REHABILITATION AND PHYSICAL FUNCTIONING AFTER TREATMENT FOR LOWER EXTREMITY MUSCULOSKELETAL TUMOURS

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You beat cancer by how you live, why you live and in the manner in which you live.

- Stuart Scott

Abstract

Physical deficits are common after treatment for musculoskeletal tumours. Good quality support services, and the use of valid and reliable physical assessments to guide rehabilitation could significantly reduce these deficits, but knowledge about this is lacking. This PhD thesis therefore, examines the national state of rehabilitation services and outcomes for patients who have an amputation for sarcoma (phase 1), systematically reviews the current state of objective clinical measurement of physical functioning (phase 2), and pilots the use of small accelerometer-based body worn monitors (BWMs) to assess physical functioning in patients treated for lower extremity musculoskeletal tumours (phase 3).

Original contributions to knowledge are:

- ***Phase 1:*** Patients have a variable experience of rehabilitation services in England, after amputation for sarcoma, with services falling short of recommended national standards. Patients also present with poor physical functioning, pain and quality of life.
- ***Phase 2:*** Studies quantifying balance, gait and physical activity (PA) are lacking in patients with lower extremity sarcomas, with most not using valid and reliable instruments.
- ***Phase 3:*** This study supports the feasibility, acceptability and general validity of using a low-cost accelerometer-based BWM for rapid physical assessments in the clinic and real world. BWM measures of ellipsis (area of postural sway), root mean square (magnitude of sway), jerk (smoothness of sway), step time, stance time, step length, step velocity, total time, instrumented timed up and go (iTUG) time, total steps/day and alpha (pattern of bouts) were most sensitive in characterising physical functioning.

The ***major conclusions*** were that patient experience of rehabilitation services and outcomes are variable after amputation for sarcoma, with scope for improvements. There is a deficit of studies on balance, gait and PA assessments in patients with sarcoma and accelerometer-based BWMs, could be a solution as the thesis supports their feasibility, acceptability and validity.

Acknowledgements

I would like to acknowledge everyone who has supported me during my four years of pursuing the PhD, at Newcastle Upon Tyne Hospitals NHS Foundation Trust and Newcastle University. This is to extend my special thanks to my supervisors Mr Craig Gerrand, Professor Lynn Rochester and Dr Alan Godfrey for their continued input and supervision throughout. I would particularly extend my sincere thanks to Mr Craig Gerrand, Consultant Orthopaedic Surgeon, as under Mr Gerrand's valuable guidance, I took on my first challenge by managing and co-ordinating the 5-centre national project, and thereafter everything was an exciting and constant journey of learning. I would also specially like to thank my second main supervisor, Professor Lynn Rochester for supporting my growth as an academic physiotherapist, through her constant supervision and support in all forms. Thanks to my supervisory team, I have grown as an academician and clinician under their constant guidance and support. It has been an exciting journey – extending from applying for grants to securing funding for this theme of research, having times of success and sometimes no success, writing manuscripts, presentation at conferences and learning the art of networking and collaboration.

The North of England Bone and Soft Tissue Tumour Service, part of Newcastle upon Tyne Hospitals NHS Foundation Trust has provided me with an excellent clinical and learning environment from experts in this field. I am indebted particularly to all staff working at the North of England Bone and Soft Tissue Tumour Service for their assistance during Phase 1 and 3, in patient screening and recruitment, in the musculoskeletal clinics and all staff from the Orthopaedic Research Unit for their support in data collection. I would also like to thank the staff nationally in the five specialist bone cancer centres, with whom we had a national collaboration to successfully manage and run Phase 1 of the PhD. I would further like to thank Dr Linda Errington for her guidance with Phase 2, especially with the methodology of the systematic review. I would also specially like to extend my sincere thanks to Dr Alan Godfrey, Dr Silvia Del Din, Dr Brook Galna and Mr Aodhàn Hickey for their technical and engineering input and complex data processing tools created and used within this project to successfully manage and run Phase 3 of the PhD.

I would also specially like to extend my sincere gratitude to all the patients, recruited for my Ph.D. projects (in Phase 1 and 3), as well as the control participants from ICICLE-GAIT Project in CARU and the Osteoarthritis project in Freeman hospital, who took time out of their tight schedules to assist me with this project. I am also extremely thankful and indebted to the funders; Quality Improvement Development and Innovation Scheme (QIDIS) Scheme, Children with cancer, Sarcoma UK charity, Shears foundation, and N.O.R.T.H. charities; for funding the PhD projects and my salary. I would also like to thank everyone for their support at the Northern Institute for Cancer Research (NICR), where I am registered for my PhD.

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Statement of work undertaken

Mr Craig Gerrand, Consultant Orthopaedic Surgeon and Clinical Lead for the North of England Bone and Soft Tissue Service, is the Chief Investigator (CI) for projects undertaken in different phases of the PhD. After a background review of literature and identifying gaps, the idea was conceived by our team to 'Explore the national state of rehabilitation services and outcomes for patients who had an amputation for a sarcoma and to improve functional assessments for these cancer patients', which formed the three main phases of the thesis. Mr Gerrand's drive to constantly collaborate and network is extremely important for this rare cancer and he is constantly striving to improve the quality of care and research in this cancer group. Gaining supervision from Professor Lynn Rochester, as a part of her team was an honour, as Phase 2 and 3 which constituted the development of objective functional assessments for these patients was only possible with Professor Rochester's oversight.

Phase 1 of the PhD was a 5-centre project led by the North of England Bone and Soft Tissue Tumour Service (Newcastle Upon Tyne Hospitals NHS Foundation Trust). The five specialist participating centres were the North of England Bone and Soft Tissue Tumour Service, Department of Orthopaedics, Freeman Hospital, Newcastle Upon Tyne, United Kingdom, NE77DN; Royal National Orthopaedic Hospital NHS Trust (RNOH), Stanmore, London, HA7 4LP; Royal Orthopaedic Hospital NHS Foundation Trust, Birmingham, B31 2AP; Oxford University Hospitals NHS Foundation Trust, Oxford, OX3 7LD; and the Robert Jones and Agnes Hunt NHS Foundation Trust, Oswestry, SY10 7AG. I was responsible for the project management of this national project, under the supervision of CI, Mr Craig Gerrand and co-investigator Ms Shona Murray. As part of my responsibilities, a literature review and patient public involvement (PPI) interviews with patients were undertaken by myself to identify the gaps in knowledge. Protocol development and compiling the data collection tools (based on literature and national standards) for the project, was completed by myself under the supervision of Mr Gerrand. I visited the participating centres, presented the project idea to multi-disciplinary teams at the centres and set-up the national project with support of senior orthopaedic consultants; Professor Tim Briggs from Stanmore, Professor Rob Grimer from Birmingham, Mr Paul Cool from Oswestry and Mr Duncan Whitwell from Oxford. Co-ordinating the project at a national level and identifying site-coordinators at each centre was conducted by myself, during visits to other centres. Site co-ordinators identified at each site were specialist physiotherapists or nurses 'Suzy Hudson and Jennifer Fulton from London Stanmore, Vicky Wren and Helen Stradling from Oxford, Lin Russell from Birmingham, Kristan Grant from Oswestry'. The site co-ordinator at each site was responsible for identifying eligible patients from their centre, recruiting them into the project and sending questionnaires either in clinic or by post. Sending questionnaire packs to participating centres and receiving completed questionnaires from patients was part of my responsibility. As part of this project, our national team have collected 105 amputation (AMP) and 63 limb sparing surgery (LSS) participant questionnaires.

Phase 2 of the PhD was undertaken at the Orthopaedic Research Unit in Freeman Hospital and in the Clinical Ageing Research Unit (CARU), Newcastle University situated on the Campus of Ageing and Vitality. Under the guidance of Mr Craig Gerrand, Professor Lynn Rochester, Dr Alan Godfrey and Dr Linda Errington, I undertook a systematic review as Phase 2, I liaised with Dr Errington who provided her expert advice about methodology and search strategy. Developing the objectives of the review, creating the data collection tools, and the quality assessment tool for the review was performed by myself, again under the guidance of our team.

Phase 3 of the PhD was conducted at two major sites, screening, recruitment and data collection was completed at the major clinic sites and Human Movement Room at the North of England Bone and Soft Tissue Tumour Service, Newcastle Upon Tyne Hospitals NHS

Foundation Trust; and data processing/analysis was completed at the Clinical Ageing Research Unit (CARU), Newcastle University situated at Campus of Ageing and Vitality. I was responsible for grant applications to secure funding for this project (co-applicant with main applicant Mr Gerrand), designing the study, running national and local PPI workshops in inform study design, project set-up and running of project. I also prepared the Integrated Research Application System (IRAS) application and co-ordinated the submission to regulatory bodies (ethics, R&D, adopting to portfolio, caldicott information governance) to gain full study approvals, for commencing the study at Newcastle hospitals for recruiting patients for Phase 1 and 3. As part of the PhD, I independently screened clinic lists, clinical records and recruited patients from Newcastle Upon Tyne Hospitals NHS Foundation Trust, and also performed the data collection. Yet this would not be possible without the assistance of extended teams, I was responsible for co-ordinating the projects and liaising with Cancer Nurse Specialists Ms Karen Fisher, Ms Elizabeth Gregory for recruiting patients from musculoskeletal clinics in Freeman, Ms Kate Jackson, Ms Helen Nicholson, Ms Emma Rogerson, specialist staff from Disability services centre (DSC) in Freeman, Dr Juliet Hale (Consultant Paediatric Oncologist) and Ms Shona Murray (Consultant Orthopaedic Surgeon) for recruitment from Paediatric joint clinics in Royal Victoria Infirmary (RVI) and Mr Richard Milner, Mr Maniram Ragbir (Plastic surgeons) from plastic clinics in Freeman Hospital. In Phase 3, full study protocol including body worn monitor (BWM) data collection, and musculoskeletal tumour disease-specific assessment was conducted independently by myself, with some assistance from a staff from the Orthopaedic Unit. As part of this project, I have completed 40 participant assessments. BWM data checking and cleaning was performed by Dr Alan Godfrey and Aodhán Hickey (Human Movement Science Research technician), and segmentation of clinic data in MATLAB® (R2012a) program was performed by all three of us. Processing of BWM data was completed by Aodhán Hickey (using MATLAB® codes developed by Dr Alan Godfrey and Dr Silvia Del Din (Biomedical Engineer, CARU). Data management and inputting of data collected during the PhD projects were performed by myself with the support of Mr Luke Wigney, database manager of Sarcoma Unit at Freeman hospital, and also the 'Orthopaedic Research Unit'. Data entry was double-checked by us both against paper copies of the data collected, to ensure robust accurate data.

Since commencement of the PhD, I have also assisted in managing multiple studies in the Orthopaedic Research Unit and also a multi-centre project led by RNOH, Stanmore. I have helped manage screening, recruitment, data collection, analysis in a wide range of orthopaedic and trauma projects (cross-sectional and longitudinal studies), ranging from hip, knee and ankle joint replacements to fracture studies. As part of the wider study in Phase 3, data were also collected using Microsoft Kinect and Xsens 3D motion tracking system by myself, the data of which is not included in this thesis. I have also assisted in data collection of a similar 'Osteoarthrtis study' using BWMs. I analysed all data collected in all phases of the PhD and completed all the statistical analysis independently, with advice taken from PhD supervisors, study team members and statisticians (especially Mr Paul Cool and Dr Simon Kometa (Research computing analyst, Newcastle University) in Phase 1 and Dr Kim Pearce (Chartered Senior Statistician, Newcastle University) and Dr Brook Galna (Lecturer (biomechanics) Newcastle University) in Phase 3. For project dissemination, I independently lead PPI workshops at national conferences, presented our project findings at national and international conferences, at local and national meetings. 2 manuscripts were published from Phase 1 in peer-reviewed journals with me as the first author and co-authors from the national team, and senior author as Mr Gerrand. I also compiled and published results of Phase 2 successfully as the first author, with my other supervisors as co-authors, and Mr Gerrand as senior author. I have also contributed as a second author in two published articles linked to this topic area. I am currently in process of preparing manuscripts from Phase 3, to publish the results in peer-reviewed journals. I was responsible for the write-up of the PhD thesis.

Awards, publications and presentations arising from or for the thesis

Awards

1. Children with Cancer UK Charity, Functional evaluation of survivors of paediatric bone and soft tissue tumours – a pilot study of two new technologies. Craig Gerrand, **Sherron Furtado,** Thomas Ploetz, Karthikeyan Muthumayandi. June 2013 until May 2014 - £47,613.29

2. Sarcoma UK Charity, Evaluation of physical functioning in adults treated for bone and soft tissue sarcomas – a feasibility study of two new technologies. Craig Gerrand, **Sherron Furtado**, Thomas Ploetz. June 2014 until December 2014 - £27390.99

3. N.O.R.T.H Charity (Northern Orthopaedic Research): Funding for Doctorate of Philosophy (PhD) course to complete from Newcastle University. **Sherron Furtado** - June 2013 until December 2016 - £3,240.

4. N.O.R.T.H. Charity (Northern Orthopaedic Research - Supporting ongoing research into new assessments of functional outcomes after treatment for Bone and Soft tissue tumour patients: Craig Gerrand, Lynn Rochester and **Sherron Furtado**. November 2014 for 6 months - £18,743.

5. RCF Funding 2014/2015: Develop musculoskeletal research programme in Sarcoma to develop the theme of Physical functioning, performance status and biomarkers in patients with sarcoma. Craig Gerrand, **Sherron Furtado**, Kenneth Rankin and Chris Snowden. November 2014 until May 2015 - £16,206.

6. Shears Foundation: Funding to develop novel rehabilitation models for assessment and treatment in patients treated for musculoskeletal cancer "Supporting patients treated for musculoskeletal cancer – Developing new ways to assess and improve physical activity levels". April 2016 until December 2016 - £18,283.

7. Sarcoma UK Charity – 'A holistic model of rehabilitation to improve QoL after sarcoma'. Mr Craig Gerrand, **Sherron Furtado**, Dr Silvia Del Din, Jan Lecouturier and Professor Lynn Rochester. January 2017 - December 2017 - £33080.28.

8. RCF 2016/2017 – To develop a national cohort of sarcoma patients to investigate physical functioning. Mr Craig Gerrand, **Sherron Furtado**, Professor Lynn Rochester. April 2017 – June 2018 – £33,382.

Publications

1. **Sherron Furtado1**, Rob Grimer3, Paul Cool4, Shona Murray1, Tim Briggs2, Jennifer Fulton2, Kristin Grant4, Craig Gerrand1, Physical functioning, pain and quality of life after amputation for musculoskeletal tumours: a national survey, Bone and Joint Journal 2015, Bone Joint J. 2015 Sep;97-B(9):1284-90. doi: 10.1302/0301-620X.97B9.35192.

2. **Furtado S1**, Briggs T2, Fulton J2, Russell L3, Grimer R3, Wren V4, Cool P5, Grant K5, Gerrand C1 "Patient experience after lower extremity amputation for sarcoma in England. A National Survey." Journal of Disability and Rehabilitation 2016 Jul 6:1-20.

3. **Furtado S1**, Errington L2, Godfrey A3, Rochester L4, Gerrand C5. Objective clinical measurement of physical functioning after treatment for lower extremity sarcoma - A systematic review. Eur J Surg Oncol. 2016 Oct 14. pii: S0748-7983(16)30933-7. doi: 10.1016/j.ejso.2016.10.002

4. T. Ng Kee Kwong, **S Furtado**, C. Gerrand. What do we know about survivorship after treatment for extremity sarcoma? 2014, A systematic review. Eur J Surg Oncol. 2014 Sep;40(9):1109-24. doi: 10.1016/j.ejso.2014.03.015.

5. C Gerrand, **S. Furtado**. Issues of Survivorship and Rehabilitation in soft tissue sarcoma, Clinical Oncology , Volume 29 , Issue 8 , 538 - 545

National and International Presentations

Oral presentations

29th May 2013 to 1st June 2013 - European Musculoskeletal Oncology Society (E.M.S.O.S) meeting - 14th Symposium EMSOS Nurse and Allied Health Professions Group Meeting at Gothenburg, Sweden.	Survivorship after bone and soft tissue sarcomas of the extremities. A systematic review of the literature.
22nd June to 23rd June 2013 - Bone Cancer Research Trust Conference (BCRT) 7th Annual Patients' and Supporters' conference: No Limb-its at Leeds, UK.	Led a patient and professionals workshop on national audit project Quality Improvement Programme: Sarcoma National Multi-centre audit.
26th February 2014 to 28th February 2014 - British Sarcoma Group (BSG) meeting at Nottingham, UK.	Service Provision after amputation for Musculoskeletal tumours – A National Audit.
26th February 2014 to 28th February 2014 - BSG meeting at Nottingham, UK. 21th May 2014 to 23rd May 2014: 27th Annual meeting of the E.M.S.O.S. meeting at Vienna, Austria.	Functional, Pain and Quality of Life outcomes after amputation for Musculoskeletal tumours - A National Survey in England.
9th May 2014 - British Orthopaedic Society Oncology (B.O.O.S) Meeting at Birmingham, UK. 25th February 2015 to 27th February 2015 - BSG meeting at Nottingham, UK 29th April 2015 to 1st May 2015 - 28th Annual meeting of the E.M.S.O.S. meeting at Athens, Greece 12th May 2015 - Scottish Sarcoma Network (SSN) Education Day held at Perth – Invited for a talk to promote and spread awareness on this novel area of research in Scotland NHS. 29th September 2015 to 2nd October 2015 - British Orthopaedic Association (BOA) 2015 (The presentation prepared by me was presented by a member of our team)	Laboratory based measurement of physical functioning after treatment for sarcoma using a triaxial accelerometer - a feasibility study. Evaluating physical activity in the community after sarcoma treatment using triaxial accelerometry. A new paradigm for outcome assessment?
Stimulating Research involvement for clinicians in the Newcastle Upon Tyne Hospitals NHS trust.	Presentation of overview of PhD.
1ST March 2017 to 2nd March 2017 – BSG meeting at Bristol, UK.	Accelerometer based measurement of balance and gait after treatment for lower extremity musculoskeletal cancer in the clinic: A feasibility and validity study.

