-0.965)	0.958 (0.943-0.973)	0.986 (0.980-0.992)	0.971 (0.959-0.983)	0.972 (0.962-0.982)	0.965 (0.950-0.980)			0.957 (0.923-0.989)
ASA grade		2.40 (2.02-2.87)	1.15 (1.07-1.23)	2.23 (1.91-2.59)	1.82 (1.61-2.06)	2.20 (1.84-2.63)	1.48 (1.26-1.74)		
Diabetes	1.44 (1.16-1.78)		0.843 (0.772-0.921)				0.718 (0.580-0.888)		
Chronic kidney disease						2.06 (1.63-2.61)			2.70 (1.69-4.33)
Congestive heart failure				1.48 (1.19-1.84)					
Chronic lung disease					1.94 (1.67-2.26)				
Stroke								4.05 (2.53-6.48)	
Statin			1.15 (1.05-1.26)						
Beta-blocker				1.38					

				(1.16-1.65)					
Abnormal ECG				1.84 (1.52-2.23)					
Chronic ischaemia							0.490 (0.367-0.654)		
Neuropathy							0.114 (0.016-0.406)		
Tissue loss							0.472 (0.366-0.608)		
Uncontrolled infection							0.289 (0.206-0.406)		
C-statistic	**0.64**	**0.63**	**0.59**	**0.75**	**0.71**	**0.78**	**0.67**	**0.61**	**0.66**

Table 2.6: Multivariate odds ratios (95% confidence intervals) for morbidity outcomes for parameters found to be significant independent predictors using minimisation of the Schwarz-Bayes criterion. The last row gives the respective C-statistics of the models. Prolonged length of stay was defined as a length of stay longer than the median value (16 days).

2.3.4.3 Length of stay

I chose to focus on post-operative length of stay rather than overall length of stay, which includes the time spent in hospital prior to major lower limb amputation, as I felt that in addition to patient-related factors, overall length of stay was likely to be influenced by a number of unmeasured non-patient related factors such as the efficiency of the inpatient referral system and theatre capacity. To simplify the analysis, I defined 'prolonged post-operative length of stay' as a length of stay which was longer than the median value, which was 16 days. Multivariate regression modelling revealed that there were eight independent predictors of prolonged post-operative length of stay: bilateral operation (OR 1.65, 95% C.I. 1.22—2.23), amputation below knee level (OR 1.18, 95% C.I. 1.08—1.29), history of diabetes (OR 0.843, 95% C.I. 0.772—0.921), emergency operation (OR 1.74, 95% C.I. 1.57—1.93), serum albumin (OR per g/l increase 0.986, 95% C.I. 0.980—0.992), ASA grade (OR per level increase 1.15, 95% C.I. 1.07—1.23), increased serum creatinine (OR per micro g per l increase 1.0009, 95% C.I. 1.0005—1.0013) and whether the patient was on statin therapy (OR 1.15, 95% C.I. 1.05—1.26).

A model using these factors to predict prolonged post-operative length of stay had poor discrimination (C-statistic 0.59), though this was significantly better than the ability of the mortality model described in Section 2.3.3 to predict prolonged post-operative length of stay (C-statistic 0.57, P=0.006).

2.3.4.4 Cardiac complications

Multivariate regression modelling revealed that there were nine independent predictors of cardiac complications: bilateral operation (OR 2.09, 95% C.I. 1.36—3.21), amputation below knee level (OR 0.719, 95% C.I. 0.602—0.858), history of congestive cardiac failure (OR 1.48, 95% C.I. 1.19—1.84), emergency operation (OR 1.94, 95% C.I. 1.47—2.57), abnormal ECG (OR 1.84, 95% C.I. 1.52—2.23), serum albumin (OR per g/l increase 0.971, 95% C.I. 0.959—0.983), ASA grade (OR per level increase 2.23, 95% C.I. 1.91—2.59), increased serum creatinine (OR per micro g per l increase 1.0010, 95% C.I. 1.0005—

1.0016) and whether the patient was on beta-blocker therapy (OR 1.38, 95% C.I. 1.16—1.65).

A model using these factors to predict cardiac complications had good discrimination (C-statistic 0.75), but this was not significantly better than the ability of the mortality model described in Section 2.3.3 to predict cardiac complications (C-statistic 0.74, P=0.140).

2.3.4.5 Respiratory complications

Multivariate regression modelling revealed that there were nine independent predictors of respiratory complications: previous procedures to the amputated limb (OR 0.784, 95% C.I. 0.680—0.903), amputation below knee level (OR 0.729, 95% C.I. 0.629—0.846), history of chronic lung disease (OR 1.94, 95% C.I. 1.67—2.26), emergency operation (OR 1.40, 95% C.I. 1.14—1.71), increased patient age (OR 1.015, 95% C.I. 1.010—1.022), serum albumin (OR per g/l increase 0.972, 95% C.I. 0.962—0.982), ASA grade (OR per level increase 1.82, 95% C.I. 1.61—2.06), increased serum sodium (OR per mmol per l increase 1.029, 95% C.I. 1.014—1.043) and increased white blood cell count (OR 1.017, 95% C.I. 1.010—1.025).

A model using these factors to predict cardiac complications had good discrimination (C-statistic 0.71), but this was not significantly better than the ability of the mortality model described in Section 2.3.3 to predict respiratory complications (C-statistic 0.69, P=0.072).

2.3.4.6 Renal complications

Multivariate regression modelling revealed that there were six independent predictors of renal complications: history of chronic kidney disease (OR 2.06, 95% C.I. 1.63—2.61), emergency operation (OR 1.96, 95% C.I. 1.38—2.77), previous procedures to the amputated limb (OR 0.704, 95% C.I. 0.573—0.864), serum albumin (OR per g/l increase 0.965, 95% C.I. 0.950—0.980), ASA grade (OR per level increase 2.20, 95% C.I. 1.84—

2.63),) and increased serum creatinine (OR per micro g per l increase 1.0026, 95% C.I. 1.0019—1.0032).

A model using these factors to predict cardiac complications had good discrimination (C-statistic 0.78), which was significantly better than the ability of the mortality model described in Section 2.3.3 to predict renal complications (C-statistic 0.74, P=0.011).

2.3.4.7 Complications related to limb ischaemia

Complications related to limb ischaemia occurred in 4.4% of patients. Multivariate regression modelling revealed that there were only five independent predictors of this: amputation below knee level (OR 1.73, 95% C.I. 1.40—2.13), emergency operation (OR 1.89, 95% C.I. 1.39—2.58), ASA grade (OR per level increase 1.48, 95% C.I. 1.26—1.74), history of diabetes (OR 0.718, 95% C.I. 0.580—0.888) and the indication for the operation (OR compared to acute ischaemia 0.490, 95% C.I. 0.367—0.654 for chronic ischaemia; 0.114, 95% C.I. 0.016—0.828 for neuropathy; 0.472, 95% C.I. 0.366—0.608 for tissue loss; and 0.289, 95% C.I. 0.206—0.406 for uncontrolled infection).

A model using these factors to predict ischaemic complications had only average discrimination (C-statistic 0.67), though this was significantly better than the ability of the mortality model described in Section 2.3.3 to predict ischaemic complications (C-statistic 0.56, P<0.0001).

2.3.4.8 Stroke

Stroke was an uncommon complication, reported after only 0.8% of amputations. The only predictive factor was a previous history of stroke (OR 4.05, 95% C.I. 2.53—6.48).

2.3.4.9 Bleeding

Bleeding was again a rare complication, also reported after 0.8% of amputations. Multivariate regression modelling revealed that a history of chronic kidney disease (OR

2.70, 95% C.I. 1.69—4.33) and serum albumin (OR per g/l increase 0.957, 95% C.I. 0.923—0.989) were independent predictors of bleeding complications.

A model using these factors to predict bleeding complications had only average discrimination (C-statistic 0.66), which was not significantly better than the ability of the mortality model described in Section 2.3.3 to predict bleeding complications (C-statistic 0.62, P=0.228).

2.4 Discussion

I have shown that morbidity and mortality after major lower limb amputation in the UK remain high. While modelling has revealed some potentially modifiable factors, most predictors, such as age and ASA grade, are difficult or impossible to modify. I have also developed an accurate predictive model for in-hospital mortality risk to aid patient counselling prior to surgery, which it would be possible to deploy in the form of a smartphone app or web-based calculator. I have made a web-based calculator which shows how this can be done. It is available from http://www.ambler.me.uk/Vascular and could easily be converted into a smartphone app for offline use. Predicting morbidity outcomes proved more difficult, though the model for mortality did provide good discrimination of whether patients would develop cardiac and renal complications.

As mentioned in the Introduction to this Chapter, there is some prior work looking at independent risk factors for peri-operative mortality following major lower limb amputation. Several of the factors I found are similar to those found in previous work. Increasing age was found to be an independent predictor of mortality in almost all studies, including my own. Emergency admission and level of amputation were also found to be predictive of mortality in several other studies, including work from large administrative databases in Japan and the USA.[14,16] Evidence of systemic sepsis in the form of a raised pre-operative white cell count has also been identified as a significant factor in previous studies.[12,46] In contrast, bilateral procedures have not been previously

shown to have a worse outcome than unilateral procedures, and increased patient weight has never been identified as an independent protective factor previously. There is little evidence in the literature that any of the previously developed models have been used in clinical practice – the only work on external validation I could identify was for the first VBHOM model, showing that discrimination and calibration for this model were poor.[15] The model I have presented has shown discrimination which is an improvement on previously published models (Figure 2.3 on page 35).

Strengths of this work include the large, national database used as a data source, the rigorous statistical methods used both to handle missing data and also the information criterion approach to reduce the chances of overfitting.

Weaknesses of this study include the fact that in many vascular surgical centres, surgeons enter their own data into the NVR and these data are not subject to rigorous external validation. However, as the national audit does not link cases to individual surgeons, there is little reason for surgeons to be selective about which cases are entered. A further weakness with the NVR is that the case completion rate is also known to be only around 60%, so it is also possible that the missing cases, if present, would provide some further insight into risk factors for adverse outcomes. It is also possible that the missing 40% of cases are systematically different from the completed cases, so it is possible that other risk factors are better predictors of outcome in this unmeasured cohort, or that the degree to which the risk factors we have identified predicts outcomes could be different. There is, unfortunately, no way of knowing this with certainty. Current case ascertainment rates are a dramatic improvement over the situation 10 years ago, when only around 30% of cases were entered. The UK National Vascular Registry reports for the past two years have highlighted the fact that case ascertainment rates vary widely between Vascular Networks, with some Networks reporting no major limb amputations, and others reporting all cases.[17,38] I am therefore optimistic that many of the missing data relate to institutional and administrative factors rather than patient-related factors. The patient-related factors I have identified as predictive of outcome should therefore be reliable.

The presence of missing items within otherwise completed cases is also a weakness. I used multiple imputation to account for this missing data, and a sensitivity analysis using only complete cases gave very similar results (Section 2.3.2.1, Table 2.4, page 29), even for parameters with a significant amount of missing data, so there is no evidence that these missing values have introduced significant bias.

A further weakness of this study is due to the limitations of the data recorded in the NVR during the study period. It is increasingly recognised that frailty is an important risk factor for peri-operative complications, including mortality.[45] Indeed, dependent functional status has been shown in other work to be important for predicting mortality in this cohort.[12] Unfortunately, until recently, no measure of frailty or functional status (such as mobility or independent living) was recorded in the NVR. While a measure of frailty has now been added to NVR dataset, this did not happen in time for the study period, so it was not possible to assess its predictive power in this cohort.

Some subgroups of patients were present in only small numbers in the data, for example hip disarticulations and simultaneous bilateral procedures. Estimates of the significance of these factors will therefore be subject to imprecision. Despite this, it was identified that patients having simultaneous bilateral procedures represented a significantly higher risk cohort, so I feel that it was appropriate to include these patients in the analysis.

A final weakness is that although the model I have generated has good internal validity, I have not tested performance on external data.

I think that a knowledge of the factors which predict poor outcomes for patients provides significant opportunities to develop interventions which may have a positive impact on clinical practice. Firstly, it will encourage surgeons to do what they can to modify negative factors where this is possible. Secondly, many of the factors predicting poor outcome, such as emergency admission and a raised white cell count, are linked to management of patients at a late stage in their disease and may reflect late presentation or recognition. This highlights the critical rôle of healthcare staff to recognise the

deteriorating foot in the community, and robust in-hospital systems and teams to treat patients quickly. Earlier recognition will reduce the number of patients undergoing amputation as an emergency when they are septic, with increased risk of both kidney and cardiac dysfunction, often following a period of chronic low-grade foot sepsis resulting in malnutrition and low albumin. Amputation is often followed by long periods in hospital. In my experience, much of this time is as a result of social or organisational factors, including the need to assess a patient's home for wheelchair suitability and carry out any necessary modifications. Earlier recognition would allow amputation to be handled in a more elective manner, so that this could be done ahead of time, facilitating shorter hospital admissions and thus reduced healthcare costs. Such systems are already in place for many patients in the form of the diabetic foot service and could be rolled out to all patients with chronic limb-threatening ischaemia. The present work highlights the fact that limb salvage must not be the only measure of the success of 'limb-salvage' clinics. Early recognition that limb salvage is unlikely to succeed will facilitate early discussion about the options and outcomes of amputation. This will in turn improve the outcomes of those patients who decide to have an amputation rather than continuing to pursue further fruitless efforts at limb salvage.

I have also developed a model which could be used to aid counselling and decision-making, either in clinic or at the bedside, by quantifying the probability of the patient surviving to hospital discharge. I have developed a web calculator for easy use in clinic which is available from http://www.ambler.me.uk/Vascular. This could be converted into a standalone smartphone app for offline use. By having a model which can more reliably predict mortality, discussions about options can be more fully explored with patients, enhancing shared decision-making.[61] Multiple previous studies have shown that surgeons systematically underestimate the chances of a patient surviving an operation.[62,63] As the choice between amputation and conservative management is sometimes the choice between amputation and palliation, it is critically important that these discussions are conducted in the context of reliable risk estimates.

Ten percent of patients returned to theatre during their index admission. This is quite a high proportion, and it would have been good to get an idea of the reasons for these returns to theatre. Unfortunately, no detail is given in the dataset so some of these patients will have had a minor debridement procedure, some will have returned for bleeding or evacuation of a haematoma, and some will have had a major revision of amputation level. This may be the reason why it was difficult to generate a model with good discriminatory power for this outcome.

Further studies are required to identify whether attempts to modify any of the factors actually have a clinically relevant impact on outcome. Firstly, improvements might be made through quality improvement programmes designed to facilitate earlier identification and treatment of patients for whom further attempts at limb salvage are at high risk of failure. Increased patient weight and serum albumin have similar, though smaller, protective effects, so it is possible that a pre-operative dietary intervention might also be helpful for patients with stable but un-reconstructable arterial disease in this patient population. Improved shared decision-making using risk quantified by these data should be encouraged, perhaps supported by a decision aid.[64] Secondly, there are more speculative options which would require testing in prospective interventional studies. One unexpected factor was that previous procedures to the amputated limb reduced mortality rates. While it is possible that having had previous procedures is simply a surrogate for 'fitness' in some way, it may also be that intervention to facilitate healing at a trans-tibial rather than trans-femoral level might have multiple benefits, both in terms of improved short-term outcomes and also in terms of the improvement in long-term functional outcomes. Increased patient weight and serum albumin have similar protective effects, so it is possible that pre-operative dietary intervention or other 'pre-habilitation' might also be helpful for patients with stable but un-reconstructable arterial disease. There is increasing interest into the putative benefits of 'pre-habilitation', with multiple on-going studies,[32] though little concrete evidence of benefit at this time.[33]

As mentioned above, further work is also needed to externally validate the predictive model. This was highlighted within Vascular Surgery recently with the publication of the

draft National Institute for Health and Care Excellence (NICE) guidelines for the treatment of Abdominal Aortic Aneurysm,[65] which found that none of the models which had been subjected to external validation were found to have good discriminatory power. The models examined were all generated some time ago from relatively small cohorts using simplistic statistical methodology for both model fitting and handling missing data, so there are reasons to be optimistic that the model developed here will not be as susceptible to these problems.

In conclusion, I have detailed independent risk factors for mortality and morbidity following major lower limb amputation and developed a prognostic model for in-hospital mortality with good predictive power. Further work is required to validate this model and investigate whether interventions targeted at the identified factors might improve outcomes for this cohort.

3 Development of core outcome sets for people undergoing major lower limb amputation for complications of peripheral vascular disease. Part 1: background, systematic review and focus groups

3.1 Introduction

This chapter describes the process of generating a "long-list" of outcomes to be considered for inclusion in a core outcome set for patients undergoing major lower limb amputation (MLLA). The background and justification for development of the core outcome set have been described in Chapter 1. The process begins with a systematic review, and then involves focus groups with a range of stakeholders, to ensure that the outcomes/outcomes measures which have been reported in previous studies capture the full extent of key issues facing this patient cohort. This exhaustive list of outcomes or measures is reduced to a shorter list, where similar outcomes are grouped together. In Chapter 4 this shorter list is then used as the basis for a Delphi consensus survey, where consensus is established on which outcomes are 'core' and a three phase Delphi consensus survey followed by a face-to-face meeting.

During development of this project, it became apparent that core outcomes for patients undergoing MLLA might be different depending on whether a study was focussed on short-term or longer-term issues. For example, as the process of rehabilitation with a prosthesis is a lengthy one, which can take over a year to complete, level of mobility may not be considered core for studies focussed on issues around the acute post-operative

phase. In contrast, acute post-operative complications such as pneumonia or peri-operative myocardial infarction may not be considered core for studies focussed on patients' return to independence following surgery, as this would generally require much longer follow-up and may not be materially influenced by such issues. I therefore decided that it would be best to develop two separate but complementary core outcome sets: one for short-term studies, which I defined as up to 30 days; and one for medium-term studies, considering issues up to two years after MLLA. The former definition was chosen to line up with common surgical outcome publications, where 30 days is the standard interval during which post-operative outcomes are recorded in Vascular Surgery. The latter limit was chosen following discussions with colleagues in rehabilitation, who stated that they would regard patients two years after their amputation as 'established' amputee patients. While this argument justifies the development of separate core sets for outcomes of studies with primary outcomes measured at different time scales, it does not justify pre-judging which outcomes are most important at these timescales. I therefore decided to collect a single exhaustive list of outcomes and use the consensus process to determine which of these to include in each of the two core sets.

Secondly, I considered whether to include all patients undergoing MLLA, or to restrict the cohort according to the indication for amputation. The common indications for MLLA in adults are peripheral vascular disease, encompassing patients with conventional atherosclerotic disease, acute limb ischaemia and diabetes as well as the rarer cohort of patients with large vessel vasculitis; trauma; and neoplastic disease. Peripheral vascular disease patients comprise well over 80% of patients undergoing MLLA in the developed world.[66,67] Patients undergoing MLLA for complications of peripheral vascular disease are generally older and have significant comorbidities such as ischaemic heart disease or diabetes. Patients undergoing trauma or tumour related MLLA often have little in the way of comorbid disease and so recover and rehabilitate more quickly and completely. It was therefore felt that core outcomes for these two subgroups might be different, with those with peripheral vascular disease likely to have significantly worse outcomes, so I ultimately decided to restrict attention to the high-risk majority of patients undergoing MLLA with peripheral vascular disease.

The objective of this chapter is therefore to present the process of generating an exhaustive list of outcomes for research and service evaluation involving patients undergoing major lower limb amputation as a result of complications of peripheral vascular disease. This is then reduced to a shorter 'long-list' of outcomes suitable for consideration in a consensus process. This shorter list should:

1. Be short enough to be practical in an online Delphi survey.
2. Be comprehensive, in that firstly all relevant outcomes in the long-list could be represented by these broad outcome areas, and secondly all of the outcome categories developed by Dodd et al.[68] (described below in Section 3.2.1.5) for which there were outcomes in the exhaustive list would also be included in the shorter list.
3. Be understandable by lay individuals (patients and carers) taking part in the survey.

The following chapter (Chapter 4) will present the process by which consensus was gained on which of the outcomes should be included in the core outcome sets.

3.2 Methods

The process for development of a core outcome set is now established, and has been described in *The COMET Handbook*.[69] This involves a mixed-methods approach, utilising both quantitative and qualitative aspects.[70] The initial stages of the process are designed to create an exhaustive list of outcomes, to be considered subsequently by the consensus panels (to be described in Chapter 4). The first stage is a systematic review to identify existing published outcomes. This is followed by focus groups involving a broad range of stakeholders.

3.2.1 Phase I: Systematic review

The systematic review process which underpins core outcome set development differs somewhat from the standard approach to systematic review as the goal of the process is different. Classical systematic review involves a structured assessment of the strength of evidence for a particular intervention.[71] As a result, assessment of the quality of evidence extracted from each source, and for each outcome, is critical. Systematic review when performed as part of the core outcome set development process, by contrast, is designed to generate as complete a list as possible of the outcomes to be considered when evaluating interventions in a particular patient cohort. Thus, I felt that elimination of low-quality reports was inappropriate, as this might cause the reviewers to miss important outcomes which simply have not been adequately addressed in high quality research, thus seriously undermining the validity of the core outcome sets. It is therefore inappropriate to follow established standards in systematic review to the letter. These standards do, however, provide a useful framework for the general process of systematic review, so where appropriate I follow the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) standards.[71]

The objective of this review is to identify all short- (defined as up to 30 days) and medium-term (defined as up to 2 years) outcomes reported in published work involving patients undergoing MLLA for complications of peripheral vascular disease. I have registered the review in the PROSPERO registry of systematic reviews (ID: CRD42017059329).

3.2.1.1 Criteria for considering studies

All clinical studies reporting at least one short- (within 30 days) or medium-term (up to 2 years) outcome involving human subjects undergoing major lower limb amputation (i.e. amputation of the lower limb above the ankle) as a result of peripheral vascular disease were included. This included non-interventional studies (e.g. case series, cohort and qualitative studies), case-control studies and non-randomised and randomised

interventional trials. Study reports describing the same patient sample were included if they reported different outcomes, but outcomes which were duplicated were only counted once in the quantification of the frequency of outcome reporting. Studies reporting only patients undergoing amputation for non-ischaemic disease such as trauma, tumour, chronic non-ischaemic pain or congenital malformations were excluded. Systematic reviews found by the electronic search were used as a source of additional references which might have been missed by the electronic search, but outcomes were not extracted from the reviews themselves, as this would duplicate work from the source references. Non-systematic reviews, commentaries, editorials and articles which discuss general principles rather than patient cases were excluded. Cross-sectional studies recruiting established amputee patients were also excluded as we were interested in outcomes for patients undergoing amputation rather than those living with amputation. Non-English language clinical studies were included if there was a publicly available translation of either the abstract or full study, and data extraction was limited to what was available in the English language.