Poster presentations

27th February 2013 to 1st March 2013 – BSG meeting at Nottingham, UK	Quality Improvement Programme: Sarcoma National Multi-centre audit – A Work in Progress What does YouTube tell us about life after hip disarticulation?
26th June 2013 - Children with Cancer Charity UK event, Poster presentation at House of Lords, London, UK	Functional evaluation of survivors of paediatric bone and soft tissue tumours – a pilot study of two new technologies
26th February 2014 to 28th February 2014 - BSG meeting at Nottingham, UK. 21th May 2014 to 23rd May 2014: 27th Annual E.M.S.O.S. conference at Vienna, Austria. 9th May 2014 - British Orthopaedic Society Oncology (B.O.O.S) meeting at Birmingham, UK. 26th February 2014 to 28th February 2014 - BSG meeting at Nottingham, UK. 16th May 2017 – Poster of Service provision for Newcastle Upon Tyne Hospitals NHS Foundation Trust (NUTH) Quality improvement Competition.	Functional, Pain and Quality of Life outcomes after amputation for Musculoskeletal tumours - A National Survey in England. Service Provision after amputation for Musculoskeletal tumours – A National Audit Project
25th February 2015 to 27th February 2015 - BSG meeting at Nottingham, UK	Laboratory based measurement of physical functioning after treatment for sarcoma using a triaxial accelerometer - a feasibility study.
1ST March 2017 to 2nd March 2017 – BSG meeting at Bristol, UK. 25th June to 29th June 2017 - International Society of Posture & Gait Research (ISPGR) World Congress held at Fort Lauderdale, USA. 2nd June 2017 - B.O.O.S meeting at Royal Victoria Infirmary (RVI), Newcastle Upon Tyne Hospitals NHS Foundation Trust, UK.	Accelerometer based measurement of balance and gait after treatment for lower extremity musculoskeletal cancer in the clinic: A feasibility and validity study. Accelerometer based measurement of Ambulatory Physical Activity in the community after treatment for lower extremity musculoskeletal cancer – A feasibility and validation study.

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Rehabilitation and Physical functioning after treatment for Lower Extremity Musculoskeletal Tumours

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Abbreviations

ACP = Displacement of amplitude of the centre of pressure

ADLs = Activities of daily living

AMP = Amputation

AP = Antero-posterior

AS = Adult cancer survivors

ASKp-38 = Activity scale for kids

α = Alpha

BACPAR = British Association of Chartered Physiotherapists in Amputee Rehabilitation

BMI = Body Mass Index

BS = Bone sarcoma

BSRM = British Society of Rehabilitation Medicine

BT = Bone tumour

Bt-DUX = Bone tumour – DUX

BWM = Body worn monitor

CS = Childhood cancer survivors

cm/s = centimetre per second

COM = Centre of mass

COT = College of Occupational Therapists

CSP = Chartered Society of Physiotherapy

CWA = Continuous Wave Accelerometer

CWT = Continuous Wavelet Transform

DWT = Discrete Wavelet Transform

/day = per day

EQ-5D = EuroQol group quality of life questionnaire

f95 = Frequency below which 95% of power of acceleration power spectrum is present

FC = Final contact

FMA = Functional Mobility Assessment

GC = Gait cycle

gcs = Gait cycles

GP = General Practitioner

GPA = General physical activity

IC = Initial contact

ICC = Intraclass correlation coefficient

ICF = International Classification of Functioning, Disability and Health

ICICLE-GAIT = Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation — GAIT

ICICLE – PD = Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation — Parkinson's disease

IRAS = Integrated Research Application System

iTUG = Instrumented timed up and go

IQR = Interquartile ranges

km/hr = kilometre per hour

L5 = fifth lumbar vertebrae

LSS = Limb sparing surgery

MANCOVA = Multivariate analysis of co-variance

MFH = Malignant fibrous histiocytomas

m = metre

mid = middle-aged group

Min – max = Minimum – Maximum

ML = Medio-lateral

m/s = metre per second

m/min = metre per minute

mm/sec = millimetre per second

MSTS scoring system = Musculoskeletal Tumour Society (MSTS) scoring system

N/A = Not available

NHS = National Health Service

NOS = Not otherwise specified

NREC = National Research Ethics committee

OMGUI = Open Movement Software Informers

PA = Physical Activity

PCI = Physiological Cost Index

PMBT = Primary malignant bone tumour

PODCI = Paediatric Outcomes Data Collection Instrument

PREHAB = Prehabilitation

Pre-AMP = Pre-amputation

PROM = Patient-reported outcome measure

QIDIS = Quality Improvement Development and Innovation Scheme

QoL = Quality of life

QoL-CS = Quality of life-Cancer Survivors

Rand-36 = Rand 36-Item Health Survey

RNL = Reintegration into normal living

RMS = Root Mean Square

RPE = Rate of Perceived Exertion

RPS-form = Rehabilitation Problem-Solving Form

RVI = Royal Victoria Infirmary

SAM = Step activity monitor

SF-36 = Short Form 36

SD = Standard deviation

s = second

$\mathbf{S}_2$ = Variability

STS = Soft tissue sarcoma

SVM = Signal vector magnitude

TESS = Toronto Extremity Salvage Score

THR = Total hip replacement

TKR = Total Knee Replacement

Total time = Total time to complete each fast walk

TUG = Timed up and go

TUDS = Timed up and down stairs

VCP = Velocity of the centre of pressure

VWA = Various walking activities

Chapter 1: Introduction

1.1 Introduction

Lower extremity musculoskeletal (bone and soft tissue) tumours are a heterogeneous group of tumours, with diverse presentations in size, anatomical location, morphology, classification, and staging. Similarly there are variations in treatments including chemotherapy, radiotherapy and surgery (Grimer *et al.*, 2010). Although 85% of patients with lower extremity sarcomas undergo limb sparing surgery (LSS); this often requires the surgical removal of significant volumes of muscle and bone, and many face complications such as implant failure, limb shortening, wound healing, and infection (DiCaprio and Friedlaender, 2003). The remainder undergo primary amputation (AMP - the removal of a major limb segment, including rotationplasty).

It is well recognised that a wide range of physical impairments and activity limitations are the long term sequelae of musculoskeletal tumour treatments (Davis *et al.*, 1999a; Davis *et al.*, 1999b; Nagarajan *et al.*, 2002; Carty *et al.*, 2009a; Winter *et al.*, 2009). Assessing physical functioning (functional) outcomes in a comprehensive manner is therefore important (Parsons and Davis, 2004), to better understand the patient experience. After amputation (AMP), prosthetic fit and rehabilitation services also have a significant impact on physical functioning (Frederiks and Visagie, 2013). Therefore exploring the patient experience of rehabilitation services (Angela Coulter, 2009) and physical functioning (Kwong *et al.*, 2014) is critical to understanding this group. Despite this, and the impression that clinical services vary a great deal, there has been little research into this. In the first phase of the PhD, therefore, patient-reported outcomes and the service experience after AMP for lower extremity musculoskeletal tumours were explored, through a national multi-centre project.

Existing disease-specific clinical scales (e.g.: Toronto Extremity Salvage Score (TESS) (Davis *et al.*, 1996) and Musculoskeletal Tumour Society Scoring system (MSTS) (Enneking, 1987; Enneking *et al.*, 1993), although helpful; are subjective and limited in the information they provide (Parsons and Davis, 2004). For instance, they do not provide information on components of physical functioning affected in this group; such as balance, gait (de Visser *et al.*, 2001; Donati *et al.*, 2012) and participation restrictions (van Dam *et al.*, 2001). This poses a challenge in monitoring the full impact of clinical decisions and delivering tailor-made rehabilitation strategies. In the past few years, a body of evidence supporting the objective

clinical measurement of physical functioning in the clinic and community has emerged (Kawai *et al.*, 2000; Marchese *et al.*, 2007; Rosenbaum *et al.*, 2008b; Donati *et al.*, 2012). Yet these tools have not formed part of routine clinical practice. Reasons for this might be that tools are cumbersome, time consuming to use, expensive or inaccurate. The use of accurate, valid and reliable outcome measurement tools to inform clinical management is vital in improving clinical effectiveness (Sim and Arnell, 1993). In the second phase of the PhD, therefore, a systematic review was conducted to explore the current state of objective clinical measurement of balance, gait and physical activity (PA) in patients treated for musculoskeletal tumours. Finally in the third phase, the use of small accelerometer-based body worn monitors (BWMs) were piloted in these patients, to measure aspects of physical functioning (including balance, gait and PA), in an attempt to develop simple clinic and community instrumented assessments. This might not only help overcome inherent limitations of existing tools but also guide rehabilitation care more effectively.

1.2 Structure of thesis and outline of chapters

1.2.1 Chapter 2: Background of rehabilitation services and physical functioning outcomes after treatment for lower extremity musculoskeletal tumours

The key objective of chapter 2 is to review the background literature, clinical problems and identify current knowledge gaps. This chapter includes a description of the complex needs of patients surviving these cancers, the importance of rehabilitation services, physical functioning, and current knowledge about underlying relationships between physical functioning and quality of life (QoL) in this clinical group. The International Classification of Functioning, Disability and Health (ICF) framework and its use to guide physical assessments in this population is introduced. At the end of the chapter the clinical problems and research gaps are identified and specific aims of the thesis are listed to address these gaps.

1.2.2 Chapter 3 (Phase 1): Patient experience of rehabilitation services after lower extremity amputation for sarcoma in England: a national survey.

Chapter 3 explores the patient experience of rehabilitation services on a national basis in an important group of patients who have had AMP for sarcoma, and are dependent on good service provision. The described work is a national multi-centre audit investigating the patient experience of limb fitting and rehabilitation services against published national standards delivered across the five recognised National Health Service (NHS) Primary malignant bone

tumour (PMBT) specialist surgical centres in England.

1.2.3 Chapter 4 (Phase 1): Physical functioning, pain and quality of life after amputation for musculoskeletal tumours: a national survey.

Chapter 4 investigates survivorship outcomes at a national level in England; with a special focus on physical functioning, pain and QoL after AMP for sarcoma. Physical functioning, pain and QoL outcomes collected are compared against published international comparators, and underlying relationships are explored between these outcomes.

1.2.4 Chapter 5 (Phase 2): Objective clinical measurement of physical functioning after treatment for lower extremity sarcoma – A systematic review

Chapter 5 systematically reviews current methods used to quantify balance, gait or PA in patients; and identify those with the potential for translation into busy clinic settings. The chapter also reviews whether these measures are fit for purpose, and have been tested for validity, reliability and sensitivity to change.

1.2.5 Chapter 6 (Phase 3): Evaluation of physical functioning after treatment for lower extremity musculoskeletal tumours – A feasibility study of accelerometer-based body worn monitors: Objectives, methods and research participants

Chapter 6 describes the methods and processes for the third phase of the thesis, which pilots the use of small BWMs to objectively assess physical functioning in the clinic and community in patients treated for lower extremity musculoskeletal tumours. The methods include the study design, ethical approvals, experimental study protocol, patient screening and recruitment, outcome measures used, specific protocol for clinic and community testing, data processing to obtain clinical outcomes, general data considerations and statistical procedures used. The chapter concludes with a description of clinical characteristics of patients recruited into the study.

1.2.6 Chapter 7 (Phase 3): Quantification of balance, fast walk and timed up and go test using a body worn monitor in a clinic setting after treatment for lower extremity musculoskeletal tumours.

The key objective of Chapter 7 is to investigate the feasibility, acceptability and validity of a

fifth lumbar vertebrae (L5) accelerometer-based BWM to quantify balance, gait and timed up and go (TUG) outcomes in the clinic in this tumour group.

1.2.7 Chapter 8 (Phase 3): Free-living monitoring of ambulatory physical activity in the community using a body worn monitor after treatment for lower extremity musculoskeletal tumours

Chapter 8 investigates the feasibility, acceptability and validity of a thigh-worn accelerometer-based BWM to quantify ambulatory behaviour (ambulatory PA) in the home environment and community.

1.2.8 Chapter 9: Discussion, recommendations for future work and conclusions

Chapter 9 synthesises results from all chapters, discusses findings of the thesis, and focusses on future recommendations and clinical implications of this work. This chapter will also propose an evidence based model (using the ICF framework) to assess and manage physical functioning in a comprehensive manner after treatment for lower extremity musculoskeletal tumours.

Chapter 2: Background of rehabilitation services and physical functioning outcomes after treatment for lower extremity musculoskeletal tumours

2.1 Summary

This chapter describes the background to the thesis, identifies research gaps and proposes a systematic approach to address them. To do this it contains the following overviews: musculoskeletal tumour disease; the survivorship experience of patients (i.e. the lived experience after treatment); the impact of rehabilitation services on patient experience; the physical domain of survivorship with a special focus on physical functioning; current approaches to assess physical functioning; and introduction of the ICF model which provides a framework for mapping current commonly used disease-specific scales. The ICF framework will help identify the gaps in current practice of outcome measurement and at the end of the chapter, the specific aims of the PhD which address these gaps are given.

2.2 Musculoskeletal tumour disease

Musculoskeletal tumours are a rare heterogeneous group of benign or malignant tumours arising in the bone or soft tissues from mesenchymal cells in almost any anatomical location (Stiller *et al.*, 2013). Primary musculoskeletal tumours consist of primary malignant bone tumours (PMBT) and soft tissue sarcomas (STS) (WHO, 2013) (Table 2-1). There is an estimated incidence of 27,908 new cases of sarcoma per year in Europe (Stiller *et al.*, 2013). About 14% of these are bone sarcomas (BS), 84% STS and the remainder are other sarcomas including Gastrointestinal stromal tumours (GIST) (Stiller *et al.*, 2013). In the United Kingdom, approximately 1035 new diagnoses of extremity BS or STS are seen each year (Matthew Francis, 2013). PMBTs are primary cancers arising in the bone (Table 2-1) and comprise only a small proportion (0.2%) of all malignant tumours, yet constitute 4.8% of malignancies in children and adolescents up to the age of 14 years ((NCIN), 2017a). The terms PMBT, BS and bone tumour (BT) are often used interchangeably in the literature and for consistency in the thesis BT will be used. Whereas, STS are primary cancers arising in the soft tissue (Table 2-1), the incidence which increases with age, and they account for 1% of all malignant tumours ((NCIN), 2017b). Although 65% of STS cases occur in people over 50 years of age, a small proportion of cases are reported in children and young adults ((NCIN),

2017b).

Table 2-1: Musculoskeletal tumour disease and sub-types

Musculoskeletal tumours	Sub-types
Primary malignant bone tumours (PMBT) or Bone tumour (BT)	Osteosarcoma (typically starts in bone) Ewing's sarcoma (typically starts in bone but can also start in other tissues and muscles) Chondrosarcoma (typically start in cartilage cells) Spindle-cell sarcomas of the bone Others
Primary soft tissue tumours or soft tissue sarcomas (STS)	Malignant fibrous histiocytomas (MFH) Leiomyosarcomas (smooth muscles) Liposarcomas (fat tissue) Fibroblastic sarcomas (fibrous tissue) Rhabdomyosarcomas (skeletal (striated) muscles) Soft-tissue Ewing's sarcoma (Extraskeletal Ewing's), Synovial sarcoma (arises around joints and tendons) Angiosarcoma (blood and lymph vessels) Malignant peripheral nerve sheath tumours (MPNST) (nerve sheath)

2.3 Management of musculoskeletal tumours

The anatomical structure in which the tumour arises, tumour type, size, morphology, and extent of spread, are important considerations when developing an individualised management plan for patients. Multi-modality management of lower extremity sarcomas includes chemotherapy, radiotherapy and major surgery (Grimer *et al.*, 2010). The main aim of surgery is complete tumour excision and involves removal of significant volumes of bone and soft tissue. In the past, the main treatment for PMBT was ablative surgery or AMP (Table 2-2). AMP may still be selected as a primary treatment (primary AMP) by clinicians and patients or may follow the failure of LSS after local recurrence or reconstructive complications (secondary AMP). Over the last few decades, with the advancement in surgical techniques and treatments such as chemotherapy and radiotherapy, it has become increasingly possible to achieve local control by preserving the limb. These techniques are referred to as LSS (Table 2-2).