3.2.1.2 Outcomes

All outcomes described as either primary or secondary outcomes from included studies were reported. When more than a single study reported an outcome, the number of studies reporting that outcome was reported.

3.2.1.3 Search strategy

MEDLINE and EMBASE were searched through Ovid using the terms given in Table 3.1. Titles were screened initially, then abstracts of potentially relevant articles were retrieved and screened. Finally, full text articles of potentially suitable studies were retrieved, and a final decision made on suitability for inclusion in the study. Reference lists of included studies were also screened, and a search using the 'Related Articles' function in PubMed was used to capture any further relevant papers. Two individuals independently screened studies for inclusion. Disagreements were resolved through discussion and consensus

with a generally inclusive policy: since the aim of the review was to identify all reported outcomes, inclusion of borderline studies was felt to be preferable, as it was felt that non-relevant outcomes were likely to be removed by the consensus process.

Item number	Search item
1	exp Peripheral Vascular Diseases/di [Diagnosis]
2	Arterial Occlusive Diseases/di [Diagnosis]
3	exp Arteriosclerosis/di [Diagnosis]
4	exp Atherosclerosis/di [Diagnosis]
5	exp Peripheral Arterial Disease/di [Diagnosis]
6	(atherosclero* or arteriosclero* or PVD or PAOD or PAD).ti,ab.
7	(arter$ adj4 ($occlus$ or steno$ or obstruct$ or lesio$ or block$ or obliter$)).ti,ab.
8	(vascular adj4 (occlus* or steno* or obstruct* or lesio* or block* or obliter*)).ti,ab.
9	(vein* adj4 (occlus* or steno* or obstruct* or lesio* or block* or obliter*)).ti,ab.
10	(veno* adj4 (occlus* or steno* or obstruct* or lesio* or block* or obliter*)).ti,ab.
11	(peripher* adj4 (occlus* or steno* or obstruct* or lesio* or block* or obliter*)).ti,ab.
12	(peripheral adj3 dis*).ti,ab.
13	arteriopathic.ti,ab.
14	CLI.ti,ab.
15	dysvascular*.ti,ab.
16	(leg adj4 (obstruct* or occlus* or steno* or block* or obliter*)).ti,ab.
17	(limb adj4 (obstruct* or occlus* or steno* or block* or obliter*)).ti,ab.
18	(lower adj3 extrem* adj4 (obstruct* or occlus* or steno* or block* or obliter*)).ti,ab.

19	1-18 combined with OR
20	amputee$.tw.
21	Amputees/
22	(knee adj3 (disarticulat$ or exarticulat$)).tw.
23	(amputat$ adj3 (transfemoral or transtibial or lower limb or lower extremity or above knee or below knee or through knee)).tw.
24	Disarticulation/
25	Amputation/
26	20-25 combined with OR
27	(transfemoral or transtibial or lower limb or lower extremity or knee).tw.
28	exp Leg/
29	27 OR 28
30	26 AND 29
31	19 AND 30
32	Remove duplicates from 31

Table 3.1: Search strategy for systematic review.

3.2.1.4 Data extraction

A standardised data collection proforma was used and is shown in Table 3.2. Extracted data included the participant details (number and demographics: age, gender and study country), study type (for example randomised or non-randomised controlled trial, cohort study, case series, qualitative), interventions (if any), stated outcomes presented in the methods (both primary and secondary), and reported outcomes. Outcomes were extracted verbatim where possible. As this study focuses on which outcomes are reported rather than the value of those outcomes, neither study quality nor risk of bias was relevant so were not assessed. Data were extracted from 10% of studies by two independent reviewers. Concordance between reviewers was maximised by discussing in detail this 10% and coming to a consensus decision. Following this, the next 10% was also

extracted independently and concordance was then assessed by calculating Kendall's τ (tau) statistic for the number of extracted outcomes. Provided that the concordance between reviewers was high (i.e. a 95% confidence interval for the value of τ excluded zero), I decided (and the published protocol stated) that the remainder of studies would be extracted by a single reviewer.[72] If concordance were poor, the discrepancies would have been investigated and a further 10% of studies would have been double-extracted. If concordance were high at this point, the remainder of studies would be single extracted, otherwise double extraction and consensus discussion would continue. This third round of double extraction was not necessary (see Results in Section 3.3.1.4 below).

Reference details								Patient demographics				Study details			Outcomes			
Reference number	Authors	Title	Abstract	Journal	Year	Volume	Pages	Number of patients	Me(di)an age	Age mean or median?	Proportion male	Interventions	Study country / countries	Study type	Planned	Number Planned	Presented	Number Presented

Table 3.2: Data extraction template.

3.2.1.5 Results synthesis and reduction to a shorter list

The principal outcome of the systematic review is an exhaustive list of outcomes, with frequencies of reporting. Following generation of this list, outcomes were grouped into appropriate domains in order to draw out common themes for consideration in qualitative focus groups, discussed below, and to take forward to a consensus process (described in Chapter 4). There are no clear guidelines on the way in which an exhaustive list of outcomes should be reduced to a more manageable list which is suitable for

inclusion in a Delphi survey. Dodd et al. performed a systematic review of published core outcome sets, finding 99 which included a systematic review to identify a long-list of outcomes.[68] Of these, only 28 used a formal system to aid in classifying the outcomes, 21 of which were developed by the authors during the development process. Dodd et al. developed a generic system for classification of outcomes into five main areas, which are subdivided into a total of 38 domains.[68] Their classification system was based on a simpler 12-domain classification by Smith et al.[73] I believe that that the use of such generic classification systems improves the reproducibility and transferability of research, so the outcomes were divided into these 38 domains. This is important, as a core outcome set is supposed to describe the core concepts which should be measured, with the precise timing or means of measuring the outcome left for further study. This also makes the consensus process more practical, as it results in a more manageable list of outcomes to be rated in a subsequent Delphi process.

While I agree with the authors that using such a system to classify outcomes is helpful as it reduces the potential for important topics to be missing from a core outcome set, I feel that the categories – which consist largely of single-word summaries of an area such as 'physical' or 'social' – are too broad to be used directly in a Delphi consensus process. The terminology used is also quite medical (for example 'hepatobiliary outcomes'), making the categories quite inaccessible to many patients. In addition, some of the domains included several quite distinct outcome groups.

Following this classification, I therefore developed a list of more descriptive outcome groups within each domain. For example, in the 'social' domain I grouped the three outcomes 'self-reported frequency of sexual activity', 'desire for sexual activity' and 'importance of sexual activity to satisfaction with life' together as the outcome 'sexual activity'. The six outcomes 'effect on home and work capacity', 'return to work', 'Reintegration into Normal Living (RNLI)', 'community participation at 12 months', 'social integration at 12 months' and 'low social functioning at 6 months' were grouped together as the outcome 'participation in work and social activities'. I felt that these would be much easier for participants to rate in the Delphi survey. Next, some of the outcomes

measured cannot be viewed as 'core' as they are only relevant to a subset of patients. For example, acute kidney transplant rejection will only be relevant to patients who have a kidney transplant. Outcomes such as these were then removed from the shorter list.

The terminology used for outcomes can, at times, be confusing, and is applied inconsistently. Some authors refer to the outcomes extracted from the systematic review as 'outcome measures', as in most cases what is reported in the literature is a specific way of measuring an underlying concept, or outcome. Unfortunately, this is not always the case – in some studies the precise definition of a measure is not given, and what is described is an outcome, measured in a way which is incompletely described. In addition, some authors refer to the shorter list of consolidated outcomes, where similar measures are grouped together, as a list of 'domains'. Others (such as Dodd et al.) use 'domain' to mean an even more generic list which may be used to group outcomes together. In order to improve the readability of this thesis, I have taken the following pragmatic decision, which is applied consistently for the remainder of the thesis.

- To refer to 'outcomes' or 'outcome measures' extracted from the systematic review as 'outcome measures', even though many of these are not well specified measures.
- To refer to the shorter list of consolidated outcomes as 'outcomes', as this is the list from which the core outcome sets will be selected.
- To refer to the categories specified by Dodd et al. as 'domains'.

The results of the short-listing were refined at study management group meetings (where trials managers, statisticians, qualitative researchers, vascular surgeons and lay representatives were present) after having been sent round via email for comments and suggestions ahead of time in order to ensure that this process had been handled in a reasonable way. The two lay representatives and the non-medically trained members of the study group also commented on the wording of the outcomes to ensure that they were as clear as possible for non-medical participants in the subsequent consensus process.

3.2.2 Phase II: Qualitative focus groups

The primary purpose of running focus groups was to ensure that published outcomes adequately capture the outcomes which are most important to patients undergoing amputation, as well as those who care for them, both informally and professionally. This is important for two reasons. Firstly, it is entirely possible that outcomes which are viewed as important by patients or their informal carers may not have been given due consideration in the scientific literature, as research is dominated by clinical practitioners. There are documented examples of this happening during the development of other core outcome sets. An example of this is that during the development of core outcome sets in Rheumatoid Arthritis, patients described 'sleeping better' as an important outcome, though at the time of the study it had not been described in any study in the Rheumatoid Arthritis literature.[74] Conversely, it is possible that healthcare professionals will raise outcomes which patients are hesitant to discuss and which, because of perceived difficulties in recruitment for such studies, are also not well represented in the literature.[75]

These two challenges highlight the rationale for qualitative research which engages with both patients and carers and also with healthcare professionals in order to reduce the risk of missing important outcomes. I therefore decided to perform focus groups which recruited both sets of individuals. Following discussions with qualitative researchers and others with prior core outcome set experience, participants were divided into three groups: one for patients and carers, one for nurses and allied healthcare professionals and one for medically trained professionals. Participants in the two healthcare professional groups were allowed to cross over into the other group if necessary, in order to improve participation, and separate interviews were held where a key stakeholder group invitee was unable to attend any of the group sessions.

3.2.2.1 Sampling strategy – Healthcare professionals

A purposive sampling strategy was used when recruiting participants of the major professions and specialties who regularly care for patients with major lower limb amputation in order to achieve broad representation of different viewpoints. Where individuals responded to say that they were unavailable, or failed to respond, we invited other individuals from that profession/specialty in order to try to be as inclusive as possible. A list of those invited is given in Table 3.6 in Section 3.3.2.1 on page 91 of this chapter. Neither of the physiotherapists who agreed to come was able to attend the focus groups due to last-minute diary conflicts, so I arranged and LB-H held a separate interview with those individuals as I felt that it was very important to obtain input from physiotherapists with experience in looking after patients who have undergone MLLA.

3.2.2.2 Sampling strategy – Patients and carers

Previous experience with focus groups with amputee patients led me to believe that it might be difficult to get many individuals to engage with the study. I therefore invited ten participants from a concurrently running randomised controlled feasibility trial (the PLACEMENT trial)[76], along with six amputee patients who had had their amputations at least one year before the date of the focus group. The former had already consented to contact from the research team for the purpose of engagement in focus groups as this was included on the PLACEMENT trial consent form. The latter were approached by the usual care team and agreed verbally to be contacted by the research team. All invited patients were encouraged to invite their carers to the group, whether or not they were willing or able to participate themselves.

3.2.2.3 Data collection

Owing to a lack of experience with running focus groups, these were facilitated by an experienced qualitative researcher (LB-H) working at the Cardiff Centre for Trials Research. I organised the focus groups, including arranging the location and inviting

participants, attended and made notes. A flexible, semi-structured topic guide was used, and the groups began with an open discussion about the care of patients undergoing MLLA, the level of importance participants place on these issues, and how these issues may change over time (i.e. over the short- and medium-term time periods). The first part of the interview was guided by participants themselves, and the areas identified in the systematic review were not revealed. However, after this open discussion, prompts from the list of outcomes developed in the systematic review were used if areas had not naturally occurred.

The facilitator (LB-H) used these prompts to explore whether the outcomes revealed by the systematic review were relevant to the real-life experiences and attitudes of the focus group participants and whether they were comprehensive to the concerns and needs of patients with lower limb amputations. Participants were encouraged to initiate and elaborate on topics most important to them and to respond directly to other participants' responses in order to generate a group discussion. Focus groups lasted around 90—120 minutes and were audio-recorded and transcribed verbatim, with references to identifiable personal details removed. Brief demographic details of participants were taken by the facilitator. Field notes were made by me and following the focus groups the facilitator reflected on the process, made overall observations and documented relevant contextual details. The data were managed using qualitative coding software (NVivo qualitative analysis software; QSR International Pty Ltd. Version 11). Data were coded, stored and analysed at the Centre for Trials Research, and kept on encrypted storage devices.

3.2.2.4 Analysis

Thematic analysis of the focus group transcripts and field notes was performed.[77] Following familiarisation with the data, the qualitative researcher (LB-H) developed a way of categorising the data into themes and subthemes (the analytical framework). An inductive approach was used, where the themes were identified directly from the focus group data, without referring to the domains identified in the systematic review. I

discussed the framework with the qualitative reviewer, and we agreed a framework. The qualitative researcher then systematically coded the focus group data, using the qualitative data analysis software NVivo, according to these themes (data topics that were common in the dataset), but also looking for contradictory views (negative cases). I then coded a proportion of the dataset independently (one of the three focus groups) and met with the qualitative researcher to discuss discrepancies in coding until consensus was reached. Any refinements were made to the analytical framework and reapplied to the data. The qualitative researcher then interpreted the coded data, taking into consideration the stakeholder group (i.e. themes according to patient, carer, healthcare professional type). The next, and final stage of analysis then involved considering this interpretation of the focus group data against the outcomes identified in the systematic review. The qualitative researcher and I then identified: (i) areas where themes in the focus group data were similar to or corresponded to those identified in the systematic review; (ii) areas where new themes were initiated by focus group participants but were not found in the systematic review; and (iii) areas where themes were found in the systematic review but not present in the focus group data. By bringing these elements together we produced a list of outcomes to be taken forward to the consensus study.

As we used an inductive approach, in which the data take centre stage, the theoretical framework was not predetermined, so that the description was derived from the data itself. We took a phenomenological approach to attempt to uncover the meaning of the 'lived experience' of groups of individuals — people who have undergone MLLA and their carers, and a range of healthcare professionals involved in the management of patients who have undergone amputation — on the phenomenon (issues or outcomes of importance to patients after undergoing MLLA). As Tavallaei and Talib describe "the major aim of phenomenology is to 'reduce' the experience individuals have about a certain phenomenon" so that finally the description of the universal essence is created which means, as VanManen has described, "to grasp the very nature of the thing".[78,79]

3.3 Results

3.3.1 Phase I: Systematic Review

3.3.1.1 Results of the search

MEDLINE and EMBASE were searched on 20th April 2017 using the search protocol detailed in Table 3.3. The search revealed 4288 studies after removal of duplicates.

Item number	Search item	Number of results
1	exp Peripheral Vascular Diseases/di [Diagnosis]	218253
2	Arterial Occlusive Diseases/di [Diagnosis]	6766
3	exp Arteriosclerosis/di [Diagnosis]	35693
4	exp Atherosclerosis/di [Diagnosis]	18165
5	exp Peripheral Arterial Disease/di [Diagnosis]	22699
6	(atherosclero* or arteriosclero* or PVD or PAOD or PAD).ti,ab.	385166
7	(arter$ adj4 ($occlus$ or steno$ or obstruct$ or lesio$ or block$ or obliter$)).ti,ab.	233846
8	(vascular adj4 (occlus* or steno* or obstruct* or lesio* or block* or obliter*)).ti,ab.	62629
9	(vein* adj4 (occlus* or steno* or obstruct* or lesio* or block* or obliter*)).ti,ab.	30643
10	(veno* adj4 (occlus* or steno* or obstruct* or lesio* or block* or obliter*)).ti,ab.	34079
11	(peripher* adj4 (occlus* or steno* or obstruct* or lesio* or block* or obliter*)).ti,ab.	39183
12	(peripheral adj3 dis*).ti,ab.	85949

13	arteriopathic.ti,ab.	462
14	CLI.ti,ab.	4890
15	dysvascular*.ti,ab.	405
16	(leg adj4 (obstruct* or occlus* or steno* or block* or obliter*)).ti,ab.	1394
17	(limb adj4 (obstruct* or occlus* or steno* or block* or obliter*)).ti,ab.	4192
18	(lower adj3 extrem* adj4 (obstruct* or occlus* or steno* or block* or obliter*)).ti,ab.	3557
19	1-18 combined with OR	966305
20	amputee$.tw.	11024
21	Amputees/	44444
22	(knee adj3 (disarticulat$ or exarticulat$)).tw.	538
23	(amputat$ adj3 (transfemoral or transtibial or lower limb or lower extremity or above knee or below knee or through knee)).tw.	11473
24	Disarticulation/	446
25	Amputation/	50788
26	20-25 combined with OR	100428
27	(transfemoral or transtibial or lower limb or lower extremity or knee).tw.	359281
28	exp Leg/	391890
29	27 OR 28	610534
30	26 AND 29	28531
31	19 AND 30	5849
32	Remove duplicates from 31	4288

Table 3.3: Numbers of results from systematic review database search.

GKA and NV independently screened titles and abstracts for inclusion, excluding 3878 as not relevant (25 of which were duplicates not excluded by the automatic system on Ovid), the majority because amputation was discussed as an outcome of other treatment rather than being the subject of the study. This left 410 studies potentially suitable for inclusion, 12 of which were systematic reviews, so useful as a source of additional studies which might have been missed by the search protocol. Thirty-eight more were excluded after review of the full text, leaving 360 studies available for extraction of outcomes. A further 153 studies were identified by screening reference lists. Of these, 63 were excluded after screening abstracts, and a further 10 were excluded after review of the full text, leaving a further 80 studies suitable for extraction of outcomes. A flow chart conforming to the format suggested by PRISMA is shown in Figure 3.1.

3.3.1.2 Included studies

Four-hundred and forty studies from 42 different countries were included in the review. Studies came most frequently from the USA (167 studies) or the United Kingdom (79 studies). Table 3.4 gives a breakdown of the number of studies included from each country. This included sixteen case reports, 292 retrospective case series or cohort studies, 100 prospective cohort studies, two studies which included both prospective and retrospective cohorts, nine non-randomised controlled trials, 20 randomised controlled trials and one qualitative study. The median number of patients included in the studies was 84 (range 1-186338). Three hundred and twenty-three (73.4%) of the studies reported the proportion of male and female patients included. The overall proportion of male patients was 61.2% (243493/397783) in studies where this was reported (range 0-100%). Four hundred and eighteen (95%) studies reported the mean or median age of participants. In those reporting the mean age, the overall mean age was 73.5 years (range 34-93.5 years).

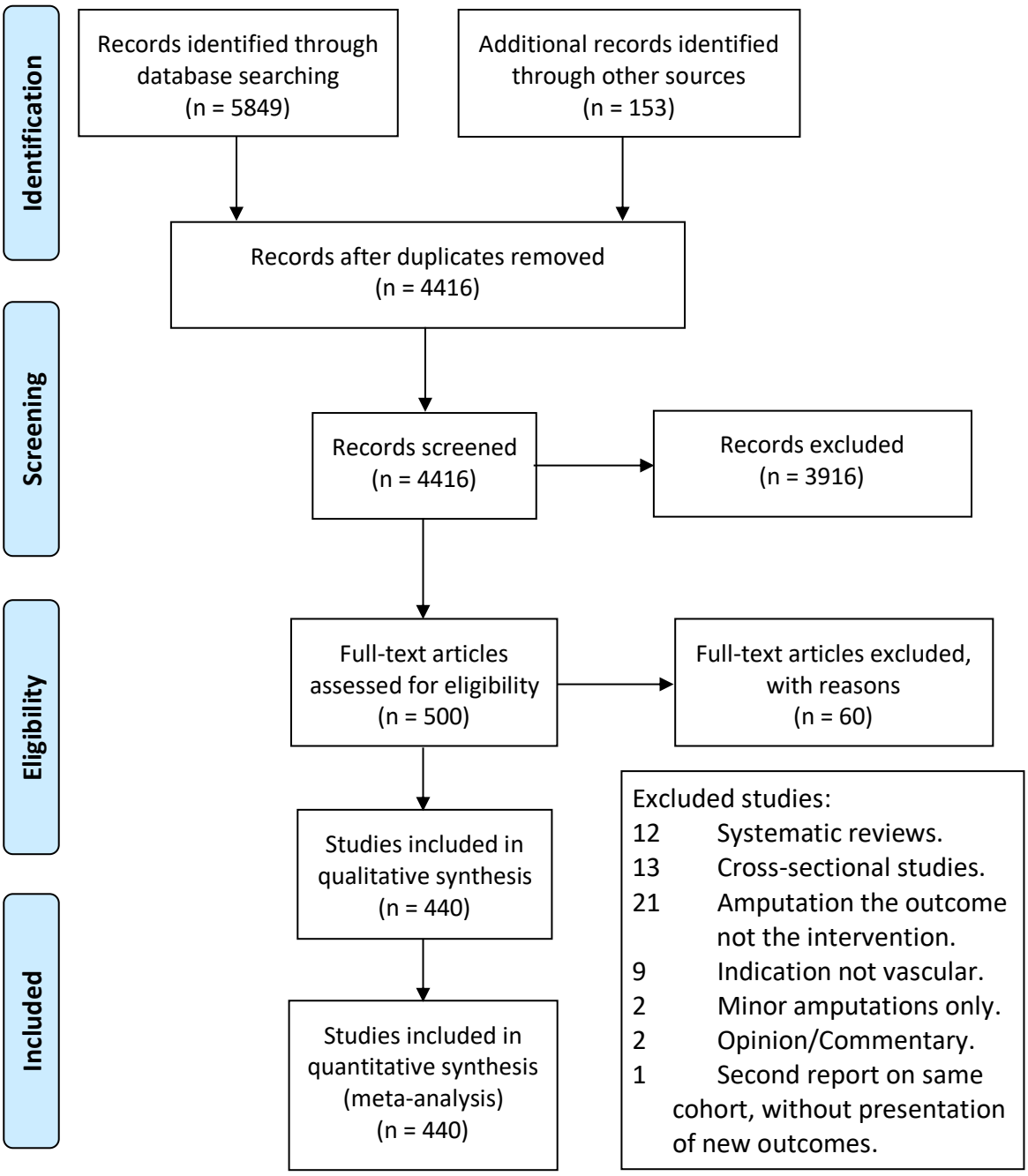

Figure 3.1: Flow diagram of article selection for systematic review.

Country	Number of studies
Argentina	1
Australia	14
Brazil	5
Canada	12
China	4
Croatia	1
Czechoslovakia	3
Denmark	21
Finland	8
France	5
Germany	18
Ghana	1
Greece	1
Hong Kong	1
Hungary	3
Ireland	3
Israel	5
Italy	4
Japan	11
Lebanon	1
Malaysia	1
Netherlands	18
New Zealand	1
Norway	1
Poland	3
Portugal	2
Russia	9
Singapore	4
Slovenia	2

South Africa	3
South Korea	1
Spain	1
Sri Lanka	1
Sweden	9
Switzerland	7
Taiwan	4
Thailand	1
Turkey	2
Ukraine	1
UK	79
USA	167
Uzbekistan	1
Total	**440**

Table 3.4: Country of origin of studies included in the systematic review.

3.3.1.3 Excluded studies

Forty-eight studies were excluded after review of the full text of the paper as it was not possible to assess suitability for inclusion on the basis of the abstract alone. Of these, 13 studies were excluded as they recruited a cross-section of patients who had undergone MLLA at some point in the past, rather than patients who underwent amputation or acute post-amputation rehabilitation, the majority of whom had undergone their amputation several years in the past. A further 21 studies examined predictors of amputation, rather than looking at the outcomes of patients undergoing amputation so reported no outcome measures. Nine studies concerned patients whose amputations were performed for cancer or trauma, not peripheral vascular disease. Two of the studies included only minor amputations at the level of the toes, foot or ankle. Two studies were opinion-based articles which reviewed principles of managing patients requiring amputation and included no patients. Finally, one study

was a second report on the same cohort of patients as another included study and reported no new outcome measures which were not reported in the first study.

3.3.1.4 Extraction of reported outcome measures

Papers found during the search were divided into 10 approximately equal batches for analysis. JARJ and I independently screened and extracted data from the first batch, going through the results and coming to a consensus decision as described in the Methods. Both then screened and extracted from the next batch and compared the number and type of outcome measures. Outcome measures appeared to be similar and calculation of Kendall's τ statistic revealed that the correlation was 0.66 (95% bootstrap confidence interval with 1000 replicates 0.463-0.827) for planned outcomes and 0.57 (95% confidence interval 0.314-0.782) for presented outcomes. As this met the criterion for continued independent extraction, a decision was made to continue extraction independently. Three-hundred and ninety-eight studies were reviewed in this phase, of which 38 were excluded (see Excluded Studies in Section 3.3.1.3 on page 68 above for details). I extracted from a total of seven batches and JARJ extracted from a total of five batches. Following extraction from the studies retrieved from the search, I compiled a list of potential studies from references of included studies and screened and extracted from these additional studies. A further 90 studies were identified in this way, of which 10 were excluded after review of the full text (see Excluded Studies in Section 3.3.1.3 on page 68 above for reasons for exclusion).

The 440 included papers reported 1447 outcome measures, giving an average number of outcomes per study of 3.29. There were 444 discrete outcome measures. The most frequently reported outcome measures were 'mortality' and 'wound healing', which were each reported in 93 studies. Two hundred and eighty-one discrete outcome measures were only reported by a single study. A complete list of the outcome measures reported, along with the frequency of reporting, is given in Table 3.5.

3.3.1.5 Division of outcome measures into main domain and reduction to a list of outcomes

There is considerable overlap across the 444 outcome measures reported in the literature. Some of this relates simply to the use of different synonyms by study authors: for example, 93 study authors reported 'mortality', whereas eight reported 'death'. In addition, some relates to the timing of measurement: there were 46 studies reporting 30-day mortality, six reporting 6-month mortality, eleven reporting 12-month mortality, etc. It is impractical to propose a Delphi survey which asks respondents to rate the relative importance of all 444 of these overlapping and sometimes semantically identical outcome measures, so it is appropriate to reduce them to discrete concepts.

The outcome measures are presented in Table 3.5, classified using the system described by Dodd et al.[68] In addition, as described in the Methods, the outcome measures have been grouped into outcomes. This reduced the list of 444 outcome measures to a list of 48 distinct outcomes. Three of the outcomes were felt not to be relevant to the majority of patients undergoing a major lower limb amputation for complications of peripheral vascular disease so were not taken forward to the Delphi survey. These were 'Problems with transplant in patients with kidney transplants' and 'Transplant rejection in patients with organ transplants', which were eliminated as the vast majority of patients undergoing major lower limb amputation would not have an organ transplant; and 'Peripheral vascular disease', as all patients undergoing a major lower limb amputation for complications of peripheral vascular disease would already have peripheral vascular disease. After removing these three outcomes we were left with 45 outcomes from the systematic review to take forward to the Delphi survey.

Domain 'Death'		
Outcome	**Outcome Measures**	**N**
Death within a specified period of time after operation, or survival time after the operation	6-month mortality	6
	mortality	93
	30-d mortality	46
	Death	8
	inpatient death in rehab	2
	in-hospital mortality	12
	in-hospital death	2
	perioperative mortality	19
	mortality at 3 years	2
	mortality at 5 years	5
	mortality at 12 months	11
	mortality at 3 months	2
	mortality at 2 years	6
	death before discharge	1
	death after discharge	1
	died within 2 years of amputation	1
	postoperative early mortality	1
	postoperative mortality	3
	Early mortality rate (within 14 days)	3
	total mortality	2
	postoperative death	2
	all-cause mortality	1
	8-year mortality	1
	90-day mortality	2
	died within 1 week	1
	died before healing	1
	patient survival at 1 year	1

	1-year survival	3
	5-year survival	1
	2-month survival	1
	24-month survival	1
	3-year survival	1
	survival	63
	long term patient survival	1
	additional amputation free survival	1
	contralateral amputation-free survival	2
Cause of death	cause of death	19
	cause of in-hospital death	1
	mortality from purulent and necrotic complications	1
Domain: Blood and lymphatics		
Outcome	**Measures**	**N**
Bleeding or need for blood transfusion after surgery	blood loss	2
	transfusion	2
	post-operative haemoglobin	3
	bleeding requiring 4 units blood within 72 hours of surgery	1
	haematoma	1
	bleeding complications	2
	haemorrhage	1
	seroma/hematoma	1
	wound bleeding	1
Domain: Cardiac		
Outcome	**Measures**	**N**
Heart related problems during surgery or follow-up	medical stability	1
	cardiac arrhythmias	3
	cardiac event	1

	heart complications	1
	cardiac complications	2
	cardiac arrest	2
	angina	1
	ECG changes	1
	resting heart rate, HRmax, %predicted HRmax, BPmax, Artificial oxygen saturation	1
	MI	15
	MI within 1 year	1
	Late MI	1
	time to readmission with acute coronary syndrome	1
	CK-B level	1
	congestive heart failure	3
Domain: Endocrine		
Outcome	**Measures**	**N**
Problems related to control of diabetes during surgery or follow-up	diabetic complications	1
Domain: Gastrointestinal		
Outcome	**Measures**	**N**
Nausea	nausea	1
	post-operative antiemetic use	1
Upper gastrointestinal tract problems	perforated duodenal ulcer	1
Constipation*	GI tract complications	1
Domain: General		
Outcome	**Measures**	**N**
	pain characterization and intensity over time	1

	highest pain score for 6 postoperative days	1
	pain intensity/frequency	1
	Successful pain control	1
	perioperative pain scores	1
	average pain scores per day	1
	post-operative pain	3
	Post-amputation chronic pain	2
	pain at 6 months	2
	pain intensity in first 24 hours	1
	pain at 3 months	1
	post-operative wound pain intensity	1
	prolonged limb pain	1
	chronic stump pain	2
Pain in residual	stump pain	9
limb/amputation stump	stump pain in first 30 days, at 3 months and at 6 months	1
	effective pain relief	1
	McGill Pain Questionnaire at 6 months	2
	Pain at 3-6 months	1
	stump allodynia	2
	Pain threshold	2
	Satisfaction with treatment of pain	1
	stump pain at 12 months	2
	VAS on days 1 and 3	1
	96-hour mean NRS pain score	1
	temporal summation of pain	1
	mean VAS intensity of stump and phantom pain after 1 week and 3, 6 and 12 months	1
	NRS pain score in first 3 days	1

	McGill Pain Questionnaire at 8 days, 6 weeks and 3 months	1
	Neuropathic Pain Scale	1
	Quantitative sensory testing	1
	reflex sympathetic dystrophy in stump	1
	nerve complications	1
Domain: Immune system		
Outcome	**Measures**	**N**
Transplant rejection in patients with organ transplants	biopsy-proven acute rejection	1
Domain: Injury/poisoning		
Outcome	**Measures**	**N**
Falls	Falls	1
Domain: Metabolism/nutrition		
Outcome	**Measures**	**N**
Nutritional status (weight loss, malnourishment, obesity, etc.)	BMI	1
Domain: MSK/connective tissue		
Outcome	**Measures**	**N**
Joint contractures	Contracture of knee joint	1
	flexion contractures	1
	Frequency and degree of contractures	1
Domain: Nervous system		
Outcome	**Measures**	**N**
Effectiveness of pain relief	Successful surgery after peripheral nerve blockade	9
	onset time of nerve block	1

	analgesic time from beginning of block	1
	Duration of analgesia	1
	block related complications	1
	time until first analgesia	1
	paresthesia and injection pain during injection	1
	pain relief with peripheral block	1
	intraoperative pain in the sciatic nerve distribution	1
	PCA prescriptions	1
	opioid consumption	5
	total morphine equivalents per day	1
	Morphine equivalents in first 72 hours	1
	post-operative opioid requirement	1
	amount of narcotics used for pain relief post-operatively	1
	need for narcotic analgesics	1
	morphine requirements	1
	opioid consumption in first 3 postoperative days	1
	Morphine equivalents on days 1 and 3	1
	opioid consumption at 30 days and 6 months	1
	oxycodone use in first 3 days	1
	analgesic medications	1
	NSAID consumption	1
	duration and dosage of ketamine	1
	amitriptyline prescription	1
Phantom sensations or pain	phantom limb pain	15
	postoperative phantom pain intensity	1
	phantom pain at 1 year	1
	Sherman's phantom limb questionnaire	1
	phantom limb sensation	5

	phantom limb sensation in first 3 postoperative days, at 6 months and at 12 months	1
	kinetic sensations, kinesthetic sensation, exteroceptive sensations, super-added sensations, all at 6 months	1
Stroke	stroke	13
	haemorrhagic stroke rate	1
	Stroke within 1 year	1
	Late stroke	1
	CVA	1
	coma 24 hours	1
Domain: Renal/urinary		
Outcome	**Measures**	**N**
Problems with kidneys	acute renal failure	6
	creatinine level	1
	renal insufficiency	1
	renal complications	1
	new onset dialysis	2
	renal/urological complications	1
Problems with urinary tract	urinary retention	1
	urinary tract infection	4
Problems with transplant in patients with kidney transplants	Delayed renal graft function	1
	primary nonfunction	1
	graft loss	1
	long term graft survival	1
Domain: Psychiatric		
Outcome	**Measures**	**N**
Drowsiness	sedation	2
	mean sedation score over first 96 hours	1
	sedation on a 1-5 NRS in first 3 days	1

Anxiety or depression	Rate of suicidal ideation	1
	PHQ-9	1
	depression at 6 months	1
	low mental health at 6 months	1
	Beck Depression Inventory while inpatient, in rehab, and after discharge from rehab	1
	Hospital Anxiety and Depression Score	1
Domain: Respiratory/thoracic/mediastinal		
Outcome	**Measures**	**N**
Pneumonia	pneumonia	11
Breathing problems	post-op ventilatory support	1
	respiratory/pulmonary complications	2
	re-intubation	1
	ventilator dependence	1
	pneumothorax	1
	aspiration	1
	Prolonged mechanical ventilation requiring tracheostomy	1
	unplanned intubation for respiratory/cardiac failure	1
	prolonged intubation (48 hours)	1
Domain: Skin/subcutaneous tissue		
Outcome	**Measures**	**N**
Problems with amputation stump healing	skin irritation at 6 months	1
	wounds from prosthesis use at 6 months	1
	Stump irritation	1
	requirement for skin graft	1
	skin maceration	1
	Stump defects and type	1
	pressure sore incidence	2

	decubitus ulcer	1
	stump related complications	1
	Wound occurrence	2
	wound complications	15
	local wound complications	2
	soft tissue complications	1
	resting TcpO2 post therapy	1
	leg oedema	1
	Stump volume reduction	1
	synovial effusion	2
	wound dehiscence	2
	Postoperative stump necrosis	4
	Wound healing	93
	primary healing rate	6
	healing rate	1
	time to wound healing	6
	mode of wound healing	1
	stump healing	8
	Delayed wound healing	4
	failed primary healing	2
	failure to heal	1
	secondary healing	1
	healing after revision	1
	healing after re-amputation to AKA	1
	not healed at follow-up	1
Stump wound infection	surgical site infection	1
	Wound infection	15
	Superficial wound infection	1
	deep wound infection	1

	stump infection	3
	wound infection requiring reoperation	1
	sepsis	5
	fever	1
	Expression of CD3, 4, 8, 19, 25, 69, IFNgamma, IL-4, phagocytosis burst capacity, oxidative burst capacity	1
	Lipid peroxidation processes	1
Domain: Vascular		
Outcome	**Measures**	**N**
Blood clots in deep veins or lungs (venous thromboembolism)	VTE (DVT/PE)	7
	PE	8
	DVT requiring therapy	1
	DVT	6
	ipsilateral DVT	1
	contralateral DVT	1
	VTE at 14 days and in first 8 weeks	1
Peripheral vascular disease	peripheral vascular disease	1
Physical		
Outcome	**Measures**	**N**
Patients supplied with a temporary or definitive prosthetic limb	successful fitting with prosthesis	66
	prosthetic prescription rate	5
	rate of prosthetic fitting at 1 year	1
	prosthetic device acquisition	1
	Prosthetic prescription within 1 year of amputation	2
	progress to definitive prosthesis	1
	unsuitable for prosthesis	1
	referral for prosthetic rehabilitation	1
	use of prosthesis on discharge	1

Prosthetic limb use, comfort and fitting	prosthetic use at 12 months	3
	Rates of abandoning prosthesis use	3
	prosthetic use at 6 months	3
	prosthetic use at 6 weeks and 4 months	1
	self-reported hours of prosthetic use at 6 months	1
	Achievement of prosthetic use	5
	Daily hours of prosthetic use	1
	prosthetic use at follow-up	5
	Daily hours of prosthetic wear at 12, 18 and 24 months	1
	Prosthetic wearing at follow-up	1
	Houghton score of prosthetic use	1
	prosthesis comfort at 6 months	1
	need for socket changes	1
	COP (Centre of pressure) trajectories and time functions	1
	distribution of reaction forces between the two legs	1
	inclination angles obtained through second order regression analysis using stabilogram data	1
	cadence	1
	velocity	1
	step time	1
	step length	1
Level of independent mobility or function achieved (may include use of mobility aids)	Prosthetic Limb Users Survey of Mobility (PLUS-M)	1
	prosthesis evaluation questionnaire-mobility section	1
	walking in prosthesis at 6 weeks, 4 months and 12 months	1
	function with a prosthesis at 1 year	2
	Independent fitting of prosthesis	1
	prosthetic restoration	1
	mobility with temporary prosthesis	1

	walking with pneumatic walking aid	1
	Locomotor Capabilities Index 5-level scale at 12 months	7
	Functional Independence Measure (FIM) total score	5
	FIM-M score	2
	LCI-5 at 6 weeks & 4 months	1
	ability to use parallel bars/walkers/crutches on discharge	1
	Ambulation	2
	K-levels	1
	2-minute walk	3
	timed up and go at 6 months	4
	5-metre gait speed	1
	patient-specific functional scale	1
	Groningen activity restriction scale at 12 months	2
	appearance and gait at 6 months	1
	Minimum Data Set Activities of Daily Living Long Form Score	1
	discharge functional status	4
	Mobility in the home at discharge from rehab	2
	independent walking/ambulation	3
	return to pre-morbid functional status	1
	Special Interest Group in Amputee Medicine (SIGAM) mobility grade at 6 months	3
	Functional independence while inpatient and in rehab	1
	Functional independence after discharge from rehab	2
	LCI while inpatient and in rehab	1
	LCI after discharge from rehab	2
	LCI at 6 months	2
	mobilized without crutches	1

	timed up and go at 12 months	1
	Barthel Index effectiveness at discharge	3
	mobility at 1 year	2
	maintenance of ambulation	4
	functional measure for amputees at 1 and 6 months	1
	LCI at 1 month	1
	Satisfactory ambulation measured by the Walking Ability Index	2
	rehabilitation success	11
	locomotor performance after prosthesising	1
	mobility unaided without wheelchair	1
	functional ambulation level	7
	Independent mobility with prosthesis	1
	mobility level	16
	Walking speed	2
	mobility with prosthesis	11
	rehabilitation status	1
	rehabilitation outcome	4
	successful maintained level of rehab at follow-up	1
	Distance walked	2
	functional outcome	2
	mobility score	1
	successful ambulation with prosthesis	6
	independence of ADL	1
	mobility aids used at follow-up	2
	degree of rehabilitation	6
	wheelchair use (dependence)	2
	method of ambulation at discharge	1
	means of ambulation	1

	walking ability at follow-up	3
	satisfactory walking results	1
	functional independence at 1 year	1
	functional activity level at 12, 18 and 24 months	1
	Stanmore Harold Wood Mobility Grade	1
	rehabilitation accomplishments	1
	Mobility at 6 months	2
	improvement of physical function at rehabilitation discharge	1
	10 metre walk velocity	1
	prosthetic gait (mobile in or outdoors with prosthesis)	1
	Rivermead mobility index	1
	walking aids used on discharge	5
	need for mobility aids at 6 months	1
	use of early walking aids	1
	use of mobility aids at 12, 18 and 24 months	1
Development of problems with the other leg	major amputation of the contralateral lower limb	15
	contralateral limb preservation	2
	time to contralateral amputation	1
	contralateral limb survival	1
Domain: Social		
Outcome	**Measures**	**N**
Participation in work and social activities	effect on home and work capacity	1
	return to work	1
	Reintegration into Normal Living (RNLI)	1
	community participation at 12 months	1
	social integration at 12 months	1
	low social functioning at 6 months	1
Sexual activity	self-reported frequency of sexual activity	1

	desire for sexual activity	1
	importance of sexual activity to satisfaction with life	1
Domain: Rôle		
Outcome	**Measures**	**N**
Independent living	independence	2
	maintenance of independent living	6
	independent living status	1
	Experiences of living with an amputation	1
	discharge supports	2
	home care arrangements	1
	social service use	1
	discharge with assistance	1
Psychological/wellbeing		
Outcome	**Measures**	**N**
Coping strategies and psychological adaptation		
	Coping Strategies Questionnaire at 6 months	1
	Psychological adaptation to limb loss	2
	low emotional functioning at 6 months	1
Domain: Cognitive		
Outcome	**Measures**	**N**
Cognitive function or confusion	Digit span	1
	list learning	1
	list recall	1
	semantic fluency	1
	short portable mental status questionnaire	1
	right-left foot recognition	1
	delirium	1
Domain: Global Quality of Life		
Outcome	**Measures**	**N**

Quality of life	quality of life	3
	EQ5D	1
	SF-36 Subscales	2
	SIP-68	1
Domain: Perceived Health Status		
Outcome	**Measures**	**N**
Satisfaction with health status	Satisfaction with mobility at 12 months	1
	Satisfaction with life at 12 months	1
	Body Image Questionnaire while inpatient, in rehab, and after discharge from rehab	1
Domain: Personal circumstances		
Outcome	**Measures**	**N**
Residential status	discharge home	3
	discharge to independent living	2
	ultimately returned home	1
	living environment	1
	proportion returned to previous living conditions at 1 year	1
	discharge destination	16
	change of residence	1
	discharge disposition	3
	discharge setting	1
	discharge placement	1
	disposition of patients	1
	residential status at discharge	1
	discharge to nursing home care	1
	institutionalization	1
Economic		
Outcome	**Measures**	**N**

Cost of treatment	resource utilization	1
	acute medical costs	1
	postacute medical costs	1
	hospital charges	2
	expenses	1
	hospital costs	1
	cost analysis	1
	financial burden of prosthesis	1
	rehabilitation charges	1
	Number and class of hypertension medications	1
Hospital use		
Outcome	**Measures**	**N**
Time in operating suite	operative time	2
	time in the recovery room	1
Time taken to complete rehabilitation	Duration required to complete rehabilitation	6
	number and duration of physio treatments during early walking aid/prosthesis use	1
	time until definitive prosthesis	5
	initial prosthetic casting	1
	time to prosthetic fitting	4
	time to reach prosthetic casting	1
	readiness for prosthetic fitting	1
	rate of progression through temporary prostheses	1
	time to walking with prosthesis	2
	time to temporary prosthetic fitting	1
	days until patella tendon bearing cast	1
	weeks to achieve maximum benefit	2
	time to mobilisation	2
	LOS in ITU	1

Length of time in intensive care/acute hospital/rehabilitation	LOS	51
	rehabilitation LOS	11
	total hospital stay	1
	time to discharge	1
	admission to HDU/ICU	1
	prolonged hospital stay	1
Need for re-admission to hospital after discharge	Occurrence of transfer back to acute service	1
	proportion having readmission	4
Compliance with guidelines for care	QIF compliance	1
	use of compression therapy	1
Domain: Need for further intervention		
Outcome	**Measures**	**N**
Need for additional operations	additional amputation rate	3
	stump revision rate	9
	Revision to AKA	24
	Ipsilateral reamputation	1
	Revision at same level	1
	revision at more proximal level	3
	time from amputation to revision	1
	need for surgical revision	1
	reamputation rate	40
	reamputation level	1
	reamputation timing	1
	reamputation at 12 months	1
	late revision or reamputation	1
	final amputation level	3
	revision rate	26
	reamputation/revision to higher level	12

	revision or reamputation within 30 days	2
	debridement of stump	1
	further procedures	1
Domain: Adverse events/effects		
Outcome	**Measures**	**N**
Side effects of medication	side effect occurrences	1
Overall perioperative complications	Perioperative systemic complications	4
	morbidity	3
	cardiorespiratory complications	1
	postoperative complications	4
	major morbidity	1

*Table 3.5: Outcomes from the systematic review, grouped into the Domains recommended by Dodd et al.[68] N: Number of times reported. *Constipation was an outcome raised in focus groups. While not directly measured by any of the studies, it can be considered a 'GI tract complication', which is why it appears in this table. Prior to incorporating insights from the focus groups, we had a single GI tract complication outcome from the systematic review, but due to the importance placed on this outcome by focus group participants we split this into 'upper gastrointestinal tract problems' and 'constipation'. Outcomes in red were felt not to be relevant to a core outcome set for patients undergoing MLLA for complications of peripheral vascular disease so were excluded from the Delphi. Some of the outcomes were difficult to categorise or could be put into several categories. For these outcomes we checked that all of the alternative categories were also included in the Delphi. The classification was approved at formal trial management group meetings.*

3.3.2 Phase II: Qualitative focus groups

The focus groups took place on 15th September (Mixed healthcare professionals; group 1), 28th September (patients and carers; group 2) and 6th October 2017 (doctors; group 3). A further interview with two physiotherapists specialising in the care and rehabilitation of amputee patients took place on 1st December 2017 (group 4), as it was felt to be important to get input from physiotherapists and none of the invited physiotherapists was able to make it to any of the focus groups.