The variation in age, tumour type, size, grade and multi-modality treatments poses a challenge to the clinical management of patients with these tumours. Patients not only face diverse challenges during recovery and rehabilitation but also have a range of long-term challenges.

The rarity and heterogeneity of these tumours warrants collaboration between centres for diagnosis, clinical decision-making, management, audits and research to improve clinical care.

Table 2-2: Types of surgery for Musculoskeletal tumour disease

Surgery	Types of Surgery	Description
Limb Sparing Surgery (LSS)	Resection/Excision	Removal of tissue
	Intra-lesional curettage	Removal of the tumour and affected surrounding tissue from the wall of the cavity in the bone
	Endoprosthesis	Resection of the tumour with bone tissue affected and insertion of a metal prosthesis to replace the bone loss or joint
	Autograft	A tissue which is taken from the patient and used for reconstruction.
	Allograft	Tissue obtained from another donor patient, usually after death.
	Osteoarticular allograft	A graft from another patient including the joint surface and bone, usually used to reconstruct a joint
	Free flap	A tissue (e.g. a fibula) harvested from one part of the body with its associated blood supply and placed in a new location, where the vessels are connected using a microvascular anastomosis.
	Pedicled flap	Tissue mobilised and transposed to the recipient site without disconnecting the blood supply
	Skin graft	Skin tissue transferred from a donor site to a recipient site. Types are split thickness or full thickness of graft
Amputation (AMP)	Hemipelvectomy	Removal of all or part of the pelvic bone.
	Hip disarticulation	AMP through hip preserving pelvis
	Transfemoral	Through femur
	Knee disarticulation	Through knee
	Transtibial	Through tibia
	Symes	Through ankle
	Rotationplasty	Van Ness Rotationplasty defined as the removal of the tumour with the joint and attachment of the distal limb to the proximal limb with the position of the foot facing backward. There are several variants of this.

2.4 Survivorship experience after treatment for musculoskeletal tumours

Over the past few years, survival has increased for most cancers, possibly due to early diagnosis and advances in treatment (DeSantis *et al.*, 2014). In the United Kingdom itself, there are about 2 million people living with cancer and about 500,000 people living with poor health, or disability after treatment for cancer (Macmillan, 2008). Survival after a diagnosis of BS increased in the 1970s due to the introduction of chemotherapy, and 5 year survival rates increased from 23% to 64% ((NCIN), 2017a). However, there has been little improvement since. As the number of survivors has increased, so has the importance of evaluating patient experience after survival and the long term effects of cancer diagnosis and treatment (Kwong *et al.*, 2014). This living experience after surviving cancer is referred to as 'survivorship' and consists of three main domains, physical, psychological and social (Kwong *et al.*, 2014).

The physical domain of survivorship includes physical functioning (functional/physical function) outcomes, which can be considered as impairments, disability and activity limitations (Kwong *et al.*, 2014). Other interlinked domains of survivorship include physical (fatigue, pain), psychological (emotional distress, cognitive functioning, depression, anxiety), and social (sexual function, employment, social) needs (Kwong *et al.*, 2014). Support and rehabilitation services for survivors need to be of high quality, multidimensional and delivered at different time points in the treatment regimes, if patients are to achieve best survivorship outcomes.

2.5 Rehabilitation services for cancer survivors

Survivorship experience and care have been championed in initiatives from Macmillan, the Department of Health, and the National Cancer Intelligence Network (NCIN) (Richards *et al.*, 2011). Good rehabilitation services must not only focus on immediate symptomatic relief, but also on treating underlying causes of reduced physical function. High quality services also have a duty to meet recommended standards of care, use comprehensive evidence based models and outcome measures to monitor outcomes and guide rehabilitation.

In the NHS in England, the rarity of sarcomas means that treatment is centralised in specialist units to which patients may have to travel long distances. This further complicates the delivery of individualised rehabilitation strategies at a distance. In 2003, there were an estimated 280000 people alive in Europe who have had sarcoma (Stiller *et al.*, 2013), many of whom might have undergone an AMP. These patients have complex needs, and require

standardised rehabilitation and limb fitting. The needs and experiences of patients undergoing AMP for lower extremity tumours differ from those of vascular amputees, who have major comorbidities, and traumatic amputees who usually have not had a diagnosis of neoplasia (Campbell *et al.*, 2001).

Therefore after an AMP for a sarcoma in the leg, access to excellent limb fitting services is critical in achieving a return to normal life. However in contrast, most patients report that they have to often rely on non-specialist local services to receive information, physiotherapy, occupational therapy, psychological counselling and prosthetic services; which have little experience of this tumour group. Given the associations between physical functioning and QoL (Stevenson *et al.*, 2016), poor prosthetic services might not only have a detrimental impact on physical functioning, but also on QoL. Despite this, little is known about patient experience of service provision after AMP for musculoskeletal tumours in England. Patients with sarcoma may, for example, might find themselves in a service largely geared towards older patients with vascular disease.

2.6 Physical functioning after treatment for musculoskeletal tumours: An integral component of survivorship

As physical functioning is linked to important health outcomes, it may be beneficial to quickly recognise a decline in physical function after treatment. One study confirmed this, as it showed that it is not the surgical treatment for sarcoma, but the reduced physical functioning which predicts diminished QoL (Robert *et al.*, 2010a). Another study showed that a major component of physical functioning i.e. physical activity (PA) was found to have significant links with survival in certain cancers (breast cancer) (Barbaric *et al.*, 2010). It is also well established that treatments for musculoskeletal tumour disease cause significant reduction in activity levels (van Dam *et al.*, 2001; Ness *et al.*, 2009). This could mean that patients treated for sarcoma are at increased risk of poor survival and reduced QoL, an aspect which needs urgent attention.

Patients treated for a tumour in the leg, in general, demonstrate low scores for physical functioning compared to healthy individuals (Nagarajan *et al.*, 2004a; Fidler *et al.*, 2015), and those with other clinical conditions (Hinds *et al.*, 2009). For instance, children with non-metastatic osteosarcoma scored low on scales assessing physical functioning in comparison to obese children (Shoup *et al.*, 2008) or chronically ill children (Varni *et al.*, 2006; Youssef *et*

al., 2006). Physical functioning scores may also vary with time, and may improve over time. For example: Physical functioning scores in children with bone tumours tend to be low for the first 12 months post-operatively, and then improve considerably for up to 18 months post-surgery (Winter *et al.*, 2012).

Physical functioning is also closely related to other aspects of survivorship, for example: return to work, which links to the physical capability of individuals to be able to meet physical demands of the work role (Colterjohn *et al.*, 1997). It is also linked with loss of the ability or confidence to perform a task and therefore a reduced participation in daily life activities (Rosenbaum *et al.*, 2008b; Winter *et al.*, 2012). This ultimately may affect social life and emotional functioning (Robert *et al.*, 2010a), causing a significant negative influence on education, employment and health insurance (Nagarajan *et al.*, 2003). Therefore physical functioning forms an integral part of a patient's survivorship experience (Kwong *et al.*, 2014).

Musculoskeletal tumour sub-types and their clinical management can have a characteristic influence on physical functioning outcomes, described below:

2.6.1 Bone versus soft tissue tumour survivors

Bone or soft tissue tumours can occur in different anatomical locations, with varying grades, aggressiveness and size. While the resection of a major bone is usually required in the treatment of a bone tumour (BT), the excision of affected soft tissues is usually required in the treatment of a STS. Physical functioning outcomes can therefore vary widely based on these factors and as a result each patient requires a personalised assessment. We therefore compared physical functioning in BT versus (vs) STS survivors, in the literature and in the thesis, where applicable.

Previous studies have shown that BT survivors reported significantly lower physical functioning in the Short Form 36 (SF-36) healthy survey, especially in physical role and pain sub-scales, but not so much with the role-emotional sub-scale (Fidler *et al.*, 2015). In the physical function scale, 54% faced limitations in 'moderate activities' and 61% in 'walking more than one mile', which is very different to the 8% and 11% respectively expected in the general population (Fidler *et al.*, 2015). Adverse health is a long-term consequence of treatment for BTs, with the most common deficits being activity limitations (29.1%) (Nagarajan *et al.*, 2011). Therefore walking seems to be significantly limited, especially in the community and monitoring this with a view to intervention might be of benefit. Patients also

reported limitations in different type of activities and return to work. On the pain scale BS survivors reported higher bodily pain (12% vs 5%) and higher pain interference (16% vs 5%) in comparison to controls (Fidler *et al.*, 2015), suggesting pain is important in this group and might also impact physical function or participation in activities.

In contrast, patients treated for STS often report disability (Kwong *et al.*, 2014), and impairments such as pain, loss of joint motion, reduced strength, oedema and fibrosis of tissue around joints (Davis, 1999). Yet some studies show good to excellent long-term functional outcomes in a large number of patients undergoing soft-tissue reconstructions (Serletti *et al.*, 1998). Differences reported might be attributed to the anatomical location of the STS (Gerrand *et al.*, 2004), as treatment of superficial tumours does not cause a significant reduction in functional scores but treatment of deep tumours does (Gerrand *et al.*, 2004). In general, patients treated for BS tend to have lower functional scores than patients treated for STS (Sugiura *et al.*, 2001), which could be associated with not only the tumour depth, but also the effect of bone as well as muscle resection and reconstruction.

2.6.2 Childhood vs adulthood cancer survivors

Bone and soft tissue tumours can affect patients of any age ((NCIN), 2017a; (NCIN), 2017b). Given that physical functioning varies with age, outcomes in these groups are likely to differ substantially.

Survivors of childhood sarcoma may report late effects, including difficulty ascending stairs and activity restrictions (Serletti *et al.*, 1998). In the long-term, however, most functional outcomes were found to be similar to controls (Serletti *et al.*, 1998), indicating the ability of patients to adapt over time. Other long-term problems related to the effects of diagnosis and treatments for a childhood cancer may include an impact on the child's psychological, mental, social and educational development (also referred to as psychosocial development) (Robison and Hudson, 2014). This could further negatively affect physical functioning leading to a vicious cycle of poor outcomes.

In contrast survivors of adult cancer commonly have problems not only related to reduced physical functioning, but also with social interactions and increased pain, compared to the general population (Eiser *et al.*, 2001; Davis *et al.*, 2002; Thijssens *et al.*, 2006). In addition, variations in functional outcomes by age must be also accounted for, as age might impact some locomotor systems more than others. For instance, some variables of postural control deteriorate with increasing age, but not in the same way as initiation of gait or turning (Park *et*

al., 2016). This might lead to worse physical function in older survivors of adult sarcoma, compared to survivors of childhood sarcoma, mainly due to the combined effect of age, pre-existing comorbidities and direct surgical impact on the locomotor system (Sugiura *et al.*, 2001). This needs to be accounted for during interpretation of physical assessments.

2.6.3 Above knee vs below knee tumours

Clinical presentations also tend to significantly vary based on the anatomical site within the lower limb. Surgical excisions of above knee tumours, located in the femur or in the pelvis, affects proximal structures, compared to below knee tumours located in the tibia or ankle/foot region. One might anticipate that above knee tumours are associated with worse outcomes than below knee tumours, however this is not always the case and depends on various factors such as depth of tumour, motor resection and surgery type (Gerrand *et al.*, 2004). Depending on the type of surgery (LSS or AMP), and location of tumour, patients might present with varying functional scores. For instance, no differences in functional scores were observed between patients who had 'above knee LSS' and those who had 'below knee LSS', but significantly better scores were observed in patients who had a 'below knee AMP' compared to those who had an 'above knee AMP' (Ginsberg *et al.*, 2007).

2.6.4 LSS vs AMP surgeries

Major effects of surgery for a lower extremity sarcoma are physical limitations, driven by factors such as tumour size, resection of bone, type of surgery and post-operative complications (Davis *et al.*, 2000). A wide range of limb sparing and ablative surgery options for patients (described in section 2.3), means that physical function might be impacted at a mild, moderate or severe level (Davis, 1999; Davis *et al.*, 1999a; Malek *et al.*, 2012a; (CCSS), 2017). With modern limb sparing procedures, LSS was thought to achieve better physical function than AMP (Malek *et al.*, 2012a; Mavrogenis *et al.*, 2012; Yin *et al.*, 2012; Mason *et al.*, 2013; Ottaviani *et al.*, 2013; (CCSS), 2017). However two systematic reviews contradicted this, as they demonstrated no significant differences in TESS and/or MSTS scores between groups (Mei *et al.*, 2014) (Nagarajan *et al.*, 2002). One reason could be that individuals treated with LSS often require long term surveillance, revision surgery and are at risk of developing complications such as implant failure, limb shortening, wound healing, and infection (Ozger *et al.*, 2010). Therefore although physical function might be better after LSS, this higher rate of complications (Renard *et al.*, 2000; Nagarajan *et al.*, 2002) can again have a detrimental impact on physical function. The impact of complications on physical function

needs to be individually examined and consistently reported.

Another important factor could be the use of broad generic terms such as 'LSS' and 'AMP', which cover a wide range of patient experiences and which may therefore lead to contrasting findings between studies. A potential solution might be grouping patients into homogenous groups with similar tumour type, surgery type and level of surgery. Sub-grouping of patients by level of surgery revealed that gait efficiency and reintegration into normal living (RNL) index scores were significantly higher in patients who had 'above knee LSS' compared to those who had 'above knee AMP' ($p<0.05$) (Malek *et al.*, 2012b). Higher Functional Mobility Assessment (FMA) scores were also reported in the 'above knee LSS' group than in the 'above knee AMP' group (Ginsberg *et al.*, 2007). In contrast, for surgeries below knee, higher absolute FMA scores were reported in the 'below knee AMP' group, than in the 'below knee LSS' group (Ginsberg *et al.*, 2007). This suggests that besides major surgery and depth of tumour, clinical factors like level of surgery could have a different impact on outcomes. These variations are not always taken into account while reporting findings.

In the long term (more than 20 years after treatment), patients with AMP are more dependent on walking aids than LSS patients (Ottaviani *et al.*, 2013). Body image is also significantly affected in AMP compared to LSS patients, whilst self-esteem and social support are not (Robert *et al.*, 2010b). Body image was particularly worse in those undergoing late AMP or secondary AMP, following failed LSS (Robert *et al.*, 2010b). Furthermore, outcomes may vary widely based on level of surgery. For example, proximal AMP such as hip disarticulation is associated with shorter survival, a higher incidence of complications and greater post-operative pain (Daigeler *et al.*, 2009). Although patients undergoing an AMP form a small proportion of the tumour population, most studies investigating physical functioning in this group, focus on those who have had an AMP for a childhood BS (Pardasaney *et al.*, 2006; Ginsberg *et al.*, 2007; Robert *et al.*, 2010a). Studies of patients who have had an AMP for cancer as an adult are lacking.

The impact of high levels of disability after an AMP for sarcoma on the survivorship experience, including the difficulty of returning back to work, has been recognised (Nagarajan *et al.*, 2003; Kwong *et al.*, 2014). Patients undergoing AMP for a tumour in the lower extremity, are therefore, a rare group of patients with special needs. Yet factors driving poor outcomes remain unclear. For example, understanding the impact of stump pain and phantom pain (Renard *et al.*, 2000) on disability might better inform management strategies. In

addition, the impact of physical limitations on QoL is not completely understood across all age groups.

2.7 Current methods of assessment of physical functioning in patients with musculoskeletal tumours

Diverse clinical presentations after treatment for musculoskeletal tumours are a major challenge. In the literature, components of physical function are assessed using different measurement techniques: studies may report impaired physiological functioning or disability (Nagarajan *et al.*, 2002), making understanding of these issues difficult (Parsons and Davis, 2004).

The most widely used disease-specific clinical scales to measure physical function are a clinician-reported measurement (MSTS) (Enneking, 1987; Enneking *et al.*, 1993) and a self-reported measure of disability (TESS) (Davis *et al.*, 1996). The outcome measurement tools assessing functional mobility in survivors of extremity osteosarcoma (Marchese *et al.*, 2004) are the TUG test (Mathias *et al.*, 1986), TUDS test (Lepage *et al.*, 1998), 9-minute walk-run test (Ness *et al.*, 2014), rate of perceived exertion (RPE) (Costa and Gaffuri, 1975), physiological cost index (PCI) (Butler *et al.*, 1984) and FMA (Marchese *et al.*, 2007). Certain generic (not disease-specific) clinical scales capturing attributes of physical functioning in patients treated for extremity sarcomas (Nagarajan *et al.*, 2004b; Fidler *et al.*, 2015; Tanaka *et al.*, 2016), are the SF-36 (Garratt *et al.*, 1993), EuroQol group quality of life questionnaire (EQ-5D) (Gusi *et al.*, 2010) and quality of life for cancer survivors (QoL-CS) (Ferrell *et al.*, 1995). Commonly used clinical scales assessing health status and physical functioning in children include the Paediatric Outcomes Data Collection Instrument (PODCI) (Pakulis *et al.*, 2005) and Bone tumour – DUX (Bt-DUX) (Bekkering *et al.*, 2009).