3.3.2.1 Focus group participants

A list of the professions/specialties invited, along with those who agreed to attend and those who actually did attend is given in Table 3.6.

Profession/specialty	Number invited	Number accepted invitation	Number attended
Doctors			
Anaesthetists	1	1	1
Vascular surgeons	4	3	2
Orthopaedic surgeons	2	0	0
Diabetologists	1	1	1
Wound care specialists	1	0	0
Rehabilitation physicians	4	1	0
GP (special interest in rehabilitation)	1	1	1
Subtotal	**14**	**7**	**5**

Nurses			
Vascular specialist nurse	2	2	1
Vascular care practitioner	1	1	1
Pain specialist nurse	1	1	1
Rehabilitation specialist nurse	1	1	0
Tissue viability specialist nurse	1	0	0
Community nurse	3	0	0
Operating theatre nurse	2	1	0
Vascular ward nurse	2	1	1
Subtotal	**13**	**7**	**4**
Allied health professionals			
Physiotherapist	2	2	0
Occupational therapist	1	1	1
Dietician	2	0	0
Podiatrist	2	2	2
Clinical psychologist	1	1	1
Prosthetist	2	2	2
Operating department practitioner	2	1	0
Subtotal	**12**	**9**	**6**
Total	**39**	**23**	**15**

Table 3.6: Focus group participants: healthcare professionals.

One non-medically trained healthcare professional (the clinical psychologist) attended the focus group intended for medically trained healthcare professionals. No medically trained healthcare professional attended the focus group intended for non-medically trained healthcare professionals.

In addition to the patients and carers whose invitation I described above, I also invited one individual who was known to the study team owing to her participation as lay representative on the PLACEMENT trial management group, whose father had had a major limb amputation. There were 10 unilateral and 6 bilateral amputee patients. Of the unilateral amputee patients, seven had below the knee amputation and three had above knee amputations. Of the bilateral amputee patients, three had bilateral above knee amputations, one had bilateral below knee amputations and the other two had one below and one above knee amputation. Eleven male and five female amputee patients were invited. Five amputee patients and five carers agreed to participate, and three amputee patients and three carers actually attended. Of the three amputee patients who attended, one (female) had a unilateral below knee amputation, one (male) had bilateral below knee amputations and one (male) had one below knee and one above knee amputation. The three carers who attended all cared for people with above knee amputation, none of whom attended the focus group.

3.3.2.2 Thematic framework

The qualitative researcher (LB-H) developed a thematic framework from analysis of the three focus groups and the additional interview (described collectively as 'groups' below). This revealed 19 themes which were covered in the discussions. Some themes were only raised in one of the four groups, some in two, some in three and some in all four. The full framework is presented in Appendix A, and the themes are discussed below.

1. Quality of life

   This theme was discussed in groups 1, 2 and 3. All three groups touched on issues of functional independence here. Group 3 also related it to issues of body image and comfort. Group 1 also discussed the way social functioning related to quality of life, highlighting the difficulty of separating different themes.
2. Social functioning

   This theme was discussed extensively by all groups. There was much discussion of goal setting in this context, and the satisfaction associated with successful return

to pre-morbid levels in relation to activities such as being able to go to the toilet without assistance or go and get a glass of water. Hobbies, holidays and family life were discussed, as was the importance of the social support network and the strain which amputation placed on relationships, with one amputee patient remarking 'I wasn't a nice person to know' when discussing the early period following amputation. Group 1 also discussed the importance of sexual activity, but only after seeing this item in the results of the systematic review.

3. Psychological and biopsychosocial factors.

   This theme was again discussed by all groups. Groups 1 and 3 discussed managing patient and carer expectations and helping them to know what to expect from rehabilitation, as well as the importance of psychological support. Both negative (grief, anger, regret, guilt, fear for the future, anxiety and depression to name a few) and positive (hope, elation, self-belief, confidence) factors were discussed by groups 1, 2 and 4.

4. Illness representations.

   These were covered by groups 1, 2 and 3. Patient beliefs around what had happened to them were explored, including the positive experiences of no longer having to deal with a smelly chronic wound, or chronic pain, with some amputee patients wishing they had had their amputation earlier. Negatives such as the question of whether the amputation could have been avoided and being treated like ''an invalid'' and dealing with other people's reactions and stigma were also discussed.

5. Communication.

   This was discussed by all groups. The importance of the communication relationship, both between the patient and the care team and also within the care team, was highlighted in terms of shared decision-making, ensuring that everyone was working towards common goals and also the continuity of care.

6. Financial issues.

   Group 3 discussed return to work and the impact that this might have on financial issues as well as the consequence that this might have on mood and

independence. Groups 1 and 2 discussed the negative aspects of patients possibly losing their home and the costs of adapting the home.

7. Amputation type.

   Groups 1 and 3 discussed technical aspects of amputation type and the impact that this might have on prosthetic fitting and function. These issues were not discussed by the patients and carers group or the amputee physiotherapists.

8. Wound healing.

   Groups 1 and 4 discussed delayed wound healing, healing of the deep or superficial tissues, scarring and removal of sutures.

9. Pain.

   This was discussed by all groups. It is possible that this was discussed disproportionately as the PLACEMENT trial, which looked at an intervention designed to reduce postoperative pain in amputee patients, was ongoing at the time of the focus groups and some of the participants were involved in the running of this trial. Outcomes discussed included the level of severity of the pain, pain in the residual limb, phantom limb pain, chronicity of pain, medication use to control pain and the use of additional, unprescribed things to control pain, such as cannabis, massage or mirror box therapy.

10. Rehabilitation.

    This was discussed by groups 1, 3 and 4. Issues around realistic goal setting, time out of bed, the importance of peer support and relationship building (continuity of care) were raised within this context.

11. Prosthesis.

    Issues related to prosthesis fitting or function were discussed by all groups, including issues related to comfort, look, function and satisfaction as well as issues related to equipment such as the supply of suitable footwear, early walking aids and walking frames. Goal setting was again discussed in this context.

12. Mobility aids other than prosthesis.

    Supply of equipment to facilitate independence was discussed by all groups. This included wheelchairs, shower adaptations, beds and walking frames.

13. Returning home.

    Groups 1 and 3 discussed the barriers to getting patients home when they were medically fit for discharge. This again included supply of appropriate equipment but also the management of wounds as an outpatient.

14. Falls.

    Patients and carers (group 2) also discussed the problems with falling, which was recognised to be a common problem among amputee patients, both because of problems with balance and also simply because patients sometimes forget that their leg is no longer there and try to stand on it.

15. Readmissions.

    Groups 1 and 3 discussed the problem of readmissions, both because of problems with the residual limb (amputation stump) and also for other reasons, as this patient cohort are often highly co-morbid.

16. Clinical state compared to pre-operative state.

    This theme was discussed by all groups. Groups 1, 2 and 3 discussed the fact that patients may be in a better state after surgery than before, as they may have been septic or in chronic pain. Patients also reflected on the fact that without their amputation they might not be alive anymore. All groups reflected on the fact that the period leading up the amputation was often long and so often patients were quite 'de-conditioned' (the phrase used in multiple groups, meaning that individuals had lost muscle mass due to immobility due to problems with their limb) by the time they had their amputation. This, together with comorbidities often led to quite a prolonged rehabilitation phase afterwards. Group 4 also mentioned that the extra energy and co-ordination required to mobilise after amputation could unmask problems which had previously been hidden such as the impact of stroke or cognitive impairment or could trigger other problems such as heart attacks due to the increased strain.

17. Fate of the other limb.

    This was discussed by groups 1, 3 and 4. The risk to the other limb of decubitus ulcers and disease progression which could lead to amputation of the other limb

was considered important. Additional strain on the contralateral hip and knee were also discussed.

18. Risk reduction behaviour.
    Groups 3 and 4 discussed the importance and impact of smoking cessation, diabetic control, drug abuse and homelessness on amputee patients and their rehabilitation.
19. Mortality.
    Group 3 discussed the importance of mortality as an outcome as it was recognised that many amputee patients do not live a year after amputation.

3.3.2.3 Conversion of the thematic framework from focus groups into outcomes

The thematic framework developed by LB-H, the study qualitative researcher, was reviewed and I converted the themes into outcomes to line-up with those developed in the systematic review. I presented these to the PLACEMENT Trial Management Group via email and discussed face-to-face at a meeting in order to get consensus on how best to translate these into meaningful outcomes. Most themes were felt to have already been covered by outcomes from the systematic review, but there were four themes which were felt not to have been covered by the outcomes from the systematic review. One of these themes (communication) was felt to be broad enough that two additional outcomes needed to be defined. Table 3.7 presents these additional themes and the outcomes derived from them.

For the purpose of keeping similar outcomes together in the Delphi survey, these five additional outcomes were also grouped using the Domains of Dodd et al.[68] Impact on family/loved ones was placed into the 'Social' domain, Shared decision making and Communication between healthcare team and patient/carers were placed into the

'Delivery of Care' domain, Use of drugs or therapies which have not been prescribed was placed into the 'Need for further intervention' domain and Number of outpatient appointments was placed into the 'Hospital use' domain.

Theme	**Suggested sub-themes**	**Comments**	**Outcomes**
Psychological/ biopsychosocial factors	3.5 Family perspective	• How will family cope	Impact on family/loved ones
Communication	5.1 Patient and health professional communication	• In terms of patient: being listened to, involved in decision making, given opportunity to ask questions, interaction with surgical team, being 'understood' and understanding what was going to happen, empowering patient • Individual patient goal setting (theory of care owners' model) • Terminology - asking the patient what they want to call the residual limb • Empathy from health care professionals	Shared decision making. Effective communication between healthcare team and patient/carers

		• Continuity of care ('knowing' the patient) • Will depend on whether elective vascular or orthopaedeic patient	
Pain	9.11 Pain management: non-medication	• Are patients supplementing due to pain (e.g. cannabis use) • Other ways of handling pain e.g. handling techniques, massage, laser or mirror box therapy	Use of drugs or therapies which have not been prescribed
Readmissions	15.2 Reduction in other hospital visits	• Difficult having to go to so many different appointments	Number of outpatient appointments

Table 3.7: Additional outcomes derived from focus groups. Blue text: themes discussed in the mixed healthcare professionals focus group; red text: themes discussed in the patients and carers focus group; black text: themes discussed in the medically trained healthcare professionals focus group; red text: themes discussed in the patients and carers focus group; black text: themes discussed in the medically trained healthcare professionals focus group; green text: themes discussed in the physiotherapists group.

3.4 Discussion

Both systematic review and qualitative research have revealed a large number of outcomes facing patients undergoing amputation as a consequence of peripheral vascular disease. Many of these overlap to a large degree, but it is interesting to reflect on the fact that some of the themes discussed in the focus groups, such as the problems with

communication (for example shared decision-making) have not been the subject of significant research within the scientific literature for this patient cohort.

This finding, where qualitative research reveals outcomes of importance to patients which have received little attention previously in the research literature, has previously been reported by Sanderson et al. in other work on core outcome sets.[74] The work of Sanderson et al. highlighted the importance of involving patient stakeholders in the development of a long-list of potential core outcomes. The importance of shared decision-making, however, was highlighted in all of the focus groups, so this was clearly recognised as important by a diverse group of both patients and healthcare professionals, despite having failed to appear in the results of the systematic review. This may reflect the under-researched nature of major lower limb amputation or may reflect the fact that searching the scientific literature is not sufficient even to develop a list of outcomes which healthcare professionals will recognise as complete.

One of the strengths of this work is the mixed methods approach I adopted, with quantitative research in the form of a systematic review being complemented by qualitative research to develop a full appreciation of the breadth of issues which are important to a patient cohort. This benefits from the advantages of both approaches to developing a long-list of outcomes, so is less likely to miss out factors which could take on an important rôle in the later phases of core outcome set development. The principal disadvantage of this approach is that it does add considerable work to the process, as both the systematic review and the organisation, running and analysis of focus groups are lengthy processes. Not only this, but after both are complete there is then a requirement to combine the results into a single list of topics for the subsequent consensus survey.

The large list of distinct outcome measures obtained from the systematic review highlights the fact that research in this area has historically been highly inefficient in two respects. Firstly, it is not likely that all of the outcomes underlying these outcome measures would be considered core by patients, carers and healthcare professionals. It would be more efficient to direct work mainly towards the outcomes which matter the

most. Secondly, as there is such a diverse range of outcome measures, it is difficult to pool the results of multiple studies to compare and contrast the effects of different risk factors or interventions.

It could be argued that one could dispense with the systematic review phase when developing a long-list. Our systematic review revealed 444 outcome measures, across 26 different domains. While the approach of dispensing with the systematic review has been adopted by some core outcome set developers, I believe that it is unlikely that a small number of focus groups would capture the full breadth of possible outcomes encountered in a full systematic review. One example of this is the fact that sexual activity was only discussed in one of the focus groups, and this only happened in the final phase of the focus group upon reviewing the results of the systematic review.

I have developed a long-list of outcomes from our systematic review, and a further collection of themes from stakeholder focus groups. The next steps for developing core outcome sets now involve identification of the most important outcomes from the combined list of outcomes I have identified. There are two further stages necessary for the completion of core outcome sets. The first is to perform a multi-round consensus survey involving a broad pool of stakeholders. Secondly, I need to ratify the results of the consensus survey at a multi-stakeholder face-to-face meeting. These steps will be discussed in the next chapter.

4 Development of core outcome sets for people undergoing major lower limb amputation for complications of peripheral vascular disease. Part 2: Delphi and face to face consensus meeting

4.1 Introduction

In this chapter I describe a Delphi consensus survey and present the results of a face-to-face meeting where consensus was established on the final core outcome sets.

My objective was to establish consensus on the most important outcomes for studies focussed on short-term or medium-term outcomes through a three-round Delphi process, followed by a consensus meeting to ratify the results of the Delphi survey and address any perceived deficiencies in the outcomes rated as core by this process.

4.2 Methods

4.2.1 Delphi survey

Following synthesis of results from the systematic review and qualitative focus groups, stakeholders (patients, carers and health and social care workers) were surveyed to

determine which outcomes should comprise the core outcome set for studies of lower limb amputation for Peripheral Arterial Disease. All individuals who participated in focus groups were invited to take part in the survey, as were all patients recruited in the PLACEMENT trial who had agreed to be contacted for this purpose. Several amputee patients who the team came across during routine clinical practice were also invited. Amputee patients were also encouraged to ask their carers to participate. In addition, the survey was advertised via multiple national and international groups including the Vascular Society of Great Britain and Ireland, the British Society for Endovascular Therapy, the European Society for Vascular Surgery Vascunet collaboration, the British Association of Chartered Physiotherapists in Amputee Rehabilitation, the Douglas Bader foundation and Blesma (the limbless veterans charity).

The survey was a three-round Delphi consensus process and used the DelphiManager software from Liverpool University. This was supplemented with paper surveys for several amputee patients who said that they would prefer to complete a paper survey.

There is little consensus on how to conduct a Delphi process. Firstly, I had to decide on the method by which outcomes are either rated or ranked. As discussed in the COMET handbook,[69] the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group recommend a 9-point Likert-like scale, with 1-3 categories, with 7-9 labelled as “essential” (must be reported in all trials), 4-6 as “desirable”, and 1-3 as “not important”. I chose this system as while some others have used alternative scales, such as a 5-point scale,[80] this seems to be the most common approach, and is easily implemented with the DelphiManager software. Stakeholders were also allowed to rate outcomes

'unable to score' if they felt that they did not have the experience or understanding to rate an outcome.

There is no clear consensus on the way in which items are added or removed between rounds, or on the definition of 'consensus'. Diamond et al. performed a systematic review of Delphi processes, selecting a sample of 100 Delphi processes to examine the issue of defining consensus.[81] Of these, 98 purported to be attempting to establish consensus, but consensus was only defined in 72 of these, of which only 43 defined it *a priori*. The most common way of defining consensus was by the percentage of respondents agreeing, and the median threshold for agreement was 75%. The second commonest was a measure of central tendency, such as the mean or median score. I therefore decided to use 'over 75% of respondents scoring 7-9' as the definition of consensus that the outcome was 'core' in the final round of the survey.

There is some debate about the appropriateness of dropping items between Delphi rounds. The COMET handbook presents both sides of the argument,[69] suggesting that where items are dropped between rounds there is likely to be less survey attrition, but that this runs the risk of eliminating items which might have gained more support in later rounds due to between-round feedback. In order to attempt to tread the middle ground here, I decided to use a less stringent criterion to remove items between rounds. This would hopefully therefore reduce survey fatigue by shortening subsequent survey rounds, while also reducing the risk of dropping important outcomes due to ill-considered responses in early rounds.

Outcomes not achieving a mean score of greater than 6 by the respondents in round 1 were therefore eliminated. Respondents were also given the opportunity to propose outcomes that they felt were essential but had been excluded from the first round. These proposed outcomes were reviewed by the study management group and any outcomes which were significantly different from outcomes already due to be ranked in round 2 were added to the list.

In the second round, stakeholders were again asked to rate the putative outcomes as essential (7-9), desirable (4-6) or not important (1-3). Stakeholders were given feedback at this stage in the form of a prompt highlighting the score they gave the outcome in the previous round, and histograms showing how other respondents had rated the outcomes. Two histograms were displayed, one showing how healthcare professionals had rated the outcome, and one showing how patients and carers had rated the outcome.

Outcomes not achieving a mean score of at least 7 in the second round were eliminated (a more stringent requirement than that used in round 1, but less stringent than requiring over 75% of respondents rating the outcome 7-9). The process then proceeded to a third round of voting.

In the third round, stakeholders were again asked to rate the putative outcome measures as essential (7-9), desirable (4-6) or not important (1-3), and feedback on ratings from the previous round was given. Outcomes voted 'essential' (7-9) by over 75% of the respondents in this final round were considered 'core'.

At each stage, participants were asked to rate outcomes separately for short-term and medium-term studies. This is because it was recognised that some outcomes may be considered more or less important depending upon the timing of the study. For example, stakeholders might consider the rate of post-operative pneumonia very important for short term studies but less important for medium term studies, whereas the rate of prosthetic limb prescription might be considered very important for medium term studies but less important for short term studies.

4.2.2 Face-to-face consensus meeting

The ultimate goal of this research was to define core sets of short and medium-term outcomes for reporting by research studies on patients undergoing major lower limb amputation for peripheral vascular disease. The results of the consensus survey were therefore discussed at a face-to-face meeting of key stakeholders and a nominal group technique applied to rank a list of short-term outcomes and a second list of medium-term outcomes which would represent the core outcome sets. Stakeholders included members of the PLACEMENT Trial Management Group, along with individuals from professions or specialties not represented by the Group, who participated in the focus groups in phase II.

I invited stakeholders from the following groups:

1. Patients
2. Carers
3. Nursing

4. Surgery
5. Anaesthetics/Pain Medicine
6. Medicine (rehabilitation, diabetes, care of the elderly)
7. Physiotherapy
8. Occupational therapy
9. Prosthetics
10. Clinical psychology
11. Trials management

Participants from all professional stakeholder groups agreed to attend the meeting. I invited eight amputee patients as previous experience had led me to believe that it would be difficult to get engagement from patients. Five amputee patients and one carer agreed to attend.

A Nominal Group technique was used rather than a straightforward vote to either accept or reject the results of the consensus survey because of the risk that by choosing somewhat arbitrary levels at which to eliminate outcomes during the Delphi process, it was possible to arrive at either a core outcome set with an enormous number of items, or a core outcome set with only a very small number of items. The members of the face-to-face meeting had the opportunity to present potential solutions to these problems, rather than simply voting to reject the result of the Delphi if they felt that there were problems. These could then be discussed and voted on by the panel members. For consistency with the Delphi survey, 75% of voting members were required to agree on a modification of the Delphi results for that modification to be adopted in the final core sets.

4.3 Results

4.3.1 Delphi survey

The Delphi Survey commenced in August 2018 and round 3 was completed in December 2018.

4.3.1.1 Round 1

One hundred and forty people participated in round 1, and 123 completed the round. In addition to rating the existing 100 outcomes, there were 67 new outcomes suggested in round 1. Some of these were very similar to each other, so were amalgamated these into single outcomes. Some were very similar to existing outcomes, so I (in collaboration with the PLACEMENT trial management group) felt that adding these would add to the work of completing the survey while adding little to the resulting set - at this stage of the project I was trying to establish a list of broad concepts which should be measured rather than the best way to measure these concepts. After looking through all of these and considering each of them carefully, 20 new items were added to the list of outcomes.

There were 30 outcomes which were given low scores and so were removed from the survey, so 90 outcomes were carried forward to round 2. In this round, outcomes rated less than 6 on average were excluded, unless one of the two stakeholder groups (either healthcare professionals or patients/carers) gave the outcome an average rating of at least 8. Short-term and medium-term outcomes carried forward to Round 2 are shown in Table 4.1 and Table 4.2 respectively.

	Mean score			Percentage rated	
Outcome	**HCP**	**P/C**	**Overall**	**1-3**	**7-9**
Death within a specified period of time after operation; or survival time after the operation	8.04	9.10	8.13	1.56	85.94
Cause of death	7.53	9.00	7.64	4.69	78.91
Bleeding or need for blood transfusion after surgery	5.51	8.40	5.73	14.06	32.03
Heart related problems during surgery or follow-up	6.69	8.30	6.82	3.91	62.50
Problems related to control of diabetes during surgery or follow-up	6.22	9.00	6.44	7.81	53.91
Pain in residual limb/amputation stump	7.19	7.70	7.23	0.78	71.88
Falls	6.80	7.40	6.84	6.25	61.72
Nutritional status	6.11	6.80	6.17	7.94	43.65
Joint contractures	6.62	7.40	6.68	10.32	64.29
Effectiveness of pain relief	7.10	7.60	7.14	2.38	73.02
Phantom sensations or pain	6.81	7.50	6.87	3.97	65.08
Stroke	6.57	8.10	6.69	7.14	57.14
Problems with kidneys	5.78	8.10	5.97	13.49	45.24
Anxiety or depression	6.74	7.90	6.83	3.97	65.87
Pneumonia	6.72	8.30	6.84	6.35	65.87
Breathing problems	6.22	8.40	6.39	8.73	52.38
Problems with amputation stump healing	8.15	8.50	8.18	0.00	94.40
Stump wound infection	8.10	8.90	8.17	0.00	94.40
Blood clots in deep veins or lungs (venous thromboembolism)	7.26	8.80	7.38	0.80	72.80
Patients supplied with a temporary or definitive prosthetic limb	6.60	8.10	6.72	11.20	57.60
Prosthetic limb use; comfort and fitting	6.30	8.10	6.45	12.00	52.80

Level of independent mobility or function achieved	6.83	7.30	6.87	5.60	63.20
Development of problems with the other leg	7.04	8.50	7.16	4.80	68.80
Impact on family/loved ones	6.43	7.20	6.50	5.60	54.40
Independent living	6.23	7.20	6.31	8.13	44.72
Coping strategies and psychological adaptation	6.58	6.70	6.59	5.69	53.66
Cognitive function or confusion	6.57	7.10	6.61	4.88	56.10
Quality of life	6.85	8.10	6.95	3.25	60.98
Satisfaction with health status	6.47	7.70	6.57	4.07	47.97
Effective communication between healthcare team and patient/carers	7.07	8.10	7.15	6.50	69.92
Shared decision-making	6.93	8.20	7.03	8.13	65.85
Compliance with guidelines for care	6.80	8.10	6.90	7.32	63.41
Residential status	6.18	8.20	6.34	9.76	47.97
Cost of treatment	6.37	8.50	6.54	8.13	48.78
Time in operating suite	5.44	8.30	5.67	17.89	36.59
Length of time in hospital	6.66	7.00	6.69	4.88	54.47
Need for re-admission to hospital after discharge	7.21	8.00	7.28	3.25	73.17
Need for additional operations	7.44	8.20	7.50	3.25	80.49
Side effects of medication	5.75	8.00	5.93	17.89	43.90
Overall perioperative complications	7.73	8.80	7.81	2.44	84.55

Table 4.1. Short-term outcomes carried forward from round 1 to round 2 of the Delphi survey. HCP: Healthcare professionals; P/C: patients or carers.

	Mean score			Percentage rated	
Outcome	**HCP**	**P/C**	**Overall**	**1-3**	**7-9**
Death within a specified period of time after operation; or survival time after the operation: 1-2 years after surgery	7.36	6.70	7.31	4.69	70.31
Cause of death: 1-2 years after surgery	6.66	7.30	6.71	7.03	57.03
Pain in residual limb/amputation stump: 1-2 years after surgery	7.37	6.70	7.32	1.56	74.22
Joint contractures: 1-2 years after surgery	6.47	6.10	6.44	7.94	57.14
Phantom sensations or pain: 1-2 years after surgery	7.04	6.50	7.00	2.38	65.87
Anxiety or depression: 1-2 years after surgery	6.79	6.40	6.76	3.97	61.90
Problems with amputation stump healing: 1-2 years after surgery	7.39	7.80	7.42	4.00	77.60
Stump wound infection: 1-2 years after surgery	7.03	7.80	7.10	5.60	72.80
Blood clots in deep veins or lungs (venous thromboembolism): 1-2 years after surgery	5.63	8.20	5.83	15.20	44.80
Patients supplied with a temporary or definitive prosthetic limb: 1-2 years after surgery	7.67	8.30	7.72	1.60	80.80
Prosthetic limb use; comfort and fitting: 1-2 years after surgery	7.70	8.80	7.78	0.80	85.60
Level of independent mobility or function achieved: 1-2 years after surgery	7.95	7.70	7.93	0.00	86.40
Development of problems with the other leg: 1-2 years after surgery	7.20	7.60	7.23	4.80	68.80
Participation in work and social activities: 1-2 years after surgery	7.35	7.30	7.34	1.60	77.60
Impact on family/loved ones: 1-2 years after surgery	6.72	6.20	6.68	7.20	59.20

Independent living: 1-2 years after surgery	7.68	6.90	7.62	1.63	80.49
Coping strategies and psychological adaptation: 1-2 years after surgery	7.04	6.80	7.02	4.07	65.04
Cognitive function or confusion: 1-2 years after surgery	6.19	6.60	6.22	8.13	48.78
Quality of life: 1-2 years after surgery	7.95	7.40	7.90	0.00	90.24
Satisfaction with health status: 1-2 years after surgery	7.18	6.80	7.15	4.07	69.92
Effective communication between healthcare team and patient/carers: 1-2 years after surgery	6.21	7.60	6.33	12.20	52.03
Shared decision-making: 1-2 years after surgery	6.16	7.10	6.24	16.26	52.03
Compliance with guidelines for care: 1-2 years after surgery	6.41	7.30	6.48	10.57	55.28
Residential status: 1-2 years after surgery	7.04	7.60	7.09	5.69	60.98
Cost of treatment: 1-2 years after surgery	6.53	8.30	6.67	7.32	52.03
Time taken to complete rehabilitation: 1-2 years after surgery	6.46	7.60	6.55	9.76	57.72
Need for re-admission to hospital after discharge: 1-2 years after surgery	6.10	7.00	6.17	13.82	51.22
Need for additional operations: 1-2 years after surgery	6.91	7.80	6.98	4.88	67.48
Side effects of medication: 1-2 years after surgery	5.52	8.10	5.73	18.70	35.77
Overall perioperative complications: 1-2 years after surgery	6.50	7.90	6.61	12.20	58.54

Table 4.2. Medium-term outcomes carried forward from round 1 to round 2 of the Delphi survey. HCP: Healthcare professionals; P/C: patients or carers.

4.3.1.2 Round 2

Ninety-nine of the 123 people participating in round 1 also participated in round 2. Of the 90 outcomes rated in round 2, there were 63 outcomes which were given low scores and so were removed from the survey, leaving 27 outcomes to rate in round 3. None of the outcomes added to the survey after they were suggested in feedback from round 1 of the survey met this threshold, so all of these additional outcomes were removed at this stage. Fourteen of the highly-rated outcomes were for studies focused on short-term outcomes (up to approximately 30 days after surgery – Table 4.3) and 13 were for studies focused on medium-term outcomes (up to 2 years after surgery – Table 4.4).

Outcome	**Mean score**	**Rated 1-3 (%)**	**Rated 7-9 (%)**
Death within a specified period of time after operation; or survival time after the operation	8.354	0.00	92.71
Cause of death	8.032	1.05	88.42
Pain in residual limb/amputation stump	7.215	0.00	74.19
Effectiveness of pain relief	7.290	2.15	76.34
Problems with amputation stump healing	8.333	0.00	95.70
Stump wound infection	8.312	0.00	93.55
Blood clots in deep veins or lungs (venous thromboembolism)	7.281	0.00	73.03
Development of problems with the other leg	7.304	4.35	72.83
Quality of life	7.044	3.30	65.93
Effective communication between healthcare team and patient/carers	7.143	6.59	70.32
Shared decision-making	7.044	6.67	67.78

Need for re-admission to hospital after discharge	7.389	2.22	80.00
Need for additional operations	7.478	2.22	81.11
Overall perioperative complications	7.955	2.25	88.76

Table 4.3. Short-term outcomes carried forward from round 2 to round 3 of the Delphi survey.

Outcome	**Mean score**	**Rated 1-3 (%)**	**Rated 7-9 (%)**
Death within a specified period of time after operation; or survival time after the operation	7.417	2.08	72.92
Pain in residual limb/amputation stump	7.473	2.15	77.42
Problems with amputation stump healing	7.710	1.08	78.49
Stump wound infection	7.108	4.30	76.34
Patients supplied with a temporary or definitive prosthetic limb	8.011	1.09	85.87
Prosthetic limb use; comfort and fitting	8.109	0.00	89.13
Level of independent mobility or function achieved	8.185	0.00	89.13
Development of problems with the other leg	7.478	2.17	75.00
Participation in work and social activities	7.283	1.09	77.17
Independent living	7.846	1.10	84.62
Quality of life	8.066	1.10	92.31
Satisfaction with health status	7.099	4.40	71.43
Residential status	7.100	3.33	64.44

Table 4.4. Medium-term outcomes carried forward from round 2 to round 3 of the Delphi survey.

4.3.1.3 Round 3

Ninety-one of the 99 people participating in round 2 also completed round 3. Of the 27 outcomes rated in round 3, 18 received high enough support to be considered 'core' according to the rules laid out in the project protocol.[72] Seven of the participants were patients or carers and the remainder were from healthcare professionals, representing the fields of occupational therapy, physiotherapy, prosthetics, nursing, vascular surgery, diabetology, and clinical psychology. Table 4.5 lists the nine short-term outcomes receiving a high level of support, together with their average scores, the percentage of respondents rating the outcome 1-3 and the percentage of respondents rating the outcome 7-9. Table 4.6 lists the same information for the nine medium-term outcomes receiving a high level of support. Table 4.7 lists the same information for the nine outcomes rated in round 3 which did not receive high levels of support. Figure 4.1 shows the distribution of ratings for the short-term outcomes rated as 'core'. Figure 4.2 shows the distribution of ratings for the medium-term outcomes rated as 'core'. Figure 4.3 shows the distribution of ratings for the outcomes not rated as 'core' in the final round of the Delphi survey.

Outcome	Mean score	Rated 1-3 (%)	Rated 7-9 (%)
Problems with amputation stump healing	8.647	0	97.8
Stump wound infection	8.604	0	96.7
Death within a specified period of time after operation; or survival time after the operation	8.549	0	95.6
Cause of death	8.330	1.10	90.1
Effectiveness of pain relief	7.253	2.20	76.9
Effective communication between healthcare team and patient/carers	7.253	6.59	75.8
Need for re-admission to hospital after discharge	7.578	1.11	83.3
Need for additional operations	7.611	1.11	85.6
Overall perioperative complications	8.202	2.25	92.1

Table 4.5. Short-term outcomes rated as 'core' by the Delphi survey.

Outcome	Mean score	Rated 1-3 (%)	Rated 7-9 (%)
Problems with amputation stump healing	7.917	1.10	78.5
Stump wound infection	7.710	1.08	78.5
Pain in residual limb/amputation stump/phantom	7.407	1.10	77.4
Patients supplied with a temporary or definitive prosthetic limb	8.122	0.00	85.9
Prosthetic limb use, comfort and fitting	8.178	0.00	89.1
Level of independent mobility or function achieved	8.264	0.00	89.1
Participation in work and social activities	7.253	1.10	77.2
Independent living	7.857	1.10	84.6
Quality of life	8.267	1.11	92.3

Table 4.6. Medium-term outcomes rated as 'core' by the Delphi survey.

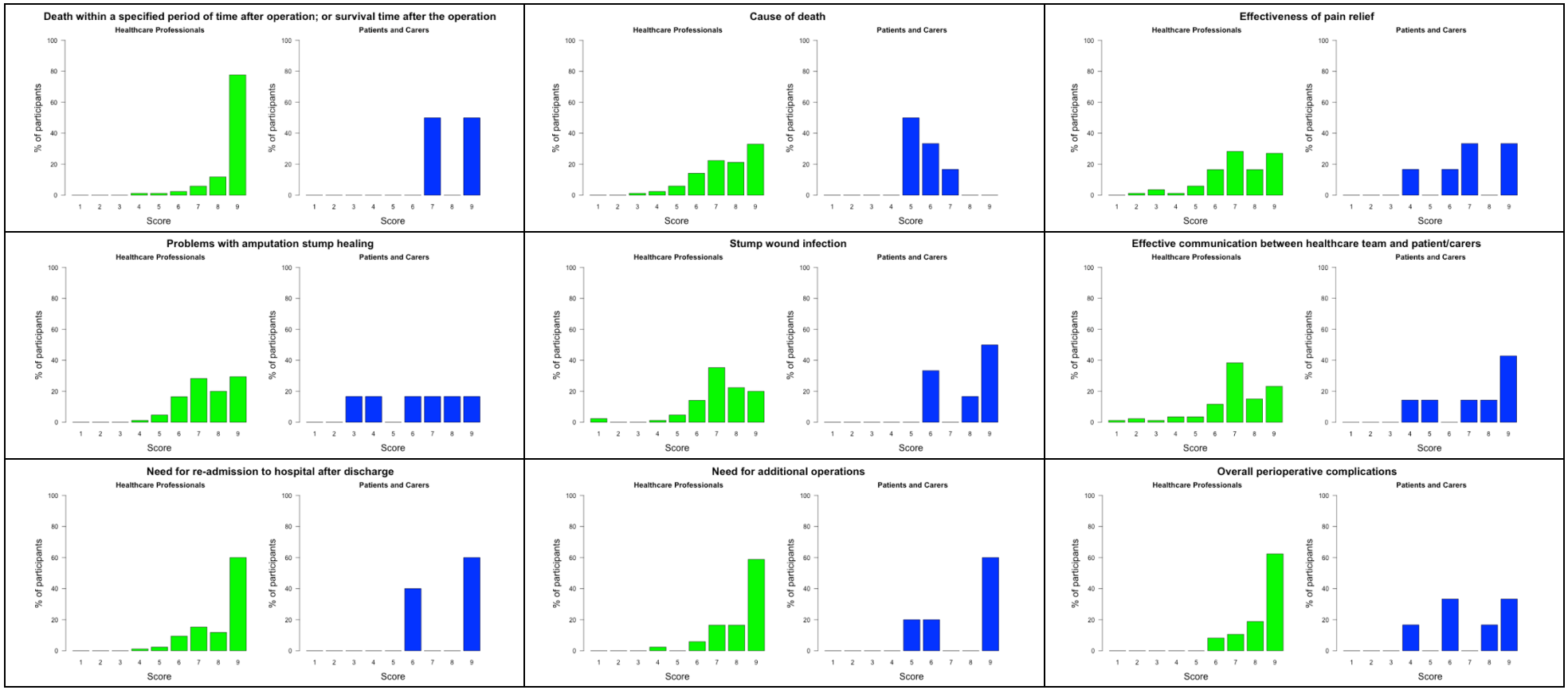

Figure 4.1: Ratings of the 9 short-term outcomes receiving a high level of support from the Delphi survey.

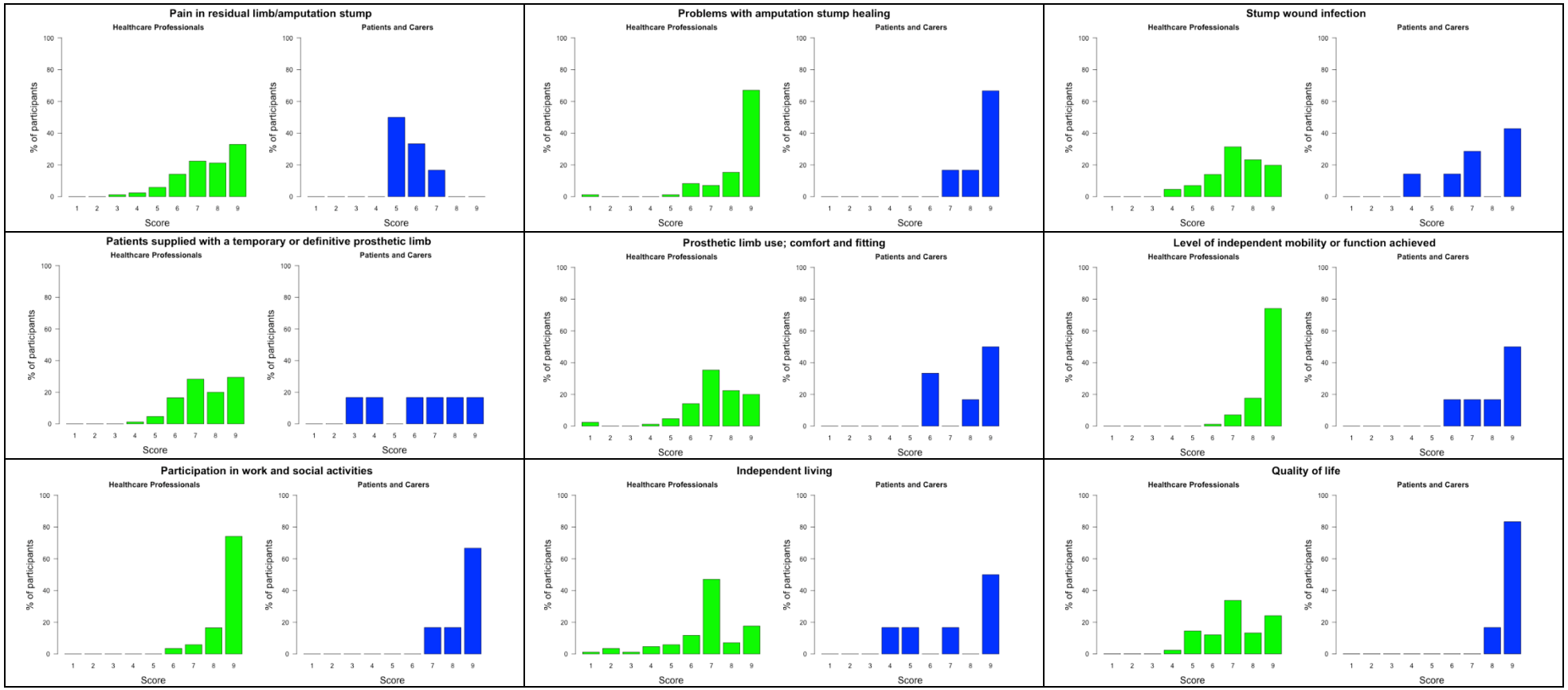

Figure 4.2: Ratings of the 9 medium-term outcomes receiving a high level of support from the Delphi survey.

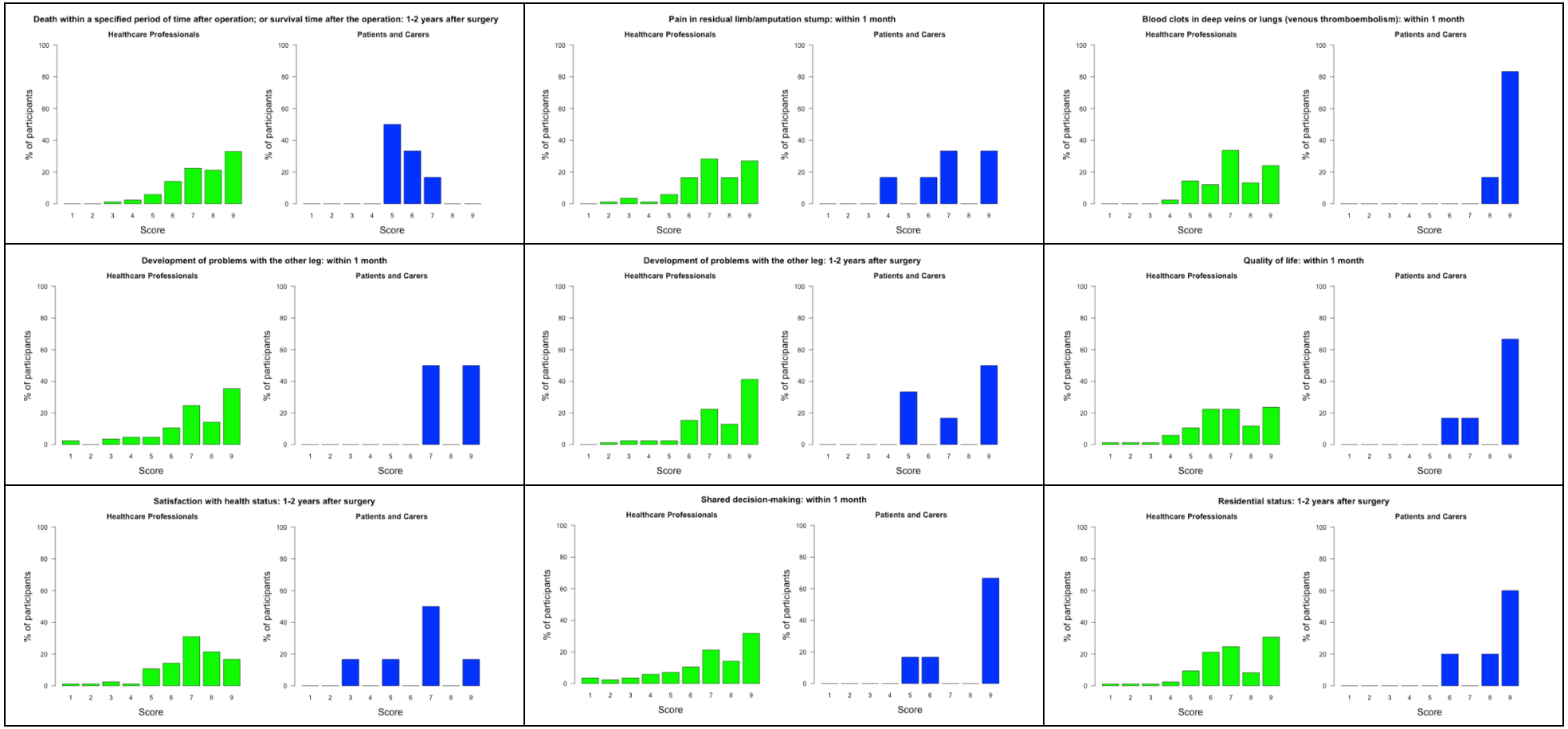

Figure 4.3: Ratings of the 9 outcomes not receiving a high level of support from the Delphi survey.

Outcome	Mean score	Rated 1-3 (%)	Rated 7-9 (%)
Death within a specified period of time after operation; or survival time after the operation: 1-2 years after surgery	7.374	1.10	72.5
Pain in residual limb/amputation stump: within 1 month	7.176	4.40	71.4
Stump wound infection: 1-2 years after surgery	6.780	5.49	71.4
Development of problems with the other leg: within 1 month	7.275	5.49	72.8
Development of problems with the other leg: 1-2 years after surgery	7.517	3.30	75.0
Quality of life: within 1 month	6.890	3.30	59.3
Satisfaction with health status: 1-2 years after surgery	6.889	5.56	68.9
Shared decision-making: within 1 month	6.945	8.79	67.0
Residential status: 1-2 years after surgery	7.111	3.33	64.4

Table 4.7. Outcomes rated in the third round which were not rated as 'core' by the Delphi survey.

4.3.2 Face-to-face consensus meeting

The final part of the core outcome sets development project was a face-to-face meeting to discuss the results of the Delphi survey and ratify the findings. This included discussion of all the outcomes rated in the final round of the survey and voting on inclusion or exclusion of these outcomes from the final published set. The meeting took place on Friday 12th April 2019 in College House, Cardiff.

Unfortunately, two days prior to the event, two of the amputee patients withdrew for personal reasons. On the day, the diabetologist, the rehabilitation physician and the specialist nurse who had all agreed to come did not attend the meeting. In addition, two of the amputee patients who had said that they would come when contacted the previous day did not attend. The final consensus group was comprised of two vascular surgeons, one vascular surgical trainee (myself), one anaesthetist, one physiotherapist, one occupational therapist, one clinical psychologist, one prosthetist, one clinical trials manager, one amputee patient and one person who had been a carer for an amputee patient.