2.7.1 Musculoskeletal Tumour Society (MSTS) scoring system

The Musculoskeletal Tumour Society (MSTS) scoring system version released in 1987 (MSTS-1987) is a clinician completed tool which gives an observer-rated score (Enneking, 1987). The MSTS-1987 assesses seven sub-domains range of motion, stability, deformity, pain, muscle strength, functional activity and emotional acceptance. The highest score in each domain is 5 (range from 0 – 5). The values of each of the seven sub-domains are added and a total score is obtained. The MSTS total score is expressed from 0-35 (worst to best physical functioning) (Enneking, 1987).

2.7.2 The Toronto Extremity Salvage Score (TESS)

The Toronto Extremity Salvage Score (TESS) captures the ability of patients to perform activities (Davis *et al.*, 1996). TESS comprises 30 self-reported items assessing physical disability. It is a valid and reliable questionnaire in patients with lower extremity musculoskeletal tumours. The score is expressed as a percentage based on the number of responses, and scores range from 0 to 100 (worst physical disability to no physical disability) (Davis *et al.*, 1996; Davis *et al.*, 1999b).

2.7.3 Timed Up and Go (TUG) test

The Timed Up and Go (TUG) test is used to assess the functional ability of an individual to perform basic activities such as rising from a chair, walking across a room for 3 metres, turning, walking back to the chair and then sitting down (Mathias *et al.*, 1986). A stopwatch is used to record the time taken to complete the task.

2.7.4 Timed Up and Down Stairs (TUDS)

The Timed Up and Down Stairs (TUDS) test is an indicator of functional mobility (Lepage *et al.*, 1998). The patients are asked to climb up and down 12 stairs with or without the use of a railing, as swiftly as possible. A stopwatch is used to record the time taken to complete the task.

2.7.5 9-Minute Run-Walk test

The 9-minute run-walk test is used to assess the cardiorespiratory endurance (Ness *et al.*, 2014). The patients are asked to walk or run as swiftly as possible in a period of 9 minutes. The main test objective is to cover as much distance as possible by the patient. A stopwatch is used to record time and a distance measurement wheel to assess distance covered.

2.7.6 Rate of Perceived Exertion (RPE)

The Rate of Perceived Exertion (RPE) test is used to assess the patient's subjective perception of the amount of effort exerted into a task, also referred to as 'intensity while performing a task. RPE rates task intensity on a 6–20 scale which corresponds to written descriptors. The increase in numbers on the scale corresponds to an increase in intensity. For instance, a rating of 7 corresponds to an intensity of very, very light, 11 to fairly light, 15 to hard, and 19 to very, very hard (Costa and Gaffuri, 1975). The scale is held in front of the patient and the RPE is obtained after completing 4 minutes of the 9-min run walk test, the entire 9-min run-walk, TUG and TUDS tests.

2.7.7 Physiological Cost Index (PCI)

Physiological Cost Index (PCI) is used to measure the efficiency of locomotion by assessing the average walking speed, the heart rate (HR) of the patient during the walking task and also while at rest (Butler *et al.*, 1984). The PCI is measured at the point of completion of 4 minutes during the 9 minute run-walk test.

2.7.8 Functional Mobility Assessment (FMA)

The Functional Mobility Assessment (FMA) consists of six broad subcategories: pain, supports, function, participation, satisfaction and endurance (Marchese *et al.*, 2007). Pain is assessed using a numeric rating scale from 0 (no pain) to 10 (worst imaginable pain), supports are assessed by questions pertaining to walking aids (crutches, brace, cane) and function is measured using TUDS and TUG time. Participation and satisfaction are measured using questions pertaining to participation in job roles, sports, school and walking quality satisfaction respectively. Endurance is assessed using HR to measure patient's aerobic fitness, RPE obtained during the TUDS and TUG tasks and PCI during the 9-min run–walk. The raw scoring is given for each of the domains in the FMA and converted into table scores. Table scores range from 0 (worst) to 5 (best). There is a maximum of 70 points available (Marchese *et al.*, 2007).

2.7.9 EuroQol group quality of life questionnaire – 5 dimensions (EQ-5D)

The EuroQol group quality of life questionnaire – 5 dimensions (EQ-5D) developed to measure health-related QoL (Gusi *et al.*, 2010) also captures aspects of physical function. EQ-5D consists of five dimensions; mobility, self-care, activities of daily living, pain/discomfort and anxiety/depression; each dimension consisting of three levels (Gusi *et al.*, 2010).

2.7.10 The Short Form-36 (SF-36)

Short Form-36 (SF-36) is a generic health-related QoL measure. SF-36 consists of eight scales; physical functioning, bodily pain, role limitations due to physical health issues, role limitations due to personal or emotional issues, mental health, social functioning, energy/fatigue, and general health perceptions (Laucis *et al.*, 2015).

2.7.11 Quality of Life for Cancer Survivors (QoL-CS)

The Quality of Life for Cancer survivors (QoL-CS) is an instrument developed to measure concerns of cancer survivors (Ferrell *et al.*, 1995). This instrument consists of 41 items capturing four domains of QoL; physical, psychological, social, and spiritual well-being (Ferrell *et al.*, 1995).

2.7.12 Pediatric Outcomes Data Collection Instrument (PODCI)

Pediatric Outcomes Data Collection Instrument (PODCI) consists of 7 sub-domains including physical functioning in the upper extremity, transfers and physical mobility, physical functioning and sports, comfort (lack of pain), happiness, satisfaction, and expectations (Pakulis *et al.*, 2005). The questionnaire includes a mix of general health and functional outcome items. The items in the PODCI questionnaire consist of three scores ranging from 'often', 'sometimes' or 'rarely or never' or six scores ranging from 'none', 'very mild', 'mild', 'moderate', 'severe', or 'very severe. Each item has different weights and for most of them a lower score indicates a better physical functioning or a better QoL, in contrast for some items, a higher score indicates a more positive outcome (Pakulis *et al.*, 2005).

2.7.13 Bone tumour – DUX (Bt-DUX)

The item scoring in Bone tumour – DUX (Bt-DUX) questionnaire is conducted by abstract faces with varying expressions using smileys, and range from very happy (score 1) to sad (score 5) (Bekkering *et al.*, 2009). The raw item scores are converted into total scores and domain scores, The scores range from 0 to 100, with the highest scores indicating a better health related QoL (Bekkering *et al.*, 2009).

Whilst helpful, these traditional methods have limitations, are subjective and may not capture the complete clinical picture. For instance, physical function captured by these tools does not indicate the underlying mechanism of poor physical function, neither does one get a clinical view on wider participation restrictions. Patients may also have difficulty with recall and assessments may not be discriminatory (Prince *et al.*, 2008). Another major limitation observed is that TESS and MSTS were not found to be sensitive to differences between major surgical groups (LSS and AMP), whereas other tools such as FMA and RNL were. This could be associated with a poor discriminatory potential of TESS and MSTS in comparison to objective tests like FMA (Ginsberg *et al.*, 2007) or gait tests (Malek *et al.*, 2012b). It was also observed that results from disease-specific scales did not correlate with quantitative measures of physical functioning; TUG test, timed up and downstairs (TUDS) test, 9-min run-walk, rate of perceived exertion (RPE), and physiological cost index (PCI) (Marchese *et al.*, 2004). The clinic-based FMA, an objective tool, was therefore developed in an attempt to fill this gap (Marchese *et al.*, 2007). The FMA required patients to physically perform objective tasks such as TUG, TUDS and other tests and was shown to assess task performance accurately (Marchese *et al.*, 2007). Objective outcome measurement may go some way to improving assessment and may therefore be warranted in this clinical group.

2.8 Concept of validity of outcome measurement tools

The concept of outcome measure validity is emphasised in current healthcare systems, as valid and reliable outcome measures are needed to capture outcomes accurately (Gadotti *et al.*, 2006). Validity and reliability are recognised as the fundamental characteristics of a good outcome measure. To demonstrate this, outcomes collected using these tools must be comparable to those in the literature or look broadly correct (face validity), must be able to discriminate between patients and controls, major surgical groups (discriminant validity) and sensibly link in with established disease-specific clinical scales (convergent validity). These measures must also agree with manual techniques routinely used in clinics (concurrent validity) and must demonstrate consistency between repetitions (repeatability).
The different types of validity (Sim and Arnell, 1993) (Table 2-3) relevant to the thesis are discussed below:

2.8.1 Face validity

Face validity, is one of the lowest levels of validity assessment. This validity is related to an 'intuitive feeling' that the measurement seems valid. The assessor works on the assumption that the measurement seems valid on its "face value"(Sim and Arnell, 1993). There is no evidence on which one can base this assumption. Face validity reflects that outcomes obtained from a measurement tool broadly make sense.

2.8.2 Construct validity – Discriminant and convergent Validity

Construct validity although similar to face validity, involves a theoretical framework and clinical reasoning to support the validity of the measurement. Construct validity is referred to the degree to which an outcome assessment tool measures what it claims to measure. Construct validity consists of convergent validity and discriminant validity described below:

Discriminant validity (also referred to as **divergent validity)** assesses whether the concepts of measurements that are supposed to be different or unrelated are in fact different or unrelated (Sim and Arnell, 1993).
Convergent validity is defined as the degree to which two constructs that theoretically must be related, are actually related (Sim and Arnell, 1993).

2.8.3 Criterion Validity - concurrent validity

Criterion validity can be assessed by comparing measurement from a tool with a particular criterion or factor. This can be classified into predictive, concurrent, and prescriptive (Gadotti

et al., 2006). Concurrent validity will be assessed in this thesis and is discussed below

Concurrent validity supports that measurements captured using different instruments show agreement with each other. It is used to evaluate whether new instruments shows agreement with an established 'gold standard' or 'valid standard method' (Sim and Arnell, 1993).

2.8.4 Repeatability of measurement (Repeatability)

Repeatability is defined as the variation in a repeat measurements made on the same participant under the same testing conditions (Bartlett and Frost, 2008). Given that the same instrument, same method and same rater is completing the repeat measurement in a short time frame, the value obtained is expected to be fairly constant (Bartlett and Frost, 2008) and is a reflection of a good measure.

Table 2-3: Different types of validity

Types of Validity	Description
Face	Outcomes are comparable to the literature and appear to make broad clinical sense
Discriminant	Outcomes are able to discriminate between patients and controls and in between major surgical groups
Convergent	Outcomes sensibly link in with established disease-specific clinical scales as per ICF framework
Concurrent	Outcomes agree with manual techniques routinely used in clinics
Repeatability	Outcomes are consistent between repetitions

2.9 Domains of the ICF model for assessing physical functioning

Evidence based rehabilitation models incorporating concepts of disability and QoL are recommended in health services (Parsons and Davis, 2004; Shehadeh *et al.*, 2013). In 2004, Parson and Davis recommended that assessments of physical functioning after treatments for sarcoma must be reported in a holistic and streamlined manner using the ICF model (Parsons and Davis, 2004). This might help us better understand the interaction between outcomes and guide targeted rehabilitation (Escorpizo *et al.*, 2010). The environmental factors also affect physical functioning and comprise physical and social factors, and personal factors consist of individual factors affecting physical functioning.

The recommended ICF model (Figure 2-1), classifies health into several domains, including *body structures, activity and participation restrictions*.

2.9.1 Body structures (Impairments)

Body structures refers to the anatomical components of the body such as limbs or organs and body functions refers to the physiological functions of the body ((WHO), 2002). Problems in this domain are referred to as impairments. Impairments can be *structural* meaning problems in bodily structures, or *functional* meaning bodily physiological dysfunctions.

2.9.2 Activity (Disability)

The *activity* domain; captures execution of a task or test and a problem in this domain is referred to as disability ((WHO), 2002).

2.9.3 Participation (Participation restrictions)

Participation, involves performance in real life situations and problems in this domain are referred to as participation restrictions ((WHO), 2002).

2.9.4 Quality of life (Reduced quality of life)

The ICF has been extended to include a quality of life (QoL) outcome (McDougall *et al.*, 2010), which also allows clinicians to gain a holistic view of links between physical functioning and QoL.

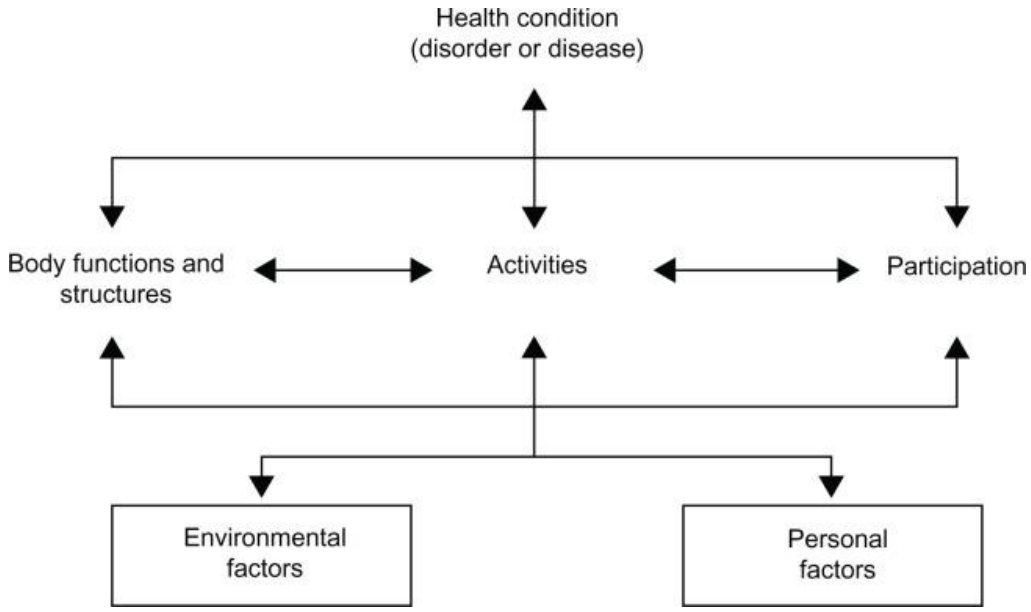


Figure 2-1: International Classification of Functioning, Disability, and Health (ICF) (Bornbaum *et al.*, 2013). The figure can be obtained directly from ((WHO), 2002)

2.10 Mapping physical functioning outcomes in musculoskeletal tumours to the ICF Framework

In order to understand gaps in current physical assessments and to understand the holistic clinical picture in musculoskeletal oncology, an exercise was undertaken by the project lead, 'Sherron Furtado (SF)' based on recommendations from Parsons and Davis (Parsons and Davis, 2004). The exercise consisted of mapping established clinical scales used in adults treated for musculoskeletal tumours, to the domains of the ICF framework (Figure 2-2) (Parsons and Davis, 2004). In this exercise MSTS mapped to structural impairments, TESS mapped to disability or limitations in activities of daily living (ADLs), and quality of life-cancer survivors (QoL-CS) mapped to QoL. Well-researched areas are highlighted in blue and research gaps in orange. Gaps addressed in the PhD thesis are highlighted in green (Figure 2-2). One major gap seen was in outcome measures assessing functional impairments and participation restrictions (Parsons and Davis, 2004). For instance, altered muscle strength, muscle activation patterns, proprioception, balance and gait problems are common deficits seen after treatments for sarcoma (De Visser *et al.*, 1998; de Visser *et al.*, 2001; de Visser *et al.*, 2003), yet not routinely assessed. As established clinical scales of disability and impairments are not sufficient (Parsons and Davis, 2004), information on balance, gait, and iTUG in the clinic might help provide a more holistic picture of the patient's outcomes.

The ICF model shows a relationship between PA and participation in society (Gray and Hendershot, 2000), arguing for the collection of PA data in the community. Another study suggested that a 7-metre instrumented TUG test, is more sensitive in the home environment than in the clinic setting (Zampieri *et al.*, 2011). Therefore, the development of community based assessments are gaining importance to promote remote monitoring of outcomes, and also relay valuable information to clinicians, patients and families to inform clinical decision-making.