4.3.2.1 Short-term outcomes

The meeting was divided into two halves. In the first half, we discussed short-term outcomes. I began by presenting the results of the Delphi survey. We then moved to the discussion phase, with each member in turn being given the opportunity to raise concerns or outcomes of interest. After each member had spoken, the group then spent time discussing the points raised, and once everyone was happy that these points had been adequately discussed, we moved on to the next member of the group to give them their opportunity to raise any concerns or outcomes of interest, which were then discussed in turn. There was some initial discussion about terminology, with the prosthetist suggesting that the term 'residual limb' was preferred to the term 'stump'. There was strong disagreement from the amputee patient about this, who said that this was 'political correctness' and that he preferred the term 'stump'. The carer raised the point that she was confused when people said 'residual limb' as she wondered whether the

term referred to the non-amputated limb. The group therefore decided to keep the nomenclature used in the Delphi survey.

The clinical psychologist said that he was disappointed that there was no measure of psychological morbidity such as depression or anxiety in the final set of outcomes. I pointed out that it had been in the original set of outcomes rated, but that it had not received sufficient support. There was, however, broad support from participants at the meeting that psychological morbidity was very important in amputee patients. It was suggested that there may have been too few clinical psychologists completing the Delphi survey to give adequate weight to this outcome.

Both the physiotherapist and the prosthetist suggested that the omission of contralateral limb deterioration (as it had not quite achieved sufficient support from the survey to be included in the final list of outcomes) should be reconsidered. There was concern that omission of this outcome might have been due to the slightly arbitrary decision about the cut-off score to use in the final round.

The carer made the suggestion that length of stay was important as getting home quickly was important to patients and extra nights in hospital were expensive for the health service. Others contributed that it was a very easy thing to measure and given this perhaps it should be considered a core outcome despite not receiving sufficient support from the Delphi survey.

Finally, the anaesthetist raised the concern that he was not sure how best to measure 'Effective communication between healthcare team and patient/carers' and he did not

think this belonged in an outcome set. There was a lot of disagreement with this viewpoint as it was viewed as very important by many people in the room.

We then proceeded to the voting phase. Nine participants voted to add a measure of psychological morbidity to the outcome set, with one against. Eight participants voted to add deterioration of the other leg to the outcome set, with two against. Six participants voted to add length of stay to the outcome set, with five against. Two people voted to remove 'Effective communication between healthcare team and patient/carers' from the core outcome set, with nine disagreeing with this suggestion.

4.3.2.2 Medium-term outcome

I again began by presenting the list of outcomes which reached the threshold for acceptance in the third round of the Delphi survey and those which did not (Tables 4.3 and 4.4). The prosthetist raised the point that stump healing and infection are similar issues, and that both affect prosthetic outcome, agreeing that these were very important for medium-term outcomes. There was then some discussion about whether these outcomes should be combined into a single outcome. The vascular surgeons commented that while infection was one reason for poor healing, a more common reason was poor blood supply. There was subsequent recognition that because of this, they should be kept separate in the list of outcomes. There was some surprise expressed that mortality had not reached the threshold for inclusion. There was quite a lot of support for adding this to the list brought forward from the Delphi, so it was decided to vote on this at the end of the discussion. The concern about omission of problems with the contralateral

limb was again raised by the physiotherapist, who suggested that this should again be added to the list of outcomes from the Delphi. It was again decided that this should be voted on at the end of the discussion. The anaesthetist suggested that he was surprised that no mention was made of phantom pain in the list of outcomes in Round 3. I explained that phantom pain had been a separate item in the Delphi but had not received enough support in Round 2 to make it into the Round 3 voting. It was suggested that perhaps it would have been better to have a single 'pain' outcome which included all types of painful sensations, and that this could be done by changing the outcome 'Pain in residual limb/amputation stump' to 'Pain in residual limb/amputation stump/phantom'. This was supported by several people, so again it was decided that this should be voted on at the end of the discussion.

The psychologist again expressed concern that no real measure of psychological morbidity was included in the final set, again suggesting that this was because of the small number of psychologists completing the survey. It was commented that psychological morbidity is covered to some extent in quality of life measures. It was recognised that this was true, but several expressed the feeling that it was important in its own right, so again it was decided that this should be voted on at the end of the discussion.

The carer asked whether the patient returning to their own home or going to a nursing/residential home might be important. I mentioned that this was one of the other outcomes in the Delphi but that it had not been given enough support to come through as 'core'.

Finally, I asked if anyone thought any of the items highlighted by the Delphi were not important and should be removed due to poor support by either professionals or patients/carers. One person suggested that perhaps quality of life should be removed, as it received less support from the panel of patients and carers. Others disagreed, saying in their view it was helpful for health economic analysis and is a good thing to incorporate into patient reported outcome measures, being a measure of overall success of the whole operation, clinical care and rehabilitation package.

We then proceeded to the voting phase. Seven participants voted to add mortality to the outcome set, with three against, so this was not added, as it failed to meet the requirement of 75% of voting members agreeing the change. Nine participants voted to add deterioration of the other leg to the outcome set, with one against. Eight participants voted to add a measure of psychological morbidity to the outcome set, with two against. None of the participants voted to add residential status to the outcome set. Finally, all 11 participants voted to change the outcome 'Pain in residual limb/amputation stump' to 'Pain in residual limb/amputation stump/phantom'.

4.3.3 Final core outcome sets

Adopting the same selection threshold as used in the third round of the Delphi (over 75% of participants rating the outcome as critical), the final core outcome set for studies focussed on short-term outcomes is as follows:

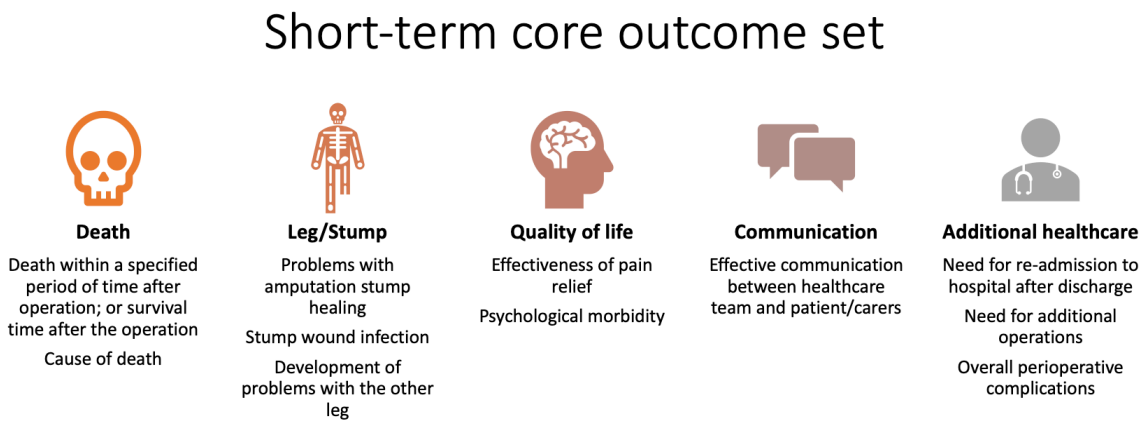

Figure 4.4: Short-term core outcome set for patients undergoing major lower limb amputation for complications of peripheral vascular disease.

1. Death within a specified period of time after operation; or survival time after the operation
2. Cause of death
3. Problems with amputation stump healing
4. Stump wound infection
5. Development of problems with the other leg
6. Effectiveness of pain relief
7. Psychological morbidity
8. Effective communication between healthcare team and patient/carers
9. Need for re-admission to hospital after discharge
10. Need for additional operations
11. Overall perioperative complications

I have organised and illustrated these in Figure 4.4.

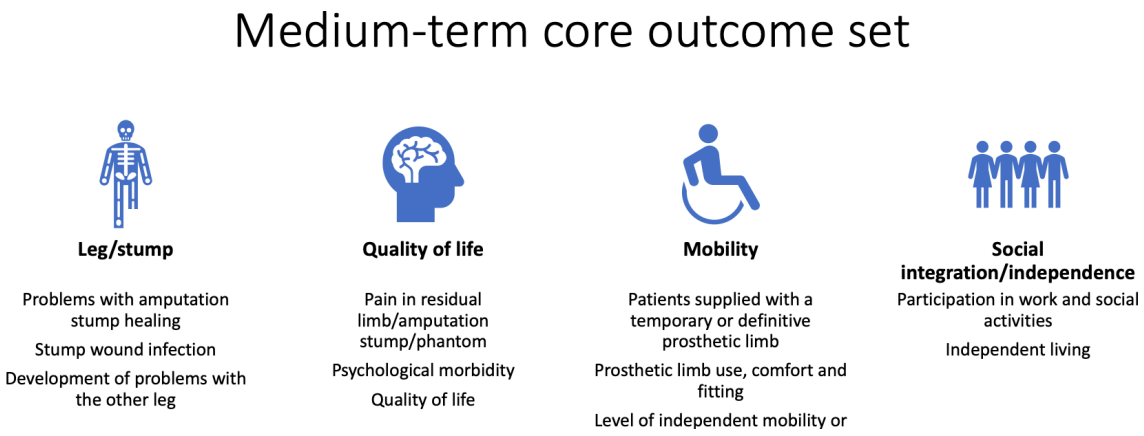

Figure 4.5: Medium-term core outcome set for patients undergoing major lower limb amputation for complications of peripheral vascular disease.

For studies focussed on medium-term outcomes, the core outcome set contains the items:

1. Problems with amputation stump healing
2. Stump wound infection
3. Development of problems with the other leg
4. Pain in residual limb/amputation stump/phantom
5. Psychological morbidity
6. Quality of life
7. Patients supplied with a temporary or definitive prosthetic limb
8. Prosthetic limb use, comfort and fitting
9. Level of independent mobility or function achieved
10. Participation in work and social activities
11. Independent living

I have organised and illustrated these in Figure 4.5.

4.4 Discussion

I have developed core outcome sets for studies recruiting patients undergoing major lower limb amputation for complications of peripheral vascular disease with both short-term and medium-term focus. Four outcomes are shared between both short-term and medium-term sets, while the remaining seven outcomes in each set were felt to be 'core' for only one time period. To my knowledge, this is the first time that core outcome sets for studies of patients with the same condition but for different durations have been developed.

Broad ranges of outcomes are present in both short- and medium-term sets, including local stump-related problems (healing, infection, pain); further health and healthcare (readmissions, re-operations, complications, problems with the other leg); psychosocial problems (psychological morbidity, work/social re-integration, communication); mobility, independence and quality of life all featuring. There are objective 'hard' outcomes such as mortality, which are easily captured in routinely collected data, but there are also multiple outcomes which require patient reported outcome measurement (PROM) instruments. To our knowledge there are no PROM tools that holistically capture mobility, pain, anxiety and depression, etc. in amputee patients.

No other work has defined core outcome sets for patients undergoing lower limb amputation, though there has been some work using the International Classification of Functioning, Disability and Health to classify factors influencing mobility in established amputee patients. While not a true core outcome set, this work did like our work find

that problems of pain, mobility, functional independence and participation in work and social activities were important for these patients.[39]

There are other examples where during the development of core outcome sets it was discovered that outcomes which are viewed as important by patients or their informal carers had not been given consideration in the scientific press, as research is dominated by clinical practitioners, highlighting the importance of this step.[74] Conversely, it is possible that healthcare professionals will identify outcomes which patients are hesitant to discuss and which, because of perceived difficulties in recruitment for such studies, are also not well represented in the literature.[75]

A strength of this work is that I had input from patient and carer representatives throughout the work. A patient and a carer on the study team reviewed all patient-facing material including information leaflets and the wording of the Delphi survey to ensure that wording was in plain English. I also used focus groups of patients, carers and healthcare professionals to ensure that outcomes important to individuals who would be unlikely to contribute to the research literature were also considered. This was clearly important, as I added five outcomes from the focus groups, two of which made it to the final consensus survey round , and one (effective communication between healthcare team and patient/carers) is part of the final core outcome sets, described by one of the patients as the most important outcome in the short-term set.

A weakness of the study is that we did not manage to get as many patients and carers to participate in the consensus survey or face-to-face meeting as we intended. This was not

for a lack of trying: I personally invited over 40 amputee patients to participate in the survey, advertised the survey through two amputee charities and encouraged clinicians participating in the survey to advertise it to their patients. I also contacted all participants from the previous round of the survey, encouraging them to complete subsequent rounds and extending the completion deadline if necessary, in order to receive as many responses as possible. Having had six patient/carer participants who had agreed to come to the consensus meeting I was disappointed that only two attended despite contacting scheduled participants in the few days before the meeting to remind them and arrange transportation.

The development of core outcome sets represents an important step forward in improving the efficiency of further research. Results of the systematic review highlighted the inefficiency of previous research in this area, with 444 different outcomes reported in the 440 included studies. Having established consensus on the most important outcomes for these patients, future research can be more focused, and meta-analysis will be more feasible. This is discussed further in Chapter 5.

Core outcome sets also have the potential to improve the quality of observational research in the form of registry studies. If national registries adopt the outcome sets then results from different registries may be pooled, improving the power of such analyses. Standardisation will also be possible, allowing appropriate correction at scale for confounding factors to be performed in a uniform way across multiple registries. Work has already begun in this direction in vascular surgery, though not for patients undergoing amputation.[82]

I have developed core outcome sets for short- and medium-term studies recruiting patients undergoing major lower limb amputation. Further work is required to explore how best to measure these outcomes, and to develop and validate patient-reported outcome measurement tools which capture outcomes such as pain, communication, mobility, psychological morbidity and quality of life.

5 Discussion

The aim of this thesis was to develop tools which could direct future research and quality improvement towards key interventions and outcomes for patients undergoing MLLA for complications of peripheral vascular disease. In this chapter I will outline the main results of this work and highlight the ways in which I have achieved this aim. No research is performed in isolation, so I will also discuss the results in the context of other work in the area. There are limitations to the work I have done, and I will discuss these before moving on to talk about further research which is needed and draw conclusions about the body of work as a whole.

5.1 Summary of findings

5.1.1 Predictors of peri-operative risk

I used data from the National Vascular Registry (NVR) to examine risk-factors for peri-operative complications following major lower limb amputation. Data were applied for through the UK Healthcare Quality Improvement Partnership and the Audit and Quality Improvement Committee of the Vascular Society of Great Britain and Ireland, and ethical approval was granted by Wales Research Ethics Committee 3. The study was registered prospectively on the Australia and New Zealand Clinical Trials Registry. The primary outcome was in-hospital mortality and secondary outcomes included length of stay and other standard peri-operative complications such as renal failure and return to theatre. Multiple imputation methodology was used to handle missing data for variables with missing data rates less than 50%. Variables with missing data rates greater than 50% were excluded from the analysis. I performed both univariate and multivariate logistic regression to look for predictors of the primary outcome. For the secondary outcomes I

performed only multivariate analysis in order to look for significant independent predictors once measured confounders had been taken into account.

Multivariate analysis revealed that bilateral operation; emergency admission; increased age, creatinine, white blood cell count or American Society of Anesthesiologists (ASA) grade; and ECG abnormalities were all associated with an increased risk of in-hospital mortality. Protective factors included trans-tibial amputation, previous procedures on the amputated limb and increased patient weight or serum albumin. In addition to these factors, univariate analysis also suggested that male sex; a history of ischaemic heart disease, congestive heart failure, chronic lung disease or stroke; current smoking; and statin, beta-blocker or ACE-inhibitor/angiotensin-receptor-blocker therapy were also significant predictors of higher in-hospital mortality when considered in isolation. A sensitivity analysis using complete case analysis revealed no unexpected differences with the analysis using the multiply imputed datasets, providing confidence that the multiple imputation procedure had not introduced unexpected bias.

A range of different variables was predictive of the different secondary outcomes (Table 2.6 on page 39). Emergency admission, trans-tibial amputation, low serum albumin and high ASA grade were all predictive of more than half of the adverse secondary outcomes. Chronic heart, kidney and lung disease were also predictive of cardiac, renal and respiratory complications respectively.

5.1.2 A prognostic model of risk

The parameters which were found to be independently associated with increased risk of in-hospital mortality were included in a logistic regression model, allowing quantification of the probability of a given patient not surviving until discharge. These parameters were selected by stepwise minimisation of the Schwarz-Bayes criterion in order to develop a parsimonious model, reducing the risk of overfitting. Model discrimination was assessed using ROC curve analysis, and this was compared to the discrimination of other available models. Calibration of the model was assessed using the Hosmer-Lemeshow goodness of fit test. The discriminative power of the model for predicting the secondary outcomes

was also assessed by calculating the C-statistic (the area under the ROC curve) and comparing this to the C-statistic of models designed specifically to predict each secondary outcome.

The C-statistic for the model developed was 0.79 (95% C.I. 0.77-0.80), suggesting good, bordering on excellent discrimination. The Hosmer-Lemeshow goodness-of-fit test found no evidence of mis-calibration (P=0.348). This test found significant evidence of mis-calibration for all the other models I found in the literature (page 33). The C-statistic for each of these models was also significantly lower than the C-statistic for the model I developed, suggesting that the discrimination of these models was inferior to the model I developed. The model was also a good discriminator of cardiac, respiratory and renal complications, though it was not a good discriminator of the other secondary outcomes.

5.1.3 Core outcome sets – development of the 'long list' of outcomes

I performed a systematic review, searching the MEDLINE and EMBASE databases for studies involving patients undergoing major lower limb amputation for complications of peripheral vascular disease. The review compiled a list of all of the outcomes which were reported in these studies. In order to capture as broad a range of outcomes as possible, I included both studies reporting high-level evidence, such as randomised controlled trials, and low-level evidence such as case reports. I then grouped the outcomes using the 38 domain classification system defined by Dodd et al.[68]

The search identified 4288 references. After screening, this was reduced to 360 studies. A further 153 potentially relevant studies were identified through screening reference lists, and after screening, 80 of these satisfied the inclusion criteria giving a total of 440 included studies, from 42 different countries. These studies reported a total of 1447 outcomes, of which 444 were discrete (different from one another). The most frequently reported outcomes were 'mortality' and 'wound healing' (each reported in 93 studies). After grouping together similar outcome measures such as '30-day mortality' and 'in-hospital mortality', both of which measure the outcome 'mortality' and removing outcomes which were not relevant I was left with 45 distinct outcomes.

In addition, I organised four focus groups, which were led by a senior qualitative researcher, to explore outcomes which healthcare professionals, patients and carers felt were important to patients undergoing major lower limb amputation, or who had recently undergone major lower limb amputation. One focus group was composed of patients and carers, one contained medically trained professions as well as a clinical psychologist, one contained allied healthcare professionals and one additional group contained two physiotherapists, as none of the invited physiotherapists had been able to attend any of the other groups and I felt that this was an important group to include. A flexible semi-structured topic guide was used, and the groups started with open discussion, with the results of the systematic review revealed later in order to prompt further discussion around topics which might not have already been raised. Thematic analysis was then performed by the qualitative reviewer to develop an analytical framework using an inductive approach. The framework was discussed with me to ensure that it adequately captured the focus groups. The qualitative reviewer then coded all of the focus group transcripts, and I re-coded one of the groups to ensure consistency/reproducibility. I then identified themes which were both similar and not similar to the outcomes from the systematic review. The qualitative reviewer then went through what I had coded to ensure that she agreed with my assessments, to ensure that I had not misunderstood what she was attempting to express in the analytical framework.

A broad range of healthcare professionals attended the focus groups, as well as three amputee patients and three people who cared for amputee patients. The analytical framework divided the results of the focus groups into 19 themes, ranging from quality of life and social functioning to communication, readmissions and mortality. Some of these were recognised as similar to outcomes found in the systematic review, while some, particularly those around communication, were quite different. After mapping the analytical framework onto outcomes, I was left with five additional outcomes which were not covered by the results of the systematic review.

5.1.4 Core outcome sets – coming to consensus

The 50 outcomes derived from the systematic review and focus groups were taken forward to a three-round Delphi consensus process, where participants were asked to rate each of the outcomes on a 9-point Likert-like scale. In the first round, participants were also able to propose additional outcomes which they felt were missing from the list of rated outcomes. As I was attempting to develop two core outcome sets – one for studies with short-term primary outcomes and one for studies with medium-term primary outcomes – participants were asked to rate each of the outcomes twice. Short-term was defined as 'within 30 days or while in hospital', while medium term was defined as up to two years following amputation. In the second and third rounds participants were given feedback on how others had rated an outcome in the previous round and reminded how they had rated that outcome in the previous round. After the first round, outcomes with a mean rating of less than 6 were removed. After the second round, outcomes with a mean rating of less than 7 were removed. Outcomes rated 7-9 by over 75% of participants in round three were taken forward to the consensus meeting for ratification as core outcomes.

At the consensus meeting, the results of the third round of the Delphi survey were presented. These were divided into short-term outcomes and medium-term outcomes. Participants were then asked to comment on what they thought of the proposed core set, and whether they thought that there were any outcomes which should also be considered core, despite not receiving sufficient support from the Delphi survey. All participants were given the opportunity to speak. Proposals for changes to the core set were then voted on, with a requirement that 75% of votes should be in favour of a change before the set of items proposed by the Delphi should be changed.

There were 123 complete responses to round 1 of the Delphi survey. Thirty outcomes received low scores so were removed from further rounds, and twenty additional outcomes were added in response to participants' suggestions. In round 2, 99 of the original 123 respondents completed the survey. Following this, 63 outcomes received low scores so were removed from consideration, leaving 27 outcomes to rate in the final

round. Ninety-one of the remaining 99 participants also completed round 3. Nine short-term and nine medium-term outcomes received sufficient support in the final round to be proposed as core at the consensus meeting. These are shown in Table 4.5 and Table 4.6 respectively on page 115.

At the consensus meeting there were several proposals for changes to the core set, including adding development of problems with the other leg and a measure of psychological morbidity to both short- and medium-term sets, adding length of stay to the short-term set, removing 'Effective communication between healthcare team and patient/carers' from the short-term set, adding mortality and residential status to the medium-term set.

In the voting phase, both 'development of problems with the other leg' and 'psychological morbidity' received over 75% support for both short- and medium-term sets so were added to the final core sets, which are given in full in Section 4.3.3.