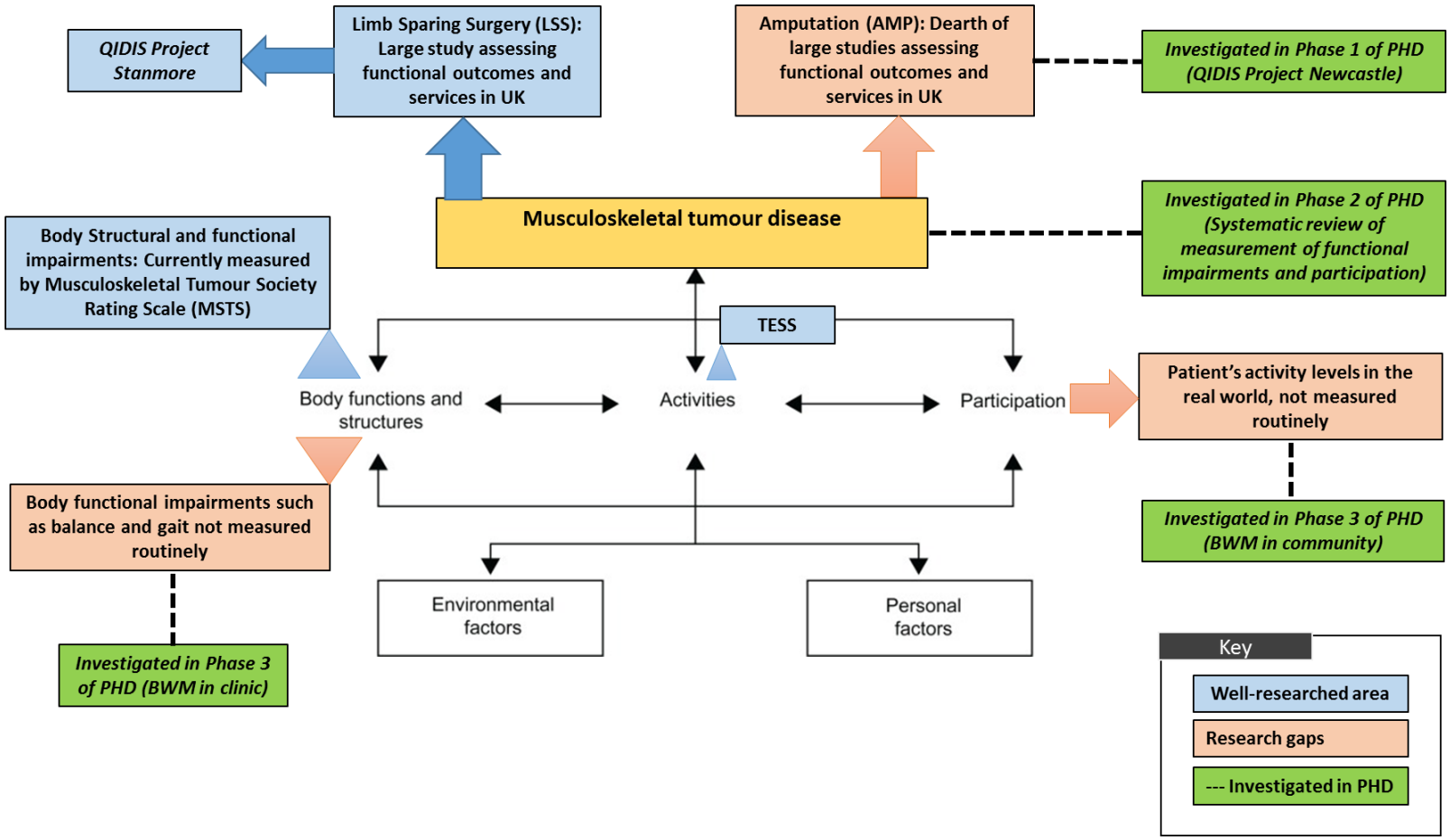


Figure 2-2: Mapping Physical functioning outcomes in Musculoskeletal tumours to the International Classification of Functioning, Disability, and Health (ICF) framework

The ICF (Bornbaum *et al.*, 2013) from the World Health Organization (WHO) website, is adapted to fit the framework for musculoskeletal tumours. The figure can also be obtained directly from ((WHO), 2002)). QIDIS Project refers to Quality Improvement Development and Innovation Scheme. BWM refers to a body worn monitor (triaxial accelerometer) in the thesis.

Although devices including uniaxial activity monitors (for example, Actilog, ADL Monitor, Continuous Ambulatory Activity Monitor), gait motion analysis systems and force platforms are used to assess balance, gait and PA, (Carty *et al.*, 2009a; Carty *et al.*, 2009b; Carty *et al.*, 2010b), the validity of these devices remains unknown. Furthermore difficulties in rolling these out into clinical practice are high costs and use of cumbersome devices which are not portable.

Over the past few years, the use of small BWMs has increased to provide more detailed information about levels of PA in the community over extended periods of time than older devices (Del Din *et al.*, 2016d). They can provide information that has traditionally been difficult to assess, including the quality and quantity of PA, energy expenditure (Murphy *et al.*, 2011), type of activity (Vissers *et al.*, 2011), gait (Hodt-Billington *et al.*, 2011; Kun *et al.*, 2011), balance and falls (Narayanan *et al.*, 2007), all of which are important to these patients.

2.11 Approaches to bridge gaps identified in the review

A national multi-centre project will be undertaken to investigate the patient experience of rehabilitation services after AMP for musculoskeletal tumours which will form the first major part of Phase 1 (Chapter 3) of the thesis. Survivorship outcomes of physical functioning, pain and QoL will be collected from patients who underwent an AMP for a lower extremity musculoskeletal tumour as part of the same national collaborative multi-centre project. Outcomes will be collected across all age-ranges and levels of AMP, to gain a better understanding of interaction between outcomes, underlying mechanisms and factors leading to poor outcomes in this rare group of patients. This will form the second part of Phase 1 (Chapter 4) of the thesis. In the second phase of the thesis, a systematic review will be performed to identify clinically useful objective measurement tools capturing balance, gait and PA after treatments for lower extremity musculoskeletal tumours, and to investigate whether they are valid and reliable for these tumour patients. In the third and final phase of the thesis, a pilot project will be undertaken to test the feasibility of utilizing a simple low-cost triaxial accelerometer as a method of quantifying physical functioning in the clinic and community in survivors of lower extremity musculoskeletal tumours.

2.12 Summary and conclusions

This chapter highlights the diverse survivorship experience in patients treated for lower extremity musculoskeletal tumours. Exploring the patient experience might highlight underlying factors affecting poor outcomes. Phase 1 of the PhD, therefore, will investigate the national state of services and outcomes after AMP for lower extremity musculoskeletal tumours. This will provide clinicians with a valuable insight into patient experience, survivorship outcomes and unique rehabilitation needs after AMP for sarcoma in England. Good rehabilitation services implement comprehensive evidence based models and outcome measures to inform routine practice. Mapping outcomes to the ICF framework revealed that balance, gait and PA outcomes are not routinely assessed; as current established scales do not capture this information. Phase 2, therefore, will highlight the current state of objective clinical measurement of balance, gait and PA after treatments for musculoskeletal tumours. Finally, Phase 3 will follow-on from Phase 2, to develop novel outcome measurement tools of physical function for this population; by piloting the use of small BWMs in these patients.

2.13 Aims of the PhD Thesis

The aims of the 3 main phases (Figure 2-3) of the thesis were:

1. To investigate the current state of rehabilitation services and physical functioning in patients who had an AMP for lower extremity musculoskeletal tumours (investigated in Phase 1).
2. To investigate the current state of objective clinical measurement of balance, gait and PA after treatments for lower extremity musculoskeletal tumours (investigated in Phase 2).
3. To pilot the use of small BWMs to develop novel objective measures of physical functioning in the clinic and community (investigated in Phase 3); in patients treated for lower extremity musculoskeletal tumours.

Specific objectives of each phase are listed at the start of each chapter.

Chapters 3, 4, 5 are almost identical to the published papers but do not include the full introduction, to streamline the flow of the thesis.

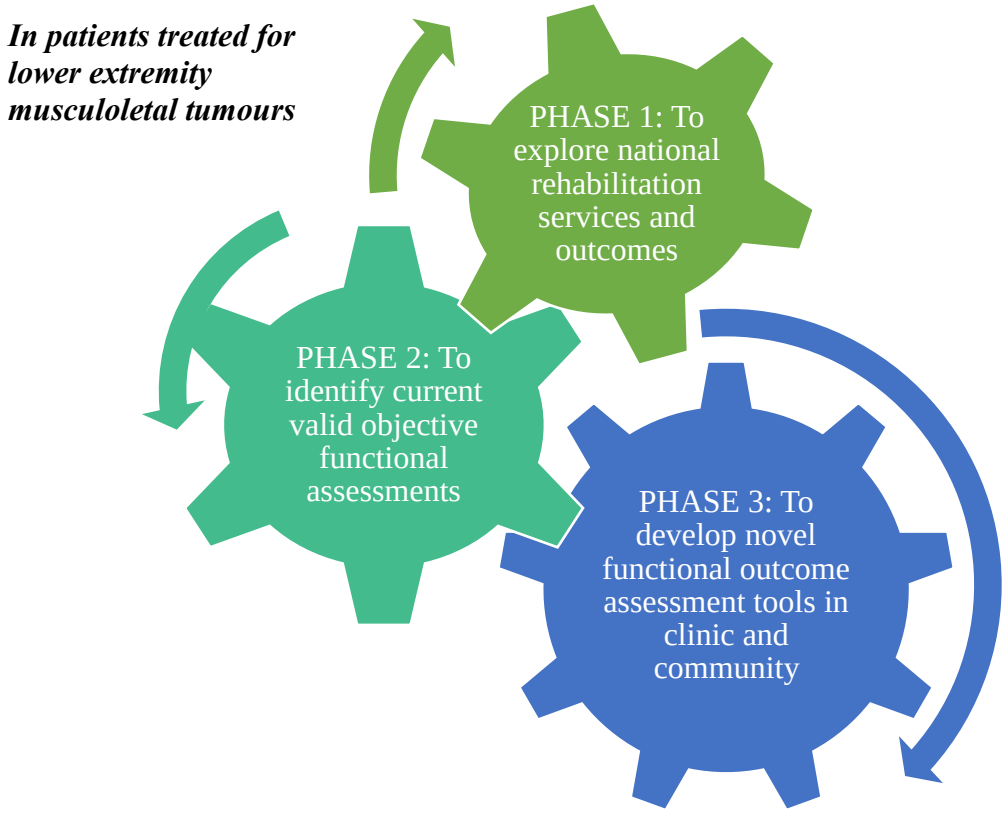


Figure 2-3: Main phases of the PhD

Chapter 3: Patient experience of rehabilitation services after lower extremity amputation for sarcoma in England: a national survey

This work has been published in the Journal of Disability and Rehabilitation with co-authors from the national participating centres (reference below).
Furtado, S., et al., Patient experience after lower extremity amputation for sarcoma in England: a national survey. Disabil Rehabil, 2017. 39(12): p. 1171-1190.

3.1 Introduction

Although there are national standards relating to the care that patients should receive around AMP (BSRM, 2003; COT, 2011; (CSP), 2012); our experience was that patients who had an AMP for a lower extremity musculoskeletal tumour received rehabilitation in limb fitting services that were highly variable in terms of their quality. We were therefore interested in exploring and describing the experiences of patients and comparing them to published national standards. We also aimed to identify opportunities to share good practice with the ultimate goal of improving outcomes for these patients.

3.2 Specific objectives

1. To describe the experience of rehabilitation in limb fitting services after AMP for lower extremity musculoskeletal tumours
2. To compare the experience of rehabilitation in limb fitting services against recognised national standards
3. To investigate national variation in limb fitting services
4. To identify areas of good practice; and
5. To identify areas where improvement is needed and make recommendations about them.

3.3 Specific methods

3.3.1 Participants

This was a cross-sectional survey of patients from five specialist centres for BT surgery in England, all of which also treat patients with STS. Inclusion criteria were: a diagnosis of primary bone or soft tissue tumour in the lower extremity or pelvis; primary or secondary AMP (removal of major limb segment, including rotationplasty); over 8 years of age when surveyed; and at least 1 year since surgery. Adults were defined as 18 years or over at assessment, children under 18 years. Children could seek the assistance of their parent/guardian if they preferred or needed to do so. Patients undergoing treatment for active disease were excluded. Eligible patients were sent a participation invitation letter containing information about the project (Appendix 1.0).

3.3.2 Outcome measures

A patient completed survey instrument was developed (Appendix 2.0). This included questions about service provision derived from existing standards (BSRM, 2003; COT, 2011; (CSP), 2012), from a Servqual questionnaire (Bosmans *et al.*, 2009) for assessing the quality of prosthetic service provision and following discussions with a small sample of service users (n=3) and staff in a limb fitting service (n=2). This survey tool was piloted in a small sample (n=3) before implementation to assess acceptability and readability. The survey tool was adjusted after the pilot, using feedback from patients and health care professionals.

The project manager ‘Sherron Furtado (SF)’ was responsible for the literature review, development of protocol and survey tool used for data collection in this project

3.3.3 Multi-centre survey

The survey was distributed from the five specialist commissioned centres for the surgical treatment of primary BT in England. These are: Royal Orthopaedic Hospital, Birmingham; Royal National Orthopaedic Hospital, Stanmore; Nuffield Orthopaedic Centre, Oxford; Robert Jones and Agnes Hunt Hospital, Oswestry and Newcastle Upon Tyne Hospitals NHS Foundation Trust. The study was coordinated from Newcastle, but patients were identified and sent questionnaires by their treating centre. Each patient was identified by participant number, the key being retained by their treating centre. A convenience sample of patients was

identified from patients in clinics and databases at each centre by the site-coordinator. A single reminder letter was sent from the treating centre to non-responders. Data about diagnosis and level of AMP were provided by the treating centre.

This study was funded by the NHS National Specialist Commissioning Advisory Group as a Quality Improvement Development and Innovation Scheme (QIDIS) project. The project was registered as a national clinical audit and hence approval was obtained from the Clinical Risk and Effectiveness and Research and Development departments in each centre.

The project manager SF independently managed the project set-up, local site co-ordination, screening, recruitment, data collection and day to day running of this project. SF held meetings with site co-ordinators on a regular basis and liaised with them for the efficient co-ordination and running of project at each site. SF also managed the applications for regulatory approvals at Newcastle and assisted staff from participating centres to obtain approvals.

3.3.4 Statistical analysis

Descriptive statistics were calculated using means (standard deviation (SD) for parametric and medians (range), and inter-quartile range (25^{th} percentile - 75^{th} percentile) for non-parametric data. Significance was taken at the 0.05 level. The Statistical Package for the Social Sciences (SPSS) software version 21 (IBM Corp., Armonk, New York) was used. The number of respondents to each item varied and is shown when reporting item scores. The Kolmogorov-Smirnov or Shapiro-Wilk test was used to test normality based on larger or smaller sample sizes respectively ($p<0.05$). Levene's test was used to assess homogeneity of variance. The Mann-Whitney U Test was used to compare continuous variables relating to patient experience between services with limb fitting centre on site vs those with no limb fitting centre on site. Pearson's Chi-square test was used to compare categorical variables and the Kruskal-Wallis Test was used to study differences in patient experience by AMP level.

3.4 Results

Two hundred and fifty questionnaires were sent from the five centres and following a single reminder, 105 responses were received, 101 from adults and 4 from children between September 2012 and June 2013, a response rate of 42%. The number of responses varied by centre (Table 3-1). The number of responses to each item is reported with each item. The one respondent from centre 5 only filled out part of the survey tool, the results from which were included where appropriate.

3.4.1 Demographics of respondents

The median age of 105 respondents was 54 years (range 14-91). One hundred and one were from adults and four from children. Sixty three (of 102 respondents to the question, 62%) were male and 39 (38%) female. 68 (of 103 respondents, 66%) had a malignant BT and 35 (34%) a malignant soft tissue tumour. Of patients who had BTs, the diagnosis was osteosarcoma in 27, chondrosarcoma in 24, Ewing's sarcoma in seven, spindle cell sarcoma in four, and one each of adamantinoma, malignant giant cell tumour, fibrosarcoma, angiosarcoma of bone, hemangiopericytoma of bone and sarcoma not otherwise specified (NOS). Of 37 patients with a soft tissue tumour the diagnosis was synovial sarcoma in seven, spindle cell sarcoma in three, angiosarcoma in five, myxofibrosarcoma in five, malignant fibrous histiocytoma in three, leiomyosarcoma in three, malignant peripheral nerve sheath tumour in two, pleomorphic sarcoma in two, and one each of fibrosarcoma, giant cell tumour of tendon sheath, liposarcoma, myxoid sarcoma, soft tissue chondrosarcoma, soft tissue Ewing's sarcoma, and STS NOS.

Of 105 respondents the AMP level was hemipelvectomy in 22 (21%), hip disarticulation in nine (9%), transfemoral in 39 (37%), knee disarticulation in two (2%), transtibial in 30 (29%), minor in two (2%) and rotationplasty in one (1%). The two patients with minor AMP were excluded from further analysis. AMP levels varied by centre, with two centres (centres 1 and 3) performing more proximal AMP (Table 3-1).

Table 3-1: Demographics and number of limb fitting services used

		Centre 1	Centre 2	Centre 3	Centre 4	Centre 5	Total
Total number of respondents		53	21	27	3	1	105
Mean age ± SD (minimum-maximum (min-max), range)		51.5 +/ 21.2 (17-84,67)	45.6 ±23.7 (14-89)	52.6 ±17.1 (23-86)	79.3 ±12.0 (67-91)	82	51.7± 21.1 (14-91, 77)
Level of AMP (% of total from each centre shown)	Hemipelvectomy	18(34%)		4(15%)			22 (21%)
	Hip disarticulation	5(9%)		3(11%)		1(100%)	9 (9%)
	Transfemoral	21(40%)	11(52%)	6(22%)	1(33%)		39 (37%)
	Knee disarticulation		1(5%)		1(33%)		2 (2%)
	Transtibial	9(17%)	6(29%)	14(52%)	1(33%)		30 (28%)
	Minor AMP		2(9%)				2 (2%)
	Others (Rotationplasty)		1(5%)				1 (1%)
Mean months after surgery ± SD (min-max, range)		62.4 ±33.9 (2-123, 121)	85.9 ±55.5 (13-194)	53.1±31.9 (21-124)	283.3 ±403.5 (36-749)	32	70.7±77.7 (2-749, 747)
Number of limb fitting services used		28	4	12	2	N/A	46

3.4.2 Access to limb fitting services

There was variation in the use of limb fitting services by patients from each centre. Centres 2, 3 and 5 had a limb fitting centre on site, whereas centres 1 and 4 did not. The number of limb fitting centres accessed by patients in centre 1 was 28, in centre 2 was 4, in centre 3 was 12 and in centre 4 was 2. There was only one respondent from Centre 5 (Table 3-1).

Time taken to be seen in the limb fitting service after AMP

The time taken to be seen in limb fitting after AMP varied by centre (Figure 3-1). The mode response in centre 1 was between 3 and 6 months and in centres 2 and 3 was between 1 week and 1 month (Figure 3-1).

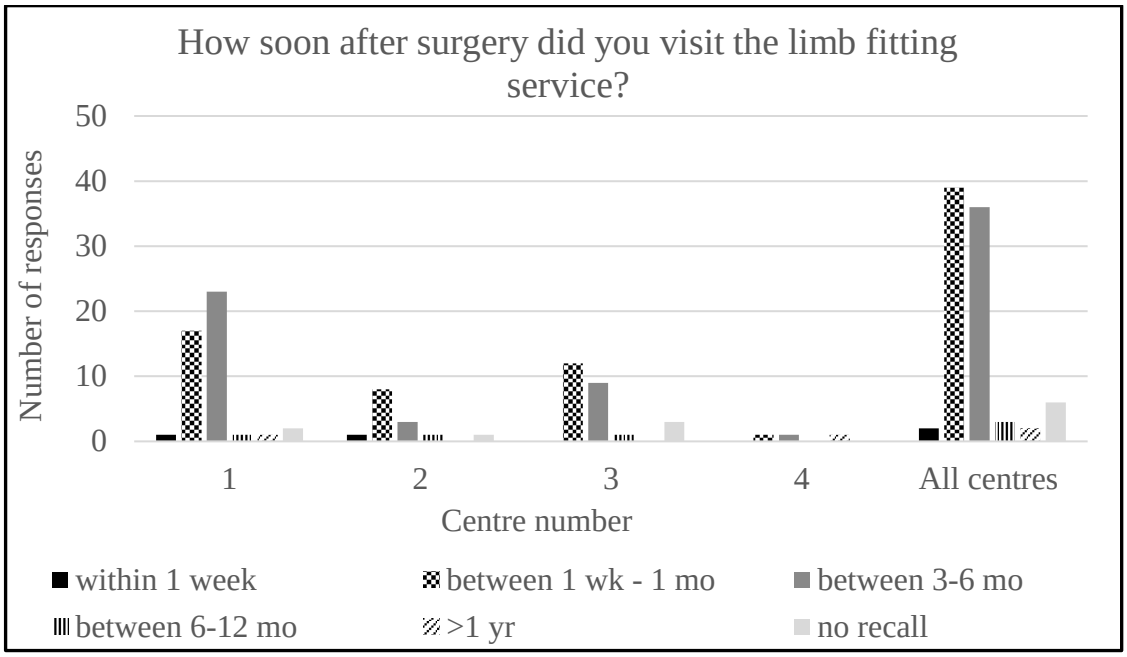


Figure 3-1: Time taken to be seen in the limb fitting service after AMP.

Mode of transport to the limb fitting service

39/84 (46%) respondents reported driving themselves to the limb fitting centre, 29 (35%) were driven by someone else in a private car, 12(14%) used an ambulance or ambulance car and 4 (5%) public transport. Therefore almost half (41/84, 49%) depended on an ambulance or on someone else to drive them to the limb fitting centre (Figure 3-2). Of those under 18 years of age who responded [2/3 (67%)] were driven to and one reported driving themselves to the limb fitting centre [1/3 (33%)].

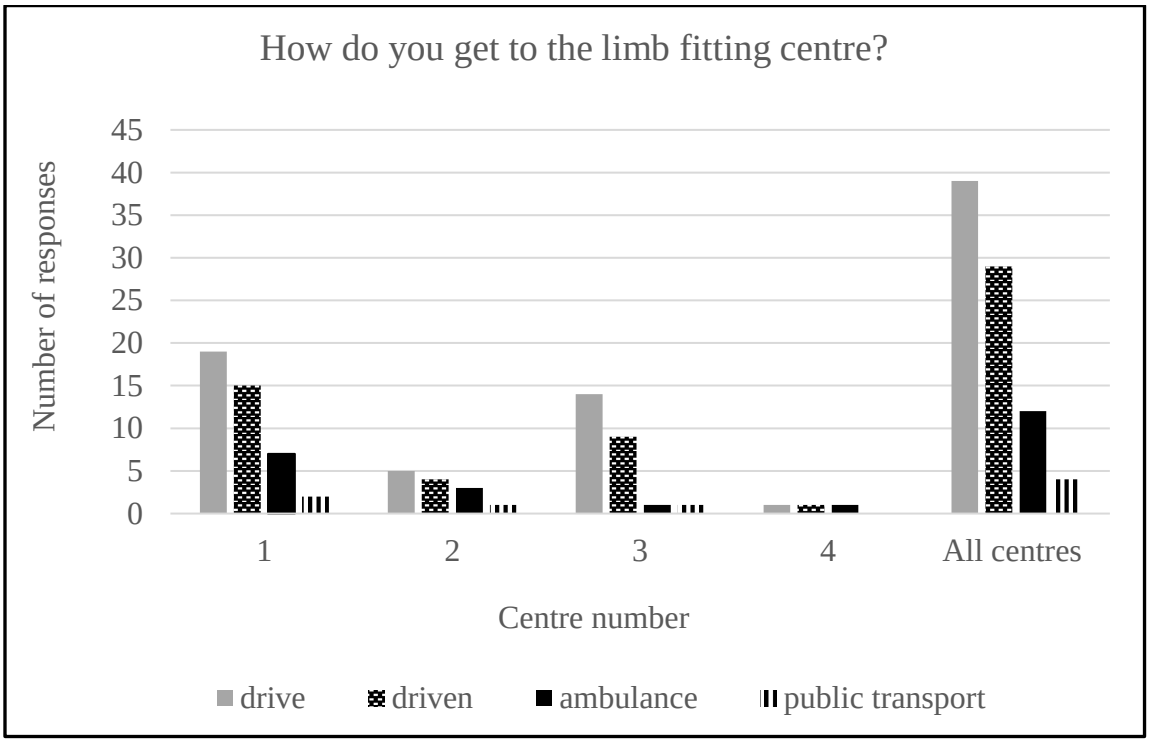


Figure 3-2: Mode of transport to the limb fitting service.

3.4.3 Rehabilitation support

Prosthesis provision

37/73 (51%) patients for whom an early walking aid was appropriate reported using an early walking (e.g. Femurett or Pneumatic Post-AMP Mobility aid (PPAM)) during physiotherapy. 8/86 (9%) respondents were given a prosthetic limb for home use between one week and one month after surgery, 45 (52%) between three and six months, 15 (17%) between six and 12 months, 3 (4%) more than a year after surgery, 12 (14%) were not given a limb and 3(4%) did not remember. Of 86 respondents, 12 (14%) were not provided with artificial limbs, 41 (48%) were provided with 1, 23 (27%) with 2, 9 (10%) with 3 and 1 (1%) provided with 4 limbs. The 12 patients not given a prosthetic limb were of median age 68 (range 24-86) years. The proportion not given a limb varied by AMP level, being 5/22 (23%) at hemipelvectomy, 3/9 (33%) hip disarticulation, 3/39 (8%) transfemoral, and 1/30 (3%) at the transtibial level. Reasons given for not having a prosthetic limb included pain, secondary complications including infection or tumour recurrence and one elderly patient who had a stroke. One patient reported being told they could not have a limb after hip disarticulation.

Prosthesis repair and maintenance

Responses to "When I have a problem with my prosthesis, the repair and maintenance of prosthesis is handled in an appropriate time?" were "strongly agree" in 27/ 74 (36%), "agree" in 22/74 (30%) "neither agree nor disagree" in 9/74 (12%), "disagree" in 10/74 (14%), and "strongly disagree" in 6/74 (8%). The proportion of patients who responded as "strongly agree" or "agree" was 21/38 (55%) from centre 1, 9/11 (82%) from centre 2, 17/23 (74%) from centre 3, and 2/2 (100%) from centre 4 (Figure 3-3).

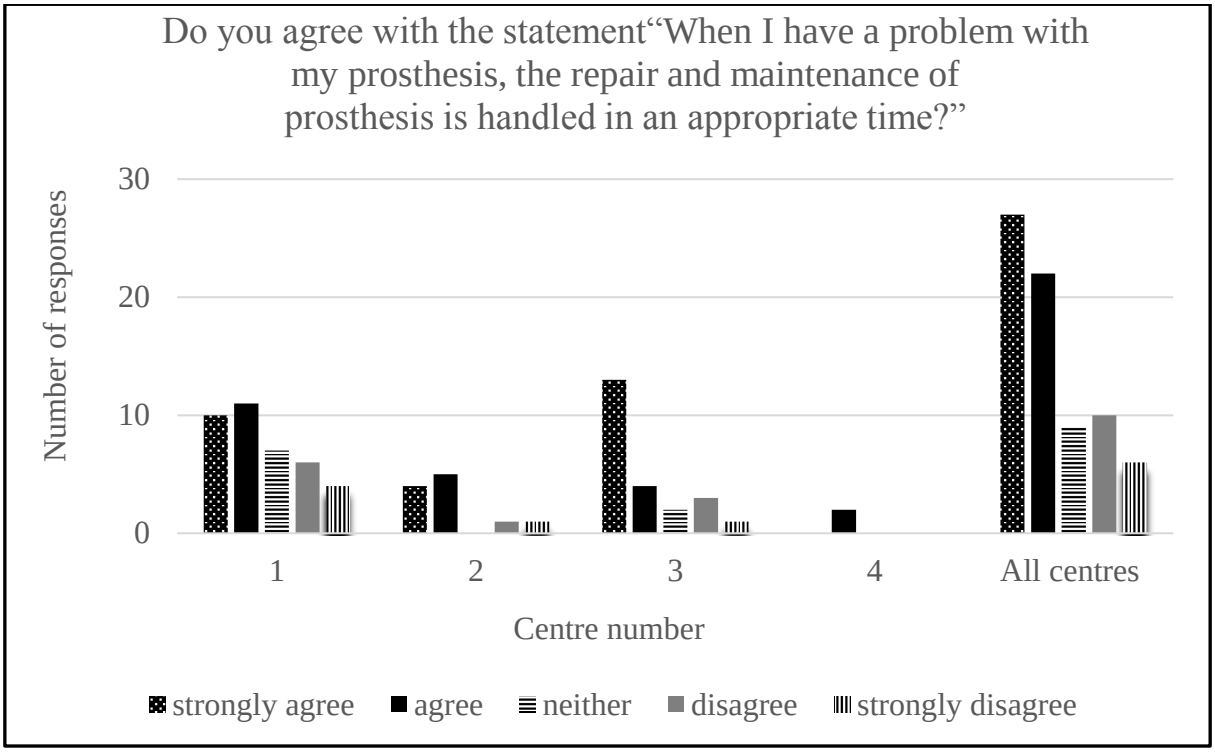


Figure 3-3: Repair and maintenance of prosthesis

Views of patients about Prosthetic service provision to athletes and military personnels

Respondents were asked to respond to the statement "Athletes and military personnel perform better because they have access to better prostheses than I do". 56/91 (62%) strongly agreed, 13 (14%) agreed, 16 (18%) neither agreed nor disagreed, 4 (4%) disagreed and 2 (2%) strongly disagreed (Box 3-1: Part B). Within this group, those under 18 years responded as follows: 2/5(50%) strongly agreed, 1(25%) agreed, and 1(25%) disagreed. Free text comments about patient views of rehabilitation services and about services for athletes and military personnels are listed in Box 3-1.

Box 3-1: Free text comments about services and views

A. Free text comments about staff and allied health professional support:

"Very short term goals"
"Once a week physio inadequate"
"Best for six weeks then nothing"
"I thought I was rushed".
"Physiotherapy was good but I felt more needed to be done, especially with going from walking with an aid to walking without an aid. I became attached to the walking stick and was scared to go outside without it - even though I could walk and didn't like the image of me with a walking stick given my age (17 years) "

"Since finishing treatment and surgery there has been no psychological support or community welfare support or support finding work."

"I'm convinced that cost and age rather than need is applied. Over the years I've used an artificial leg. I've broken the foot on many occasions - Not fit for purpose? Only recently been given an "upgrade". Appointments take ages ever for minor repairs. Actually repairs sometimes takes weeks."

B. Free text responses to the question Do you agree with the statement "Athletes and military personnel perform better because they have access to better prostheses than I do":

"I strongly support that the military should have access to these prostheses, however anybody who loses a limb through whatever reason should also have access and the right to be as normal and pain free as possible."

"With my level of amputation there is only one level of fitting limb, but I think athletes probably have more than one limb to use for different environments/jobs/sports. "
"As to athletes and military personnel having better performances due to better prostheses. This I would assume to be because of different types of funding available**"**

Pre-AMP consultation

The majority (65/86, 76%) of patients recalled being offered pre-AMP counselling. Of those who received it, 44/65 (68%) felt it prepared them well. Of those who did not receive pre-AMP counselling, 11/20 (55%) thought it would have been helpful. Similarly, only 25/94 (27%) were given the opportunity to meet someone who had already undergone a similar AMP before surgery, but most of those who had (22/24, 92%) found it useful (Figure 3-4).

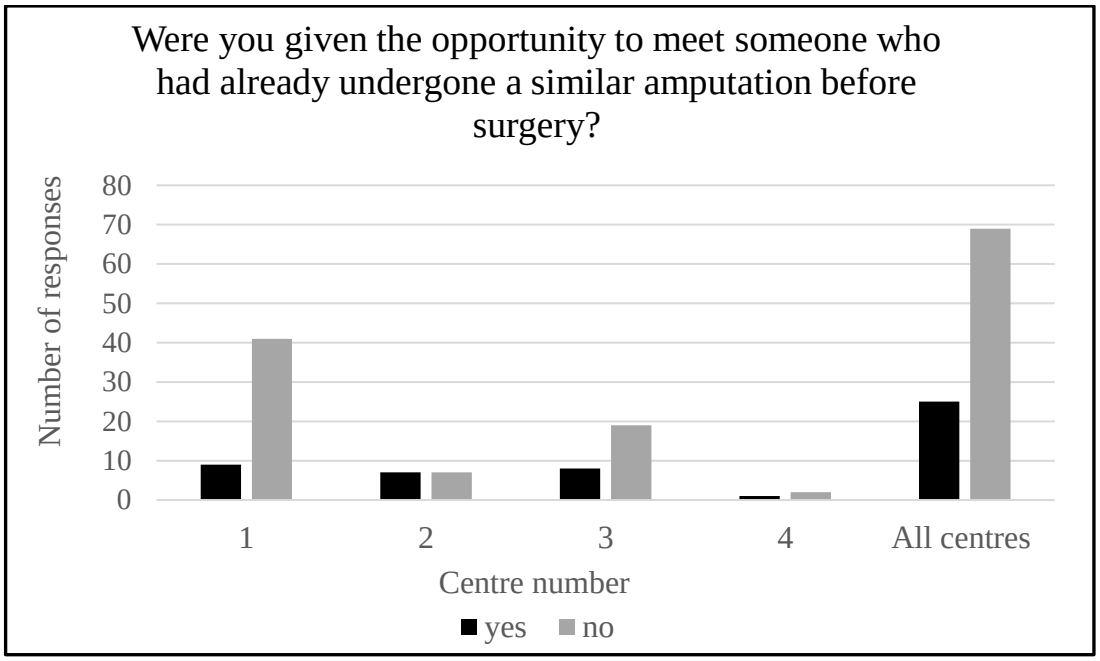


Figure 3-4: Meeting someone with a similar AMP before surgery.

Physiotherapy

63/85 (74%) patients visited the limb fitting service for physiotherapy. Of those that did, reports suggested that care was limited (Box 3-1: Part A).

Falls

Falls were common, reported by 54/87 (62%) patients. However, of those who fell, most (45/52, 87%) felt that their falls were dealt with appropriately by the limb fitting centre. The rate of falling varied by AMP level: 10/22 (50%) patients with hemipelvectomy, 2/9 (22%) hip disarticulation, 23/39 (59%) transfemoral AMP and 19/30 (63%) transtibial AMP patients reported falls. Of patients who fell, most (45/52, 87%) felt that their falls were dealt with

appropriately by the limb fitting service.

Occupational therapy

Patients reported variable satisfaction with occupational therapy and for return to work and the work role. 10/85 (12%) were very satisfied, 8 (9%) were somewhat satisfied, 11 (13%) were neither satisfied nor dissatisfied, 4 (5%) were somewhat dissatisfied, and 6 (7%) were very dissatisfied. 46/85 (54%) reported this item was not applicable.