5.2 Context of other literature

5.2.1 Predictors of peri-operative risk

As mentioned in Chapter 2, there have been some previous studies which attempted to use multivariate statistical techniques to identify predictors of short-term mortality in patients undergoing major lower limb amputation.[10,12,14] All of these, in common with my work, identified that patient age was a good predictor of mortality. Beyond this common factor, however, results have been quite varied. Studies from Scotland and Japan identified sex as an important factor. This was predictive of outcome on univariate analysis in the NVR dataset, but not on multivariate analysis after taking other confounding influences into account. Level of amputation (trans-tibial or trans-femoral) and emergency operation were found to be predictive of outcome in the study from Japan, in line with my work.[14]

Studies from the USA and Japan both identified dependent functional status as important.[12,14] This is not a variable which was recorded in the NVR dataset so it was not possible for me to assess the significance of this factor in a UK dataset. However it has been shown to be predictive of outcome following multiple other major vascular and general surgical operations, so it is likely that this is an important factor which is not presently recorded in the NVR.[83] Both of these other studies also identified key co-morbidities as being important predictors: cardiac disease in both studies; chronic renal disease and malignancy in the study from Japan;[14] and dialysis and COPD in the study from the USA.[12] In contrast, in my work while these were predictive of in-hospital mortality on univariate analysis, none of these were chosen as significant predictors in the multivariate model selection process. This may be as a result of including the ASA grade as a predictor, as this will be highly correlated with comorbidity, since the definitions of grades 2-4 are 'a patient with mild systemic disease', 'a patient with severe systemic disease' and 'a patient with severe systemic disease that is a constant threat to life'.[84] In addition, pre-operative serum creatinine, included in my model, will be strongly correlated with a history of chronic renal disease/dialysis, again possibly removing the need for both to be included in the model.

5.2.2 A prognostic model of risk

The model I have developed has good apparent discrimination – and better than previously available models.[12,15,16,46] This brings major lower limb amputation into line with other major vascular procedures such as abdominal aortic aneurysm repair, where rigorously developed risk calculators with good discrimination in UK datasets are already available.[37,85] Previously available models were either developed using small UK samples,[15,46] or using data from the USA – a quite different healthcare system.[12,16] The models from the USA also suffer from the problem that they contain data items which are not routinely collected in healthcare data in the UK, making them difficult to apply in practice.[12,16] I conclude that the model I have developed is therefore an important step forward in this field, as it is a valid tool for prognostication, can potentially be used for

discussion of options with patients and can be used for selecting patients who will have better outcomes with surgery.

5.2.3 Core outcome sets – development of the 'long list' of outcomes

I found 444 outcome measures in the systematic review from 440 studies, which I reduced to 45 outcomes for rating in a Delphi survey. The number of outcome measures reported in studies which systematically record outcomes from previous studies as part of core outcome set generation is widely variable, from 83 in tooth decay in children,[80] to 370 in head and neck cancer,[24] 766 in colorectal cancer,[86] and 901 in oesophageal cancer resection surgery.[40] The number of outcomes which this is reduced to prior to consideration in a Delphi process is also highly variable: 24, 370, 7 and 68 in the studies referred to above.[24,40,80,86] Interestingly, the vast majority of outcomes (281 of 444) were reported in single studies only, meaning that none of these outcomes would be amenable to any form of research synthesis such as meta-analysis. This implies that that there is potentially a large amount of research waste in the existing literature as it is difficult to pool or compare results from different studies in any meaningful way.

I supplemented the systematic review with focus groups, in order to reduce the likelihood that I would miss key outcomes simply because they had not been reported in previous research in my patient population. In doing so I revealed five additional outcomes for consideration. This phenomenon of discovering outcomes which have not been the topic of previous research is common to other core outcome set development projects and highlights the need for this mixed-methods approach to creating a list of possible outcomes to take to a consensus process.[74,75]

5.2.4 Core outcome sets – coming to consensus

The final core outcome sets contained 11 short-term and 11 medium-term items. These sets are similar in size to other core outcome sets mentioned above , which had 5 outcomes in tooth decay in children, 19 in head and neck cancer, 12 in colorectal cancer and 10 oesophageal cancer resection.[24,40,41,80] One of the interesting things about the final list of core outcomes is that one of them (Effective communication between

healthcare team and patient/carers) came from the focus groups, having not been found in any previous literature on patients undergoing amputation. This again highlights the benefits of the mixed-methods approach which we have taken.

A further interesting feature of my core sets is that the consensus meeting added back in two of the outcomes which had not received enough support in the Delphi survey. One of these – deterioration of the other leg – was on the borderline of being accepted by the Delphi survey, so the inclusion of this item is perhaps not controversial. The other outcome – psychological morbidity (such as anxiety and depression) – is more controversial, as it was voted out after the second round of the Delphi so did not make it into the final round of voting. The process of reaching consensus has been done in a number of ways in the literature. Some studies do not have a consensus-meeting at all and simply publish the results of the Delphi survey as the core set.[80] Some bypass the Delphi survey stage altogether and discuss all outcomes from outcome discovery at a consensus meeting.[24] A systematic review of core outcome set development reports found that 9 of the 19 development processes held face-to-face consensus meetings and that each one used a slightly different method.[87] The commonest general approach appears to be to have a discussion phase where every member is encouraged to contribute, followed by a voting phase where proposals raised during the discussion phase may be voted on, which is how I designed our consensus meeting. The COMET handbook recommends that both a consensus survey and a face-to-face meeting should be held, but does not proscribe the precise methodology to be used in either step.[69]

5.3 Implications for practice

5.3.1 Predictors of peri-operative risk

I have identified 11 parameters which are independently associated with increased risk of in-hospital mortality, and a further 12 parameters which are associated with the secondary outcomes. Some of these factors, such as age and co-morbidity, are not modifiable in any meaningful sense. Some, such as white blood cell count and creatinine

may be modifiable in the peri-operative period through a short period of pre-operative optimisation, though it is possible that these factors are simply reflective of the advanced clinical state of the patient. If so, they would only be modifiable by treating the patient much earlier in the disease process. Likewise, modification of other factors such as whether the patient is admitted as an emergency, are also only possible through changing the patient population presenting for amputation. This is clearly a significant challenge and may require significant changes to the way patients with peripheral arterial disease and diabetes are cared for.

I am optimistic, however, that in the UK we have already begun to put the pieces in place which may help with this. There is a growing movement internationally to develop 'limb salvage' services, incorporating multi-disciplinary clinics and rapid referral pathways.[88] There is mounting evidence that these services result in lower major amputation rates.[89] For many centres, this is a radical shift in the way in which foot ulceration is managed. Traditionally, patients have mainly been seen only by non-specialist district nurses, whose rôle was to change soiled dressings. As a result, the recognition that a wound was failing to heal and that decisions needed to be made about further revascularisation, continuing conservative management, or amputation were not made until the next scheduled outpatient appointment, often several months later. Addressing this problem is challenging. One idea which is currently being trialled in some UK centres is a combination of education and the establishment of a 'hot-foot' line, which allows community nurses easy access to urgent specialist review for any wound which is failing to heal or has become a cause for concern.[90] Evaluation of the efficacy and effectiveness of this strategy, alongside its cost-effectiveness is still lacking. The recent GIRFT (Getting It Right First Time) report on Vascular Surgery in England supports the development of these services and has further led to the development of an ambitious Quality Improvement Framework by the Vascular Society of Great Britain and Ireland.[91,92] This quality improvement framework sets ambitious targets of two days between referral and assessment for severe limb ischaemia or foot sepsis and seven days for stable disease.[92]

While the principal goal of these services is limb preservation, the added benefit is that patients without reasonable limb salvage options can have early discussions about the option of amputation. By doing so, we have the opportunity to perform a higher proportion of amputations on an elective basis when patients are not acutely septic or malnourished from the effects of chronic sepsis and/or pain, which is likely to have consequent benefits in terms of improved survival and reduced complications. My risk model suggests that an elective patient with a white cell count $5x10^9$ cells/L lower and 5kg heavier would have 2.8 times the odds of survival to hospital discharge when compared with an identical patient admitted as an emergency with reciprocal changes in white cell count and weight.

5.3.2 A prognostic model of risk

The development of an accurate model of peri-operative risk is also important for practice. As I have discussed in Chapter 2, it could be used to aid counselling and decision-making, either in clinic or at the bedside, by quantifying the probability of the patient surviving to hospital discharge, and I have developed a web calculator for easy use in clinic which is available from www.ambler.me.uk/Vascular. The General Medical Council (GMC) advice on consent states that 'discussions with patients should focus on their individual situation and the risk to them.'[93] As previously highlighted, surgeons are poor at estimating individual patient risk.[62,63] The lowest-risk 10 percent of patients had estimated in-hospital mortality risk of 0-1.2%, while the highest risk 10 percent had an estimated risk of death exceeding 22%.

With this wide range of absolute risks, I feel that the information gained from a risk calculator is essential if we are to satisfactorily individualise risk estimates in the way suggested by GMC guidance. As the choice between amputation and conservative management is often the choice between amputation and palliation, it is even more important that these discussions are conducted in the context of reliable risk estimates. One possible use of this calculator might be in highlighting those patients who are unlikely to have a good outcome from amputation. For example, an underweight 85-year-old patient with sepsis who would need an above knee amputation would have a

low chance of surviving amputation. Rather than intervening, which entails a high chance of prolonged and greater morbidity and eventual (unavoided) death, it may be better to consider and discuss palliative management, having now identified them accurately with this prognostic model.

Previous procedures to the amputated limb were associated with reduced mortality rates. While it is possible that having had previous procedures is a surrogate for 'fitness' in some way, it may also be that intervention to facilitate healing at a trans-tibial rather than trans-femoral level might have multiple benefits, both in terms of improved short-term outcomes and also in terms of the improvement in long-term functional outcomes. Supporting this hypothesis is the fact that 51% of patients with a previous procedure had a trans-tibial amputation, whereas only 43% of patients without a previous procedure had a trans-tibial amputation. While it is possible that some of the effect seen for trans-tibial amputation is due to unmeasured confounding, the association was strong even when all measured confounders were taken into account in multivariate modelling (adjusted odds ratio for in-hospital mortality 0.61, 95% C.I. 0.52-0.72).

The other area where accurate risk estimates are potentially important is in routine surgical audit. In 2013, publication of surgeon-specific outcome data became compulsory in England for key index procedures in nine surgical specialties.[94] The problems associated with the publication of unadjusted outcomes were highlighted by the first specialty to report outcomes – Vascular Surgery – where newspapers immediately reported on high unadjusted mortality rates.[95] These were subsequently revealed to be well within the normal range once case mix adjustment had been performed.[95,96] While not without its problems, publication of outcomes has been shown, time and again, to be followed by improvement in those outcomes – a Hawthorne-like effect. As a result, publication of outcomes is unlikely to be discontinued. It is important, therefore, that this is done in as constructive a way as possible, and the availability of an accurate method for calculating individual patient risk could be used to reduce problems such as the penalisation of surgeons who take on higher risk cases in the future, by facilitating appropriate risk adjustment.

5.3.3 Core outcome sets – development of the 'long list' of outcomes

The huge number of outcome measures revealed by the systematic review highlights the need for core outcome sets in order to improve the efficiency of research. Resources for research studies are limited and it is therefore critical that attention is paid to the outcomes which matter most to patients, carers and healthcare professionals. In addition, the focus groups revealed several outcomes which had not previously received attention in research studies. There was evidence of huge inefficiency in the research which has been done into improving outcomes for amputee patients. This inefficiency must be addressed if we are to make adequate progress in improving outcomes for these unfortunate patients.

5.3.4 Core outcome sets – coming to consensus

It is clear from the broad range of outcomes in both short- and medium-term core outcome sets that there is a plethora of different issues facing amputee patients. In the short-term, there are issues relating to the amputation stump itself in terms of healing, infection, pain and whether the patient needs to go back to theatre for further surgery, such as revision of the amputation stump. There are care-related issues such as peri-operative complications (in Chapter 2 I showed that respiratory, cardiac and renal complications are all common following amputation), need for re-admission to hospital and effective communication with the healthcare team. Mortality is also common and both the fact of and the cause of death are short-term core outcomes. The possibility of deterioration of the other leg is also a concern. Given the life-changing nature of major limb amputation it is not surprising that the psychological health of this patient group is an important concern. In the medium-term, in addition to the stump-related issues mentioned above, more functional outcomes predominate such as mobility, independent living and overall quality of life.

Improving outcomes for amputee patients will require a multifaceted approach. At present, the British Association of Chartered Physiotherapists in Amputee Rehabilitation (BACPAR) have produced guidance on the interventions that may be performed in

amputee rehabilitation, but this is more of a long list of possibilities than a short-list of recommended rehabilitation techniques or therapies.[97] The Vascular Society of Great Britain and Ireland has also produced a quality improvement framework for patients undergoing amputation.[8] This covers many of the areas measured by the core outcome sets I have developed, but fails to cover issues of communication or psychological morbidity. The core sets I have developed therefore highlight important outcomes which are not well covered by existing guidelines.

5.4 Limitations of the project

5.4.1 Predictors of peri-operative risk

Limitations of my work on identifying predictors of peri-operative risk include the fact that the case completion rate in the NVR is only around 60%.[17] While this is a dramatic improvement over the situation 10 years ago, when only half this number of cases was entered,[98] there exists the possibility that the non-submitted cases might be systematically different from submitted cases. This would introduce bias into my results. The UK National Vascular Registry reports for the past two years have highlighted the fact that case ascertainment rates vary widely between Vascular Networks.[17,38] It is possible that many of the missing data relate largely to institutional and administrative factors rather than patient-related factors.

In addition to missing cases (patients), there was also a degree of missing data items within otherwise completed cases. Most data collection items in the NVR are compulsory. Of those that are not, missing data rates ranged from around 10% for ECG findings up to 36% for pre-operative haemoglobin level. While this sounds like a high level of missing data it is important to realise that there were still over 6000 cases in the registry where haemoglobin level was recorded. This means that the multiple imputation methodology has large amounts of data from which to calculate the likely values for the missing items. Multiple imputation methodology is the gold-standard method for handling missing data in clinical research.[56] It is preferred over complete case analysis,

where cases with missing items are discarded, and single value imputation methods, as it makes use of all available data and also allows information on the uncertainty about the true values of missing data to be used to correct P-values and confidence intervals, allowing these to be calculated reliably. Sensitivity analysis using only complete cases gave similar results (Table 2.4 on page 29), so there was no evidence that the imputation process introduced significant bias.

Validation of data within the NVR is also lacking. This is a general criticism of registry-based studies, as to my knowledge, no national registry of major lower limb amputation cases has been rigorously validated. The Swedish Vascular registry (SwedVasc) and the Hungarian registry have been validated (and reasonable levels of validity identified), although the former only for aortic aneurysm repair and carotid surgery while the latter also for infra-inguinal arterial reconstruction.[99,100] Plans are in place for a validation exercise of the UK NVR in 2020, but this also may not include the major lower limb amputation subset.

A further weakness of this study is due to limitations of the variables recorded in the NVR. For example it is increasingly recognised that frailty is an important risk factor for peri-operative complications, including mortality.[45] Dependent functional status has been shown in other work to be important for predicting mortality in patients undergoing amputation.[12,14,16] However, until recently no measure of frailty or functional status has been recorded in the NVR. A measure of frailty was added to the NVR dataset in January 2019, which will allow further investigation of this factor in the future.

I have modelled in-hospital mortality, as that is the audit standard within the UK Vascular Registry. Unfortunately, this is different from many other national audit databases such as SwedVasc, which reports 30-day mortality. As I have highlighted in Chapters 3 and 4, inconsistency in outcome reporting presents difficulties for clinical audit and research, as it makes pooling of information between studies (meta-analysis) challenging. This further justifies the development of core outcome sets, which I have developed in Chapters 3 and 4 of this thesis.

Finally, I only used data from the UK. This makes extrapolation of these results to other healthcare settings questionable. One of the things which makes international studies difficult is that different registries report both different outcomes and different baseline characteristics. Some work has been undertaken to establish a core minimum *information set* for patients with both acute and chronic limb ischaemia.[82,101] This work complements the work I have done in Chapters 3 and 4 on core outcome sets by establishing consensus on the other data which registries should collect.

5.4.2 A prognostic model of risk

Any risk model is only reliable if the data used to generate it are reliable. Therefore, all the comments above about missing cases, missing data within cases, missing parameters and the lack of external data validation are also relevant to the risk model I have developed. While the apparent discrimination of the model is good on internal validation, it is entirely possible that the introduction of other unmeasured parameters might result in a different model with improved discrimination. Examples of these might be functional status and frailty. As mentioned previously, dependent functional status has been shown in several other studies to be a good predictor of poor outcome.[12,14,16] It is possible that if this were recorded in the data and used to generate the risk prediction model, a different optimal model may have been selected by the automatic parameter selection method. In addition, around 40% of cases were missing from the database. The availability of the additional data would most likely have led to improvements in the model by improving the precision of parameter estimates. It is also possible that other parameters might have come out as more important as a result of this.

A second limitation is the lack of external validation of the model. I can therefore only talk about the 'apparent' discrimination and calibration of the model, as it is possible that overfitting has resulted in optimistic estimates of the C-statistic. Poor discrimination and calibration of models when tested on external data is an established problem in risk prediction,[102] so assessment of the true discrimination and calibration of the model will need to be assessed in future work. I guarded against overfitting by using the stringent Schwarz-Bayes criterion to determine whether parameters should be included in the

model, and the fact that the model is based on data from almost 10,000 cases makes it unlikely that the sample is unrepresentative. One option would have been to use only a subset of the data to generate the model and to validate it on the remaining data. This approach is efficient in terms of avoiding the need for a second validation study, but inefficient in terms of model generation, as it results in a model with poorer estimates of the parameters than would have been possible if all of the data were used. Studies which perform validation using a subset of available data have also been criticised by the UK National Institute for Health and Care Excellence (NICE) as validation was performed on data which could not be truly regarded as 'unseen'.[65] I therefore feel that it is better to generate the best possible model using all of the available data and to defer validation to a follow-up study. By using truly unseen data for validation, we then also get more reliable estimates of the discrimination and calibration of the model in practice.

Finally, though the model is good at discriminating between patients who die in hospital and those who are discharged alive, it is much less good at predicting morbidity outcomes. This is not unexpected as the model has been optimised to predict in-hospital mortality. In addition, even models developed specifically to predict morbidity outcomes had C-statistics which were not as good as the C-statistic for the model for in-hospital mortality when assessed against that outcome. It is possible that the difficulty with predicting morbidity outcomes could be related to under-reporting of complications. This phenomenon is well reported in other large healthcare administrative databases such as NHS England's Hospital Episode Statistics publications.[21,103] Data on in-hospital mortality are far more likely to be accurate. It is possible, therefore, that under-reporting of complications is making it more difficult to predict these outcomes.

5.4.3 Core outcome sets – development of the 'long list' of outcomes

There are some limitations to the process used to develop the long list of outcomes for the core outcome sets. Firstly, although screening of search results was done by two independent people and discrepancies were then resolved by careful examination of the studies, discussion and reference to a senior author, outcome extraction was largely done by only a single individual. I and one other person extracted outcomes from 10% of

studies independently, compared results and came to a consensus. We then repeated this for a further 10% of studies. Results from this second 10% were very similar, so we then extracted outcomes from the remaining studies independently – I extracted from a further 50% of studies and the other reviewer extracted from the remaining 30% of studies. As there was not duplicate extraction from these studies it is possible that we may have missed some previously studied outcomes. I feel that any deficiencies from this are likely to have been minimal, owing to the number of studies and outcomes identified, and compensated for by the fact that I went on to hold focus groups to supplement the outcomes revealed by the systematic review, and I also allowed participants in the Delphi survey to suggest additional outcomes in the first round.

A further deficiency is the limited size of the focus groups, with only three patients and three carers represented. I did invite a much larger number of participants but found it difficult to get engagement from patients. Those who did not agree to attend either cited a lack of interest in the process or difficulties with transportation. While I provided wheelchair-suitable transport from patients' homes to the venue, some patients still felt that it was a lot of effort to get to and from the venue and so were unwilling to attend. I did, however, manage to get engagement from all major stakeholder groups apart from orthopaedic surgeons. In our area, few orthopaedic surgeons are involved in major limb amputation so it may be that they felt it was not particularly relevant to their practice.

A final limitation is that there is no objective way of reducing the outcomes from the systematic review and the themes from the focus groups to domains. I used a recognised system to categorise the outcomes in order to help me in this process, making the process somewhat more objective.[68] The system I developed was also checked carefully with both my thesis supervisors and the PLACEMENT trial management group in order to reduce bias introduced by this process as much as possible. The inherently subjective nature of this process does, however, mean that it is possible that the way in which outcomes were grouped, and the wording used for the domains, may have introduced bias. I am hopeful that allowing participants in the Delphi to suggest new outcomes/domains in round one will also have minimised the effect of this.

5.4.4 Core outcome sets – coming to consensus

Limitations also exist in the consensus process for core outcome set development. The first of these is in the number of patients and carers who completed the survey. The study team invited all of the amputee patients they came across in clinical practice. I invited all of the patients recruited to the PLACEMENT trial who had given consent to be approached for further qualitative work, by sending out letters of invitation and also by telephoning. Despite this, only ten patients and one carer completed the first round of the consensus survey, with seven patients and one carer completing all three rounds, compared with 112 healthcare professionals who completed the first round and 83 who completed all three rounds. Healthcare professionals did represent many different professions, including surgeons, anaesthetists, physicians, nurses, prosthetists, physiotherapists, occupational therapists and clinical psychologists, so it is inevitable that there would be a larger number of healthcare professionals than patients and carers. I attempted to reduce the impact of this imbalance by retaining outcomes which were rated highly by either healthcare professionals or patients/carers in round one of the survey and also presenting separate response histograms when asking participants to rate outcomes in rounds two and three of the Delphi survey. As I did not feel that there was an entirely natural way to weight responses from the different groups, I took the pragmatic decision to weight all responses equally, as I was concerned that if I gave equal weight to each group rather than to every individual, that individual views from patients or carers would carry a disproportionate amount of weight.

A further limitation is that health service commissioners and policymakers were not invited to participate in the consensus process. It is possible that the outcomes which commissioners and/or policymakers view as 'core' may be different from those which healthcare professionals, patients and carers view as 'core'. In hindsight, this may have been an oversight: neither I nor my advisors thought of this point when devising the study protocol.

Finally, the fact that I allowed the face to face meeting to modify the results from the (much larger) consensus survey could be considered a limitation. I added two outcomes

which had not been rated as 'core' to both short- and medium-term core sets, and modified the wording of one of the outcomes slightly in order to highlight that pain in the phantom limb (pain experienced by an amputee patient which appears to be coming from the part of the body which has been amputated) should be considered when reporting medium-term pain. One of the outcomes added (development of problems with the other leg) was on the threshold for acceptance from the Delphi survey. The other added outcome (psychological morbidity: anxiety or depression) was not even rated in round 3 of the survey, having not received enough support in round 2 to be carried forward. It was successfully argued by the clinical psychologist on the panel that this was because only one clinical psychologist responded to the Delphi survey, so their voice had not been 'heard' in the survey.

5.5 Future directions

I approached this project with the hope that through identifying predictors of poor outcomes, developing a risk model and developing core outcome sets I would then be able to produce recommendations for standardising research and for a programme of quality improvement for the care of amputee patients. Having now successfully achieved those objectives, I find, however, that I have become aware of more questions than answers and have come to realise that a further large programme of work is required before such firm recommendations can be drawn up. I will look at each part of the project in turn and lay out some of the key work which is still necessary.