When asked about occupational therapy delivered training for recreational activities 16/75 (21%) were very satisfied, 14 (19%) were somewhat satisfied, 25 (33%) were neither satisfied nor dissatisfied, 9 (12%) were somewhat dissatisfied and 11 (15%) were very dissatisfied.

Psychological support and counselling

35/79 (44%) of patients had access to psychological support and counselling during limb fitting, but these were all patients from centres 1 and 3 (21/41 (51%) and 14/23 (61%)) respectively (Figure 3-5).

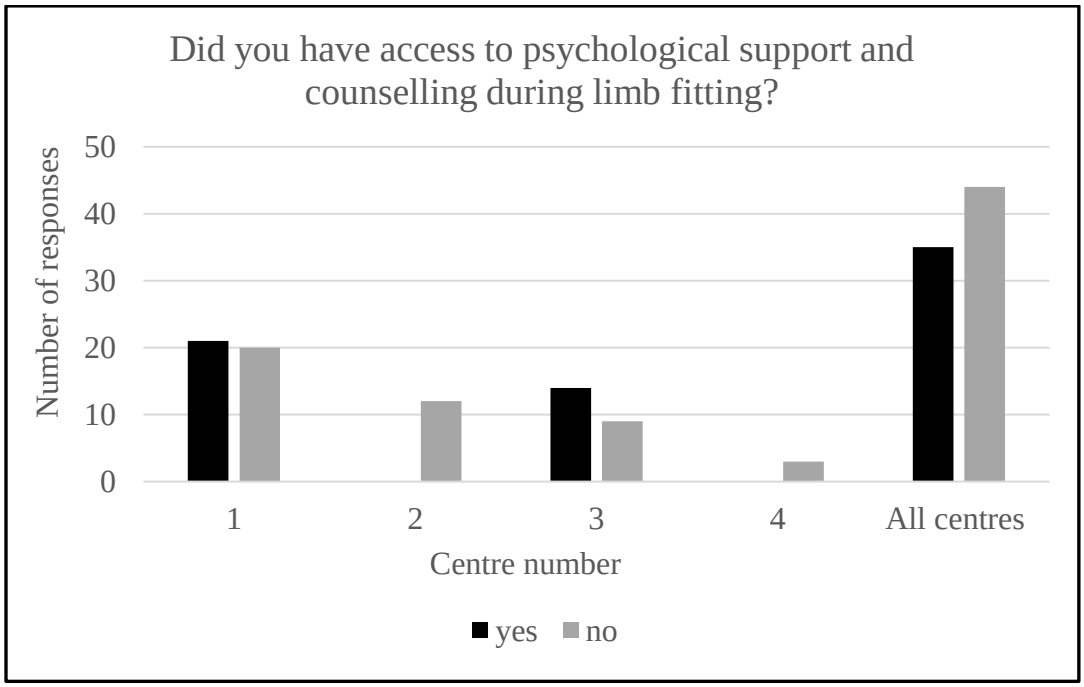


Figure 3-5: Psychological support and counselling during limb fitting

Complaints and feedback

53/67 (79%) patients felt their complaints and feedback were dealt with appropriately; 14 (21%) patients felt that their complaints were not dealt with on time.

3.4.4 Examples of good practice and suggestions for improvement

As described in free text responses, the characteristics of good practice in centres included access, a personal approach by staff, listening and responding proactively to patient needs, and information provision (Box 3-2)

Suggestions for improving services included the provision of better and consistent information, in an appropriate format, such as video (Box 3-2). Some patients believed that cost was a major influence on the availability of limbs. Putting a limb in for repair was a significant problem for many. Some respondents commented that their experience of private providers had been better than that in the NHS, including the availability of the C-leg

Box 3-2: Free text comments about good practice:

A. Free text comments giving examples of good practice:

"I can see them whenever I need to and they take the time and care to fully listen to me. They also show me information useful to me , such on driving, without me having to request it "

"I was allowed time to express my views and was actively involved in my care"

"I think the people make it easier than the equipment /physical part of the service itself"

B. Free text comments including recommendations about promoting good practice:

"It would be great to have a DVD featuring amputees talking about their experiences. Also, some visual images of what a hind quarter amputation looks like!"

"I was told I would have to have an amputation over the phone, when I was alone at home. Prior to surgery I was led to believe I would be able to have an artificial limb once I had healed in spite of not having "a stump", and was shown the type of prosthesis that would be suitable for me. Unfortunately after operation this was not thought to be practicable, so was never tried"

"What fitters don't seem to understand is that socket comfort is the only thing that needs to be right. If the socket is comfortable, doesn't rub etc, then you could put a broom handle underneath and it would be fine. The other thing is that it is impossible to tell if a socket is suitable in those fitting rooms"

"I have developed a kind of phobia towards my limb, almost like a hatred of it because it is so heavy and uncomfortable. I wish there was another way of attaching it to my body, instead of around the waist. I really miss my leg and I would love to look normal again. I would love if an engineer or someone could invent a way of attaching prosthesis instead of wearing around the waist. Then I think I would persevere with it a bit more."

C. Free text comments from family members/guardians of children with amputations:

"Care needs to be consistent. You can't tell a child they can have a change of limb then move the goal posts without discussion. Patients need input with regards to their prosthetic prescriptions (which) would be helpful to give them better control of their life."

"The only problem… had with his prosthesis was the lanyard occasionally snapped. We fully understand the reasons behind the decision. … enjoys his sporting activity and this motivates him. He asks if any limbs or limbs are available for these activities (football/running etc)"

3.4.5 Geographic variation in rehabilitation support

There was significant variation in the experience of patients treated in each centre. In general, patients treated in units with a limb fitting centre on site (n=49) appeared to have a better experience of care than others (n=56). Demographics of these groups are reported in Table 3-2 and detailed description is provided below:

Repair and maintenance of prosthesis: Patients treated in centres with a limb fitting service on site demonstrated significantly higher levels of agreement with the statement "When I have a problem with my prosthesis, the repair and maintenance of prosthesis is handled in an appropriate time", than those seen with in centres without a limb fitting service on site. (Mann-Whitney U Test, U = 494.500, Z = -2.097, p=0.036).

Comfort of limb fitting: Patients treated in centres with a limb fitting service on site demonstrated significantly higher levels of agreement with the statement "The artificial limb(s) provided is (are) comfortable", than those who were seen in centres without a limb fitting service on site. (Mann-Whitney U Test, U = 641.500, Z = -2.191, p=0.028)

Frequency of use of limb: Patients treated in centres with a limb fitting service on site reported a significantly higher frequency of limb use in comparison to patients treated in centres without a limb fitting service on site. (Mann Whitney U Test, U=607.000, Z=-2.264, p=0.024)

***Experience of physiotherapy rehabilitation*:** Patients treated in centres with a limb fitting service on site reported significantly higher levels of agreement with the statement "my physiotherapist set clear rehabilitation goals", than patients treated elsewhere (Mann-Whitney U Test, U=675.000, Z=-2.230, p=0.026).

Experience of occupational therapy provision: Patients treated in centres with a limb fitting service on site demonstrated significantly higher levels of satisfaction with occupational therapy support for training for recreational activities, than those treated in centres without a limb fitting service on site (Mann-Whitney U = 386.000, Z = -3.376, p=0.001).

Patients treated in centres with a limb fitting service on site were more likely to: receive pre-AMP consultation (31/42 (74%) vs 34/53 (64%)); meet a patient with a similar level of AMP before surgery (15/41 (37%) vs 10/53 (19%)); be seen sooner after AMP (20/39 (51%) patients treated in centres with a limb fitting service on site were seen between 1 week and 1 month post-surgery, compared with 12/36 (33%) patients in centres without a limb fitting service on site); be given a limb to use at home (3/38 (8%) patients were not given a limb in centres with a limb fitting service on site vs 9/48 (19%) in other centres); be issued with a limb sooner (6/38 (16%) patients given a limb to use at home between 1 week and 1 month post surgery vs 2/48, (4%)). Further exploratory analysis examined whether differences in service experience were driven by differences in AMP level between centres. No significant differences were found for experiences of repair and maintenance of prosthesis, physiotherapy, occupational therapy, or access to expert medical/nursing care (Kruskal-Wallis Test, $p>0.05$). However differences in comfort of limb fitting and frequency of limb use appeared to be driven by AMP level ($p<0.05$).

Patients treated in centres with onsite limb fitting services did not differ from others by age (Mann-Whitney U Test, U=1097.0, Z=-0.722, p= 0.470), time since surgery (Mann-Whitney U Test, U= 1290.5, Z=-0.169, p=0.866), gender (Pearson's chi-square test p = 0.541) and type of tumour (bone or soft tissue tumour) (Pearson's chi square p=0.880). However there was a higher number of proximal AMP in centres without onsite limb fitting services (Pearson's chi square test with important AMP level groups (hemipelvectomy, hip disarticulation, transfemoral and transtibial AMP) and no cells having an expected frequency<5, p=0.002*) (Table 3-2). When the results of the survey are compared against national standards, services fell short in providing pre-AMP counselling, meeting with an appropriate established amputee before surgery, access to psychological support and support with return to work (Table 3-3)

Table 3-2: Comparison of demographics between centres with limb fitting service on site vs services with no limb fitting service on site

Physical functioning	Sub-categories	Centre with limb fitting service on site	Centre with no limb fitting service on site	p-value
Age (Median (range), Inter-quartile range (25^{th} percentile - 75^{th} percentile)		50 (14-89), 32 (34 – 65)	61 (17-91), 41 (29 – 70)	0.398
Time post surgery(Median (range), Inter-quartile range (25^{th} percentile - 75^{th} percentile)		49 (13-194), 70 (32.5 – 102)	63.50 (2-749), 63 (33-95.8)	0.910
Gender	*Male (M)*	31/48 (64.6%)	32/54 (59.3%)	0.581
	Female (F)	17/48 (35.4%)	22/54 (40.7%)	
Type of tumour	*Bone tumour (BT)*	32/49 (65.3%)	36/54 (66.7%)	0.884
	Soft tissue tumour(STS)	17/49 (34.7%)	18/54 (33.3%)	
Amputation (AMP) Level	*Hemipelvectomy*	4/49 (8.2%)	18/56 (32.1%)	0.002* (Pearson's chi square test with important AMP level groups with 0 cells having expected frequency<5 , p=0.002* included hemipelvectomy, transfemoral and transtibial AMP groups)
	Hip disarticulation	4/49 (8.2%)	5/56 (8.9%)	
	Transfemoral AMP	17/49 (34.7%)	22/56 (39.3%)	
	Through knee	1/49 (2.0%)	1/56 (1.8%)	
	Transtibial	20/49 (40.8%)	10/56 (17.9%)	
	Minor AMP	2/49 (4.1%)	0/56 (0.0%)	
	Other(Rotationplasty)	1/49 (2.0%)	0/56 (0.0%)	

p-value – difference between levels (*=statistically significant), n=sample number, --- = Not enough data available for test

Table 3-3: Comparison against national standards

S.No	Recommended National Standard	Type of Standard	Results of audit
1.	A pre-AMP consultation with an appropriate PARC member should be arranged where AMP is a treatment option (as opposed to treatment necessity)	British Society of Rehabilitation Medicine (BSRM) (BSRM, 2003) Type B : Good practice	65/86, 76% of patients
2.	A meeting with an appropriate established amputee should be considered before every case of elective AMP	BSRM (BSRM, 2003) Type C : Desirable practice	25/94, 27% of patients
3.	Each PARC must have an established complaints procedure.	BSRM (BSRM, 2003) Type A: Essential Practice	53/67 (79%) patients felt their complaints and feedback were dealt with appropriately; 14 (21%) that their complaints were not dealt with on time.
4.	Rehabilitation programmes should include education on preventing falls and coping strategies should a fall occur.	Evidence Based Clinical Guidelines for the Physiotherapy Management of Adults with Lower Limb Prostheses. British Association of Chartered Physiotherapists in Amputee Rehabilitation (BACPAR) guidelines ((CSP), 2012)	Of patients who fell, most (45/52, 87%) felt that their falls were dealt with appropriately by the limb fitting service
5.	Service users within any district should have access to all appropriate rehabilitation services which aim to maximise physical, psychological and social well being	BSRM – (BSRM, 2003) Type B : Good practice	35/79 (44%) of patients had access to psychological support and counselling during limb fitting, but these were all patients from centres 1 and 3 (21/41 (51%) and 14/23 (61%)) respectively. No patients from Centre 1 and 4 had access to psychological counselling.
6.	Support should be provided from the multidisciplinary team regarding successful work reintegration and maintenance of the work role.	Occupational therapy with people who have had lower limb AMP – Evidence Based Guidelines, College of Occupational Therapists (COT, 2011)	10/85 (12%) were very satisfied, 8 (9%) were somewhat satisfied, 11 (13%) were neither satisfied nor dissatisfied, 4 (5%) were somewhat dissatisfied, and 6 (7%) were very dissatisfied. 46/85 (54%) reported this item was not applicable.

3.5 Discussion

3.5.1 Overview of study findings

This is a novel national survey which has investigated the reported service experience of a complex and varied subgroup of patients who have had amputation for extremity sarcoma. This study has clearly shown that services across England are highly variable and fall short of recognised national standards. This may have an impact on disability, dependency and employment. In patients treated with amputation for sarcoma, physical functioning is associated with quality of life (Stevenson *et al.*, 2016) and therefore poor quality rehabilitation services are likely to have significant impact on other aspects of life and the burden on society. We have therefore shown that there is an urgent need to improve service provision to patients diagnosed with sarcoma who have undergone or are facing amputation. The frequency of long term problems such as pain, psychological and physical disability in this population demands the provision of appropriate psychological support, pain and rehabilitation services if outcomes are to be optimised (Kwong *et al.*, 2014). As this is a broad topic area, the clinical implications of this work have been discussed under individual sub-headings below.

3.5.2 Access to limb fitting services

Access to limb fitting services remains challenging: our survey shows most patients are dependent on others driving them or ambulance transport. As with other aspects of health care, there is a balance between the provision of specialist services and their proximity to the patient's home, but this can be a particular issue when patients travel long distances for specialist care.

3.5.3 Rehabilitation support

Pre-AMP consultation

Pre-AMP counselling is an important part of the rehabilitation pathway. The consultation allows the patient to understand what life after AMP and rehabilitation involves and supports informed decision making about care, particularly if AMP is being considered as an option, rather than a necessity. We have shown that many patients did not receive pre-AMP counselling and other approaches, such as the use of a video or patient leaflets might be

helpful (BSRM, 2003).

Prosthetic provision and maintenance

Repair and maintenance of prostheses are very important, particularly if the patient is only issued with one prosthetic limb, and the British Society of Rehabilitation Medicine (BSRM) (BSRM, 2003) recognises ready access to prosthetic repair and maintenance is important. Patients may be unable to pursue normal activities while a limb is in the workshop. Our survey suggests that this could be improved, with only a proportion (49 of 74, 66%) reporting that when they had a problem with their prosthesis, repair and maintenance were handled in an appropriate time.

Physiotherapy care, Occupational therapy and Falls

Although there are recommended standards for allied health support after a major limb loss (COT, 2011; (CSP), 2012), our study showed that physiotherapy care and occupational therapy is limited and variable, with scope for improvements. Targeting service improvements might not only help improve the overall patient experience but could also optimise outcomes e.g.: a better active participation in ADLs, work and RNL (Kwong *et al.*, 2014). We have also shown that patients who have AMP for sarcoma often fall, and therefore services should be able to deal with this appropriately, given that rehabilitation programmes are of benefit after falls (Dyer *et al.*, 2008). It was interesting to note that falls were reported more frequently in patients with more distal AMP, perhaps reflecting greater activity levels. However, we only collected limited information about this.

Psychological support

We have clearly shown that access to psychological support is variable and represents a major gap in the service, although the demand in this population is high, with those who undergo lower limb AMP tending to report anxiety and depression (Singh *et al.*, 2007; Kwong *et al.*, 2014). Although psychological treatment is important and improves overall outcomes in this population (Srivastava and Chaudhury, 2014), the availability of such support is variable, being unavailable in some centres (centres 2 and 4) and only offered to a proportion of patients in others (60% in centre 3; 51% in centre 1).

3.5.4 Strengths

This is a unique study which has attempted to describe the patient experience of limb fitting and rehabilitation after AMP for sarcoma at a national level. A major strength is the use of an evidence based survey instrument designed following literature reviews, and patient and clinician consultation as well as the use of the Servqual questionnaire, which allowed us to capture the varying service provision in this population. This work has built on a previous systematic review, which showed that disability and impaired physical functioning are major issues for survivors of extremity sarcoma and which therefore demand high quality rehabilitation services (Kwong *et al.*, 2014).