5.5.1 Predictors of peri-operative risk

Many of the comments already raised in this Chapter require further work. Firstly, more work is needed to assess whether the new frailty parameter in the NVR is a good predictor of outcome in amputee patients. Frailty has been shown to predict outcomes in a general cohort of vascular surgery patients,[45] as well as more specifically in abdominal aortic aneurysm repair and lower limb revascularisation.[104] While functional dependence has been shown in other studies to be predictive of outcome in patients undergoing

amputation,[12,14,16] there has not to my knowledge been any work looking at the similar but related concept of frailty. In addition, the NVR has chosen to use a bespoke four-point frailty score rather than an established (validated) measure of frailty such as the Edmonton Frail Scale.[105] As a result, it is not currently known whether this four-point scale will be a useful prognostic indicator for vascular patients. Further work is required to assess the utility of this measure as a prognostic indicator and the relationship it has to outcomes such as in-hospital mortality or length of stay.

Secondly, the data in the NVR have never been subjected to external validation in terms of either formal linkage with routinely collected data such as English Hospital Episode Statistics or the Welsh Secure Anonymised Information Linkage datasets. In fact, no amputation registry has ever been subjected to this rigorous process of external data validation. Both the Hungarian and Swedish national vascular registries have been validated for patients undergoing abdominal aortic aneurysm repair or carotid endarterectomy, but this process has not been undertaken for the amputation subsets of these registries.[99,100] In order to provide confidence that the results of analysis from the amputation subset of the NVR are valid, I believe that it is necessary to undertake such a project.

Finally, I have suggested above that it is possible that limb-salvage services may improve outcomes for amputee patients as well as for the patients where limb salvage is successful. This is unknown at present but there are good reasons (discussed above) to believe that it might be the case. This is not something that lends itself to a randomised trial, as the very presence of an active limb-salvage service in a hospital is likely to have an impact on any patients who might be randomised to 'usual care'. Unfortunately, this means that this is an area of practice where running a randomised controlled trial would be difficult, so high-quality 'level one' evidence may never, therefore, exist. The next best thing would be a comparison with historical controls, perhaps matched using a propensity scoring approach. A brief search of the literature around modern limb-salvage services revealed only one study looking at results before and after implementation of the new service, and this focused (understandably) on limb salvage rather than the outcome for

amputee patients.[89] While this was not a systematic review, it highlights the fact that there is much work still to be done in this area.

5.5.2 A prognostic model of risk

The prognostic model I have developed needs to be externally validated. This could be done using data from the NVR over the next two years (which became available in December 2019). Once the performance of the model has been validated on new data it will then be possible to accurately risk adjust outcomes and to develop benchmarks for unit performance which could then be used as part of a quality improvement process designed to drive up standards.

I discussed the unavailability of a measure of frailty within the NVR over the study period and the introduction of a new measure of frailty into the NVR dataset above. Once it has been established whether this new frailty measure is predictive of outcome it will be important to evaluate whether the addition of this measure significantly improves the discrimination of the model I have developed.

In addition to this, an accurate risk prediction model for in-hospital mortality is a reasonable first step in prognostication for patients undergoing major lower limb amputation. However, the standard short-term mortality endpoint used in most of the world is 30-day mortality rather than in-hospital mortality. In order to accurately compare results in the UK with those of other healthcare systems so that we might learn lessons from both good and bad performance, it is therefore necessary to standardise the measurement of this outcome. This can be achieved through linkage of the NVR to the UK death registry maintained by the Office for National Statistics. This linkage would also allow longer term outcomes such as mortality at one year to be modelled. To my knowledge, only one model exists which predicts mortality at one year following lower limb amputation.[106] This model was developed using data from the USA Veterans Affairs Surgical Quality Improvement Programme and found a mortality rate at one year of 28.8% for patients undergoing above the ankle amputation. It is therefore questionable how much benefit the approximately 20% of patients who survive to hospital discharge

but who then die within the first year after surgery are getting from their amputation, as there is little work which has been done looking at the quality of life of amputee patients in the first year following amputation or their satisfaction with their health status. I therefore think that mortality at one year may be an important measure to be able to discuss with patients.

5.5.3 Core outcomes

I have developed core outcome sets which are applicable both to studies focussed on short-term outcomes such as post-operative pain, and medium-term outcomes such as prosthetic rehabilitation. To my knowledge, this is the first time that core outcome sets for studies of patients with the same condition but for different durations have been developed. This is important in conditions such as major lower limb amputation where recovery to steady state following surgery takes a long time, as it makes the core sets more applicable. I was not surprised to discover that while there was some overlap between the two core sets, with four outcomes common to both the short-term and medium-term sets, the majority of outcomes in the two core sets were actually different, as the importance of outcomes such as immediate perioperative complications reduces with time, whereas the importance of outcomes such as independent living increases. This highlights the need to consider the appropriate timing of core sets in future research.

The final core sets include a wide range of outcomes, from hard clinical outcomes such as mortality, to softer outcomes which are more difficult to measure and lend themselves to patient report such as social re-integration (participation in work and social activities). Further work is needed to identify the best way to measure these outcomes. Part of this must include the development of a multidimensional patient reported outcome measure (PROM). There are currently several PROMs which measure mobility and function in prosthesis users, and two others which measure mobility alone in all amputee patients (ongoing, unpublished work). There are no PROMS which are designed to measure multiple domains of health-related quality of life in amputee patients which are applicable to both prosthesis users and those who do not mobilise with a prosthesis (who represent approximately 60% of amputee patients).[107] A new PROM is therefore needed

to adequately capture disease-specific health-related quality of life, which would then need to be assessed for face and construct validity as well as reliability and responsiveness.[108]

In addition to the patient-reported outcomes in the core set there are some clinician-assessed outcomes such as wound healing and infection. There are multiple definitions for these, so there is need for consensus on the best way to measure them. Putting this together with a newly designed and validated PROM, it would then be possible to define a *core measurement set* to go alongside the core outcome set I have developed. This would require a further consensus process. With these two pieces, if we can encourage trialists and registries to adhere to these standards we will finally be able to realise the goal of efficient future amputation research by ensuring that we measure the outcomes which are most important to patients, carers, professionals and the health service in a consistent manner. Standardisation of reporting is as least as important in national registries as it is in clinical trials, as observational studies require adjustment for confounding influences and results become more robust if it is possible to pool data from multiple registries. This requires standardisation of the collection of confounding variables as well as outcomes, but with such standardisation it would also be possible to perform correction for confounding factors at scale in a uniform way across multiple registries. This is much needed work, as we saw in Chapter 2 the problems related to the generation of prognostic models from different national registries which collected data about different risk factors. Work has already begun in this direction in vascular surgery, though not for patients undergoing amputation.[82]

5.6 Conclusions

The objectives of this thesis were:

1.
    a. To identify the principal risk factors for peri-operative mortality and morbidity in patients undergoing MLLA using routinely collected national data.
    b. To use these risk factors to develop a prognostic model for peri-operative mortality, again using routinely collected national data.
2.
    a. To develop an exhaustive list of outcomes for research and service evaluation involving patients undergoing major lower limb amputation as a result of complications of peripheral vascular disease.
    b. To establish consensus on core outcome sets for both short-term and medium-term research and service evaluation involving patients undergoing MLLA for complications of peripheral vascular disease, using the list developed in 2.a. above as a starting point.

In the preceding sections of this chapter I have highlighted the ways in which I have achieved these goals, highlighting some limitations and areas where further work is needed.

Major lower limb amputation is a mutilating procedure, which is performed for end-stage peripheral vascular disease when surgeon and patient agree that it is the best option to either prolong life or improve its quality. As it is viewed by many as a 'failure' of surgical reconstruction, research has mainly been focussed on prevention. In order to improve outcomes for this group of individuals, we must accept the fact that sometimes it is the best option available, and work to make it the best option that it can be. The components of my thesis have sought to tackle this in different ways. It is my hope that by highlighting the predictors of perioperative mortality and morbidity in these patients

that it will stimulate researchers to develop interventions which might improve these outcomes. By developing a model for predicting perioperative mortality risk it is my hope that this will enable clinicians to better inform patients and their relatives about the expected outcomes of surgery. By developing core outcome sets I have highlighted the outcomes which matter the most, so should receive attention for those designing both interventional trials and quality improvement projects, allowing future studies to be more focussed. Finally, by defining the list of outcomes which should be reported by all of these studies, different studies will become more comparable, so that effective interventions will be identified more readily and implemented widely, and research waste minimised.

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Appendix A. Thematic framework for core outcome sets focus groups

Aim: To identify outcomes for patients following major lower limb amputation

Data: 4 qualitative focus groups with patients, carers and health care professionals, fully transcribed verbatim.

Analysis: Thematic analysis. Focus Group 1 with mixed health care professional group = blue font, Focus Group 2 with patients and carers = red font, Focus Group 3 with health care professionals (medics) = black font, Focus Group 4 with physiotherapist health care professionals = green font

Overview of themes

1. Quality of life
2. Social functioning
3. Psychological/ biopsychosocial factors
4. Illness representations
5. Communication
6. Financial issues
7. Amputation type
8. Wound healing
9. Pain
10. Rehabilitation
11. Mobility: Prosthesis
12. Mobility: other mobility aids
13. Returning home

14. Falls
15. Readmissions
16. Clinical state
17. Fate of other limb
18. Risk reduction behaviour
19. Mortality

The thematic framework is presented in full on the following pages.

	Theme	Suggested sub-themes	Comments	Outcomes
	Quality of life	1.1 Body image		Body image
		1.2 Comfort	• Free of pain and complications	Pain in amputation stump/phantom pain/prosthesis comfort and fitting
		1.3 Independence	• Return to previous e.g. whether can only use 1 room in the house, whether leading an "active life", whether carers needed at home	Level of independent mobility or function achieved/independent living/ability to return to work
	Social functioning	2.1 Social goals	• Relates to personalised individual patient's goals both social e.g. going away to their caravan/holiday home, going out for meal, going out for drink, pushing grandchild in pram, walking daughter down church aisle at her wedding, walking into lounge on Christmas day with grandchildren	Participation in social activities
		2.2 Practical goals	• Relates to practical goals e.g. filling car with petrol, shopping (reaching high shelves, pushing trolley),	Independent living

			access to buildings, getting taxis, getting on aeroplane. Mobility e.g. are they able to get out of house, are they able to move around house	
		2.3 Relationships	• Relationships affected ("I wasn't a nice person to know")	Coping strategies and psychological adaptation
		2.4 Hobbies and exercise	• Hobbies and exercise: Golf, working in shed, cycling, Zumba fitness class, getting into garden	Level of independent mobility or function achieved
		2.5 Personal care	• Personal care: cooking for self, shaving self, getting up to go toilet, getting own drink of water, housework	Level of independent mobility or function achieved
		2.6 Personal space	• Ability to have 'personal space'	Independent living

		2.7 Social support	• Existence and use of social network/social support	Participation in social activities
		2.8 Driving	• Patient able/allowed to drive. Patient has gained "the blue badge" for parking • Suggested that this might be more of a concern for family members	Participation in social activities/Independent living
		2.9 Sexual activity	• Not mentioned spontaneously but only mentioned briefly in relation to literature review prompts	Sexual activity
	Psychological/ biopsychosocial factors	3.1 Managing expectations	• Managing expectations and feeling psychologically prepared. Will depend on whether elective vascular or orthopaedeic patient (e.g. patient doing own research before surgery, time for visit from nurse, read leaflet, visit unit/talk to surgeon in advance) /	Coping strategies and psychological adaptation

			• Being prepared might involve psychologist, CBT counselling, chronic pain counselling, pain management programme	
		3.2 Negative	• Grief/bereavement/loss for the future, depression, anger, anxiety, disappointment, shock, frustration, regret, guilt/forgiving self, blame, sadness, fear (and fear of unknown/pain), uncertainty (e.g. could amputation have been avoided?), emotional trauma	Coping strategies and psychological adaptation/Anxiety or depression
		3.3 Positive	• hope for a new start, positive mood, motivated, euphoria/elation, self-belief, confidence •	Coping strategies and psychological adaptation
		3.4 Recognising 'difference'	• Physical: Phantom sensations/forgetting haven't got leg (try to cross legs, think can still feel feet)	Phantom sensations or pain/falls

		3.5 Family perspective	• How will family cope	Not covered – Impact on family/loved ones
	Illness representations	4.1 Narrative around amputation	• Patient beliefs around what has happened to them. (see Weiman Model Common Sense Model). • E.g. Amputation can be seen as positive by some patients if have experienced pain previously, or if had experienced "nibbling", or if had had "smelly open wound" which required frequent visits to hospital and restricted social functioning. Some patients wish they had had the amputation earlier. "amputation is not always a failure" • Could amputation have been avoided? • Not being treated like "an invalid" • Dealing with other people's reactions/stigma/staring/derogatory	Satisfaction with situation

	Communication	5.1 Patient and health professional communication	• In terms of patient: being listened to, involved in decision making, given opportunity to ask questions, interaction with surgical team, being 'understood' and understanding what was going to happen, empowering patient • Individual patient goal setting (theory of care owners' model) • Terminology - asking the patient what they want to call the residual limb • Empathy from health care professionals • Continuity of care ('knowing' the patient) • Will depend on whether elective vascular or orthopaedeic patient	Not covered – two new outcomes: • Shared decision making. • Effective communication between healthcare team and patient/carers
		5.2 Multi-disciplinary communication	• MDT meeting amongst health professionals	Compliance with guidelines for care

	Financial issues	6.1 Return to work	• Suggested that this might be more of a concern for family members • Not only about financial concerns but may also be psychological issue relating to positive mood, independence etc.	Ability to return to work
		6.2 Financial worries	• Loosing home, cost of adapting home	Cost of treatment
	Amputation type	7.1 Amputation technique	• 'Good' and 'bad' amputation • Amputation technique – long posterior flap or skew flap – will have impact on mobility and rehabilitation e.g. prosthesis fitting e.g. months of dressings being changed and months of attending outpatients appointments. Different perspectives – to surgeon could be failure of treatment but in terms of	General stump or wound problems

			rehabilitation could save months. Positioning of scar line	
		7.2 Level of amputation	• Level of amputation (i.e. through, below or above knee) – different perspectives – to surgeon could be failure of treatment but in terms of rehabilitation could save months (will also impact on time until can go home – if home not already adapted, above knee amputation might mean cannot go home to existing accommodation)	Prosthesis use/satisfaction with situation/prosthesis comfort and fitting/Time until mobile with temporary or definitive prosthesis/Length of stay
		7.3 Shape of residual limb	• Shape of residual limb (can be changing shape for up to 12 months afterwards). Fixed flexion deformity. "Stump volume reduction"?	Stump swelling/joint contractures
	Wound healing	8.1 Wound healing	• wound healing (or prolonged wound healing, deep or surface healing, strength of wound, scarring, skin	Problems with amputation stump healing

			grafting) and on amount of energy required to walk, stitches removal	
	Pain	9.1 Level of pain	• Free of pain? Is the pain controllable? (Pain should be controllable but relies on the patient telling health professional) • Chronic pain, does the pain escalate. • For some even 12 months later residual limb may be changing – complex. Need to consider time periods. • Pain will be categorised/asked about at different time periods – post operative setting: are you in pain? Is it mild/moderate/severe? • Later is pain persistent? What does it feel like? Where is it coming from?	Pain in amputation stump

		9.2 Residual limb pain		Pain in amputation stump
		9.3 Nerve pain/neuroma		Pain in amputation stump/peripheral nerve problems
		9.4 Wound pain/surgical site pain	• e.g. Pressure ulcer	Pain in amputation stump
		9.5 Sepsis pain		Pain in amputation stump
		9.6 Phantom limb pain	• Phantom limb pain deals with emotional and physical aspects	Phantom sensations or pain
		9.7 Arterial pain		Pain in amputation stump
		9.8 Walking pain	• (e.g. muscle cramps)	Pain in amputation stump
		9.9 Prosthesis pain		Pain in amputation stump/problems with skin of amputation stump/prosthesis comfort and fitting
		9.10 Pain management: Medication	• Referral to others for pain e.g. pain team, GP, plastic surgery, psychology, • OTC e.g. paracetamol • Opiates e.g. Morphine. Side effects e.g. vomiting • Type of anaesthetic Side effects e.g. vomiting	Amount of painkillers needed

			• Co-codamol • Gabapentin	
		9.11 Pain management: non-medication	• Are patients supplementing due to pain (e.g. cannabis use) • Other ways of handling pain e.g. handling techniques, massage, laser or mirror box therapy	Not covered – use of drugs or therapies which have not been prescribed
	Rehabilitation	10.1 Rehabilitation	• Continuity of care (confidence, trust, building relationships) • Peer support • Time out of bed • Rehabilitation generally and self-awareness and setting realistic goals for mobility	Amount of physiotherapy during rehabilitation/ time taken to complete rehabilitation

	Mobility: prosthesis	11.1 Prosthesis comfort	• Generally and length of time able to wear prosthesis comfortably, being able to bear weight for different lengths of time	prosthesis comfort and fitting
		11.2 Prosthesis look	•	Prosthesis use/satisfaction with situation/prosthesis comfort and fitting
		11.3 Prosthesis function	• Walking gait 'normal' or acceptable, Stairs, steps, indoor/outdoor walking, walking on slopes, getting up if fall, walking various distances, picking up objects off floor, carrying objects, Taking on and off prosthesis	Prosthesis use/characteristics of gait with prosthesis
		11.4 Overall satisfaction with prosthesis	• prosthesis won't fit sometimes, satisfaction/overall experience of using limb daily	Prosthesis use/satisfaction with situation/prosthesis comfort and fitting
		11.5 Time to walking	• Patient's desire to walk (walking training)	Time until mobile with temporary or definitive prosthesis

		11.6 Time to start physiotherapy	• Required equipment available: Suitable footwear (e.g. insoles), early walking aid (inflatable), compression sock, Frame. Sticks. Crutches. • Self-awareness and setting realistic goals	Amount of physiotherapy during rehabilitation/Need for mobility aids/satisfaction with situation/prosthesis comfort and fitting
	Mobility: other mobility aids	12.1 Use of crutches	• Frame. Sticks. Crutches. Patients have desire to be at same level as others (rather than lower down as in wheelchair).	Need for mobility aids
		12.2 Use of wheelchair	• Indoor/outdoor wheelchair. Stump board. Slide board	Need for mobility aids
		12.3 Mobility scooter	•	Need for mobility aids
		12.4 Transfers	• Transfers (shower, toilet, bed, car, wheelchair)	Need for mobility aids

	Returning home	13.1 Length of hospital stay	• Will be influenced by needing to have the house altered, whether a catheter is still in, whether amputation was above the knee or not • Managing wound as outpatient	Length of time in intensive care/acute hospital/rehabilitation
	Falls	14.1 Experiencing falls		Falls
		14.2 Injury as a result of falls		Falls
	Readmissions	15.1 Readmission relating to surgery	• Whether there has been a need for revision surgery or not. In 10 post-operative days (short term) or after (mid-term?)	Need for re-admission to hospital after discharge
		15.2 Other hospital visits	• Difficult having to go to so many different appointments	Not covered – Number of outpatient appointments
		15.3 Revision surgery		Need for further operation on stump
	Clinical state compared to pre-operative state	16.1 Clinical state	• Medical stability. Improvement in clinical state. Before surgery patient may have been very unwell	Overall perioperative complications/stroke/ myocardial Infarction (heart attack) during surgery or follow-up

			e.g. toes removed, sleeplessness, septic, low functioning therefore loss of muscle, and reduction in stamina and fitness. • Co-morbidity will affect timescale in which to try and achieve patient's goals • Operation clinical success (but people still need support) • Without amputation might be dead • Extra energy needed for walking could trigger other health problems e.g. stroke, heart attack, vascular dementia	
	Fate of other limb	17.1 Amputation of other leg	• Pressure on other limb due to desire to walk. May have to stop walking due to risk on other leg	Need for amputation of other leg

		17.2 Deterioration of other leg	• Blisters, strain on other knee/hip. Deterioration of other limb (may be worsened by longer hospital stay, pressure ulcer), Pressure heel sores	Development of problems with the other leg
	Risk reduction behaviour	18.1 Risk reduction behaviour	• Smoking cessation • Diabetic control • Drug abuse • Homeless status	Diabetic control, use of unprescribed drugs and discharge destination already covered. Smoking cessation can be included in Compliance with guidelines for care
	Mortality	19.1 Mortality		Death within a specified period of time after operation, or while still in hospital after initial amputation/length of survival after amputation

Appendix B – Publications and Presentations

B.1 Publications

Much of the content of Chapter 2 was published in the *European Journal of Vascular Surgery.* The citation for this work is as follows.

Ambler GK, Thomas-Jones E, Edwards AGK, Twine CP. Prognostic Risk Modelling for Patients Undergoing Major Lower Limb Amputation: An Analysis of the UK National Vascular Registry. *Eur J Vasc Endovasc Surg.* 2020; 59(4):606–613. doi: 10.1016/j.ejvs.2019.12.006.

Much of the method described in Chapters 3 and 4 was published as a protocol in *Trials*. The citation for this work is as follows.

Ambler GK, Bosanquet DC, Brookes-Howell L, Thomas-Jones E, Waldron CA, Edwards AGK, Twine CP. Development of a core outcome set for studies involving patients undergoing major lower limb amputation for peripheral arterial disease: study protocol for a systematic review and identification of a core outcome set using a Delphi survey. *Trials*. 2017;18(1):628. doi: 10.1186/s13063-017-2358-9.

B.2 Presentations

All of the work in this thesis has been presented at national and international vascular surgery conferences. Some of these presentations were published in abstract form in peer-review journals. Details of the presentations are given below.

2019 Plenary talk in the Sol Cohen Prize session at the Vascular Society of Great Britain and Ireland Annual Scientific Meeting in Manchester, UK: "Development of Core Outcome Sets for patients undergoing major lower limb amputation for complications of peripheral vascular disease."

2019 Plenary talk at the European Society for Vascular Surgery annual conference in Hamburg, Germany: "Development of Core Outcome Sets for patients undergoing major lower limb amputation for complications of peripheral vascular disease."

2018 Parallel talk at the Vascular Society of Great Britain and Ireland Annual Scientific Meeting in Glasgow, UK: "Risk factors for in-hospital mortality following major lower limb amputation: analysis of 10,000 patients' data from the UK National Vascular Registry."

2018 Parallel talk at the European Society for Vascular Surgery annual conference in Valencia, Spain: "Risk factors for in-hospital mortality following major lower limb amputation: analysis of 10,000 patients' data from the UK National Vascular Registry."

2018 Parallel talk at the Charing Cross Vascular Symposium in London: "Outcomes in major lower limb amputation: a systematic review".

2017 Invited talk at the Vascular Society of Great Britain and Ireland Annual Scientific Meeting: "Development of Core Outcome Sets for Amputation".