3.5.5 Limitations

It is recognised that the response rate is relatively low (42%) and there is therefore a risk of response bias, but nevertheless the cohort is the largest described in England, and the sample size seemed reasonable given the aim of the study. Furthermore, the number of responses from each centre varied widely, likely reflecting the size of each centre. For example: 53/105 responses were from one of the largest centres, and only 3/105 (2 and 1) were from smaller centres (centre 4 and 5) (Table 3-1). Given the small number of respondents in centre 4 (n=3) and centre 5 (n=1), descriptive statistics only were used to explore patient experiences in all five centres. However, there were statistically significant differences between units with a limb fitting service on site (n=49) compared to those without (n=56). There was further variation in the range of "time since surgery" (2 – 749 months), and "mean time since surgery" between centres (Table 3-1), which we recognise are potential sources of bias. We attempted to send reminders, but the study was structured such that centres were asked to communicate directly with patients in order to maintain central anonymity of the data. This meant that only one reminder was sent. Furthermore, some patients had been treated for sarcoma several years ago, meaning there is a risk of recall bias, even though "I do not remember or cannot remember" was included as an option. However, questions about ongoing treatment are likely to remain relevant.

3.5.6 Recommendations for future work

The number of limb fitting services used by each centre reflects the referral patterns of each as patients travel long distances for specialist sarcoma care. It is undoubtedly difficult to establish and maintain standards of specialist care across a large number of services but mechanisms for this would be helpful. Having a limb fitting service on site for sarcoma patients appears to be advantageous, with patients experiencing better services, including pre-AMP counselling, being seen sooner after surgery, and being issued with a limb for home use sooner. The concentration of expertise and facilities for patients who have had AMP after trauma, particularly of military patients has been seen as advantageous. Given the differences between our patients and the majority of patients who have AMP, there is an argument for reducing the number of limb fitting service providers for sarcoma amputees in order to develop expertise, as for military amputees (Dyer *et al.*, 2008). However, there is clearly a tension with the ability of patients to travel for limb fitting and the convenience of a more local service. Solutions for delivering highly specialised rehabilitation care close to home are therefore also required. Remotely supporting patients using telehealth interventions may be a helpful and cost effective approach (Henderson *et al.*, 2013).

Rehabilitation services can also be improved through the delivery of improved assessments and treatments which have an impact on survivorship outcomes. We have suggested recommendations for improvement of rehabilitation services which include development of services with a special interest to raise the overall standard and disseminate good practice, encouraging good communication between treating centres and limb fitting services, provision of better information to patients, and improving the experience of patients to help pre-operative understanding. An excellent example of the direct translation of recommendations into clinical practice is that one of the participating centres has subsequently set up a dedicated AMP clinic, to ensure patients are provided with specialized care. In another centre, the rehabilitation team has started contacting local physiotherapists to ensure appropriate follow-up of patients and delivery of specialized care in locally. Ongoing audit of the patient experience will be important to inform commissioning of services which should include psychological support, pain services and should consider access including transport.

3.6 Conclusion

There is wide variation in the experience of limb fitting services following AMP for sarcoma and services fall short of recommended national standards. Variations in service provision include access to psychological support, use of pre-AMP consultation, physiotherapy, access to services, including early walking aids and prosthetic repair. Addressing variation in care through developing services and solutions for delivering expert care close to home are needed, which we have discussed in subsequent chapters.

Chapter 4: Physical functioning, pain and quality of life after amputation for musculoskeletal tumours. A national survey

This work has been published in the Bone and Joint Journal with co-authors from the national participating centres (reference below).

Furtado, S., et al., Physical functioning, pain and quality of life after amputation for musculoskeletal tumours: a national survey. Bone Joint J, 2015. 97-b (9): p. 1284-90.

4.1 Introduction

As seen in Chapter 2, the impact of poor physical functioning and disability on the survivorship experience of patients undergoing AMP for musculoskeletal tumours is evident (Nagarajan *et al.*, 2003; Kwong *et al.*, 2014). Previous studies have shown that physical functioning is related to pain and QoL outcomes (Eiser *et al.*, 1997; Eiser *et al.*, 2001). In spite of this, to date, little is known about the overall survivorship experience of patients who undergo AMP for extremity sarcoma in the United Kingdom within the NHS. We were interested in understanding physical function, QoL and pain after AMP for sarcoma in England, in order to improve services, provide appropriate information and improve outcomes. Given the rarity of sarcoma we took a national, collaborative approach. The aim was therefore to investigate survivorship outcomes after AMP for lower extremity musculoskeletal tumours in England.

4.2 Specific objectives

1. To describe survivorship outcomes including physical functioning, pain and QoL after AMP for sarcoma
2. To compare outcomes by AMP level
3. To investigate relationships between measures.
4. To compare outcomes with published series.

4.3 Methods

4.3.1 Participants

The screening and recruitment of participants were the same as Chapter 3.

4.3.2 Outcome measures

We developed a patient reported outcome tool as follows. An overview of the relevant literature review had identified validated measures of physical functioning, pain and QoL appropriate to this population. Measures were piloted in a sample of three patients. The tool comprised the lower extremity TESS (Appendix 3.0) (Davis *et al.*, 1996), Brief Pain Inventory (BPI) (Appendix 4.0) (Poquet and Lin, 2016) and QoL-CS scale (Appendix 5.0) (Ferrell *et al.*, 1995). TESS, a patient-reported measure, detailed in Chapter 2 (Section 2.7, Sub-section 2.7.2), comprises 30 self-reported items evaluating physical disability after treatment for extremity sarcoma (Davis *et al.*, 1996). Although the Musculoskeletal Tumour Society Score has been widely used in this population, as an observer-rated score it was unsuitable for use in a postal survey (Enneking *et al.*, 1993). QoL-CS is a 41-item questionnaire for cancer survivors. It includes four QoL domains; physical, psychological, social and spiritual. It is reliable and valid and has been used after extremity sarcoma surgery. QoL-CS scores range between 0 and 100 (worst to best QoL) (Ferrell *et al.*, 1995). The BPI – Short Form assesses pain severity and impact on daily functions: mild pain is defined as a worst pain score of 1 to 4, moderate pain as 5 to 6, and severe pain as 7 to 10 points (Poquet and Lin, 2016).

4.3.3 Multi-centre survey

The survey was conducted from the five specialist commissioned centres for the surgical treatment of primary BTs in England. All centres treat patients with bone and soft-tissue sarcomas. These are: Royal Orthopaedic Hospital, Birmingham; Royal National Orthopaedic Hospital, Stanmore; Nuffield Orthopaedic Centre, Oxford; Robert Jones and Agnes Hunt Hospital, Oswestry and Newcastle Upon Tyne Hospitals NHS Foundation Trust. The study was co-ordinated from Newcastle, but patients were identified and sent questionnaires by their treating centre. Each patient was identified by participant number, the key being retained by their treating centre. A convenience sample of patients was identified from patients in clinics and databases at each centre by the site-coordinator. A single reminder letter was sent from the treating centre to non-responders.

This study was funded by the NHS National Specialist Commissioning Advisory Group as a QIDIS project. The project was registered as a national clinical audit and approval was obtained from the Clinical Risk and Effectiveness and Research and Development departments in each centre.

4.3.4 Statistical analysis

Descriptive statistics were calculated using means and SDs for parametric data and medians with ranges and/or interquartile ranges (IQR) (25th percentile value to 75th percentile value) for non-parametric data. Pearson correlations were calculated to examine relationships between variables. Regression analysis assessed the influence of individual factors on survivorship outcomes. Factors investigated were AMP level, months after surgery, age, pain severity and pain interference and diagnostic category. For the latter, patients were categorised according to whether chemotherapy was part of standard treatment (i.e. osteosarcoma, Ewing's sarcoma spindle cell sarcoma of bone, sarcoma NOS of bone and fibrosarcoma of bone) as 1 (chemotherapy standard) and 2 (chemotherapy not standard). As there is a possible interaction between TESS and QoL-CS outcomes, multivariate analysis of co-variance (MANCOVA) was used to investigate the influence of these independent variables on TESS and QoL-CS, with Kruskal–Wallis tests used to explore differences in TESS item scores. Significance was taken at a p-value < 0.05. The SPSS software version 21 (IBM Corp., Armonk, New York) (IBM Corp., Armonk, New York) was used.

4.4 Results

4.4.1 Participants

Questionnaires were sent to 250 patients identified at five centres, and following a single reminder, 105 responses were received (response rate of 42%) between September 2012 and June 2013. Of these, four were children and were excluded from this analysis. Of 101 adults, 100 returned correctly completed tools, which were used for final analysis.

The mean age was 53.6 years (19 to 91; five non-responders) at a mean of 72 months after surgery (2 to 749) In total 60 (62%) were male and 37 (38%) were female (three non-responders). Details of the patients' tumour types and diagnoses are provided in Table 4-1. In total 20 tumours were located in the hip or pelvis, 31 above the knee, 32 between knee and ankle and 17 in the ankle or foot. The AMP level was hemipelvectomy in 22, hip disarticulation in nine, transfemoral in 35, knee disarticulation in one, transtibial in 30, minor

(AMP of toe or toes) in two, and rotationplasty in one (Table 4-2). 42 (43%) had a right sided tumour.

Table 4-1: Tumour types and diagnosis

Tumour type	Diagnosis	Number of patients
Primary bone sarcoma (63)	Osteosarcoma	24
	Chondrosarcoma	24
	Ewing's sarcoma	5
	Spindle cell sarcoma	4
	Adamantinoma,	1
	Malignant giant cell tumour	1
	Fibrosarcoma	1
	Angiosarcoma of bone	1
	Haemangiopericytoma of bone	1
	Sarcoma NOS	1
Soft-tissue tumours (37)	Synovial sarcoma	7
	Spindle cell sarcoma	3
	Angiosarcoma	5
	Myxofibrosarcoma	5
	Malignant fibrous histiocytoma	3
	Leiomyosarcoma	3
	Malignant peripheral nerve sheath tumour	2
	Pleomorphic sarcoma	2
	Fibrosarcoma	1
	Giant cell tumour of tendon sheath	1
	Liposarcoma,	1
	Myxoid sarcoma,	1
	Soft-tissue chondrosarcoma	1
	Soft-tissue Ewing's sarcoma,	1
	Soft-tissue sarcoma NOS.	1

Outcomes by AMP Level

Physical function, pain and QoL outcomes have been listed by AMP level in Table 4-2 and are detailed in sections below.

4.4.2 Physical function

Mean TESS was 56.4% (SD 23.4). TESS varied significantly by level: proximal AMP were associated with lower scores than more distal AMP (Table 4-2, Figure 4-1). There was no significant difference in TESS when diagnostic categories were compared ($p = 0.07$, independent *t*-test). Of 81 respondents, 57 (70.4%) depended on walking aids, with a trend to increased use with more proximal AMP (Table 4-2). Patients with hemipelvectomy or transfemoral AMP were significantly more likely to use walking aids (chi-squared test; $p = 0.005$ and $p < 0.001$, respectively).

Table 4-2: Physical functioning, pain and quality of life outcomes by AMP Level

Patient group	Number of patients	Use of prosthetic limb at least daily (number of respondents shown)	Use of walking aids (number of respondents shown)	TESS (Mean ± SD)	QoL-CS (Mean ± SD)	BPI-SF – Pain Severity (Mean ± SD)	BPI-SF – Pain Interference (Mean ± SD)
Total scores for all 100 patients	100			56.4±23.3	5.1±1.8	3.6±2.3	3.4±2.9
Hemipelvectomy	22	1/21 (4.8%)	15/18 (83.3%)	50.48±20.26	4.93±1.62	3.67±1.67	2.73±2.47
Hip disarticulation	9	1/9 (11.1%)	3/5 (60.0%)	36.32±20.79	4.91±1.41	3.94±2.50	4.35±3.29
Transfemoral	35	22/33 (62.9%)	25/28 (89.3%)	53.52±21.29	4.97±2.03	4.13±2.37	3.95±2.67
Through knee	1	0/1 (0%)	0/1 (0%)	17.30	5.00	1.5	4.86
Transtibial	30	27/30 (90%)	14/28 (50%)	70.10±19.60	5.18±1.66	3.05±2.37	3.08±3.21
Minor AMP	2	-	0/1 (0%)	92.25±9.83	7.58±1.83	0.63±0.88	0.43±0.61
Others(Rotationplasty)	1	-	-	27.80	3.81	5.25	7.83
p-value		p<0.001*		p<0.001*	p=0.555	p=0.198	p=0.215

p-value – difference between levels (*=statistically significant), n=sample number

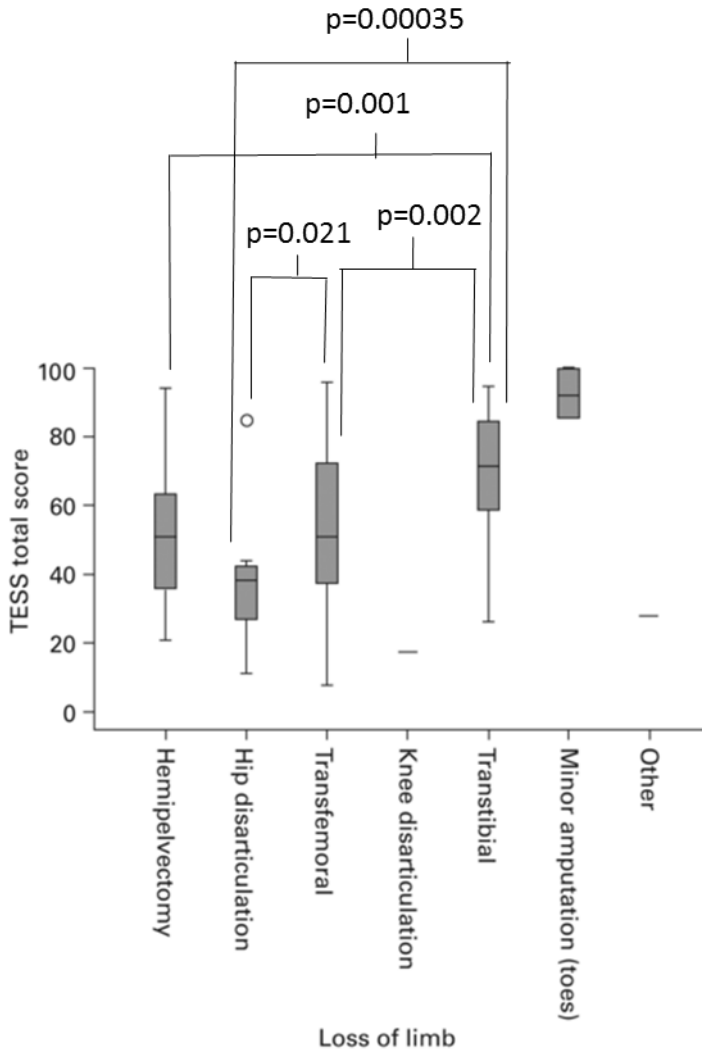


Figure 4-1: TESS by AMP level ($p<0.05$)
Box and whisker plot showing the Toronto Extremity Salvage Score (TESS) by AMP level ($p < 0.001$). (Plot shows median value, box limits represent first and third quartile limits. Whiskers represent data range, excluding outliers (> 1.5-times the interquartile range below the first or above the third quartile).

Within TESS item scores, activities most often reported as impossible or extremely difficult to do were kneeling (63% of respondents), gardening and yard work (52%), participating in sports (46%), walking upstairs (38%), walking outdoors (37%), and participating in leisure activities (36%). In contrast, 43% found light household tasks only a little or not at all difficult.

Patients with more proximal AMP had lower item scores than those with below knee or minor AMP. There were significant differences between patients with hemipelvectomies and those

with below knee AMP for light household chores such as tidying and dusting ($p < 0.001$, Mann–Whitney U test), gardening and yard work ($p = 0.001$, Mann–Whitney U test), walking in the house ($p = 0.001$, Mann–Whitney U test), walking outdoors ($p = 0.003$, Mann–Whitney U test), standing upright ($p = 0.028$, Mann–Whitney U test), participating in sexual activities ($p = 0.009$, Mann–Whitney U test), getting up from kneeling ($p = 0.023$, Mann–Whitney U test), completing usual duties at work ($p = 0.011$, Mann–Whitney U test) and working the usual number of hours ($p = 0.019$, Mann– Whitney U test). There were significant differences between patients with transfemoral and transtibial AMP for putting on socks or stockings item ($p = 0.023$, Mann– Whitney U test).

In free text responses, patients with hemipelvectomy or hip disarticulation reported difficulty in ADLs such as showering, toilet activities, PA in the house, carrying objects in the house, household chores, using crutches or wheelchairs and going outdoors. It is not surprising that patients with above or below knee AMP reported difficulties with daily activities, employment and sports.

A small number of patients also reported complications which interfered with PA including lymphoedema, a leaking sinus and phantom pain. Others reported that psychological symptoms including depression, lack of motivation, and anxiety interfered with physical functioning. Patients using walking aids had significantly higher pain severity and pain interference scores than those who did not (median pain severity using walking aids 4.3 vs 2.5 for those not using walking aids, ($p = 0.030$, Mann–Whitney U test); median pain interference using walking aids 3.7 vs 0.8 for those not using walking aids, ($p = 0.024$, Mann–Whitney U test). Prosthetic limb use varied significantly by level; patients with more proximal AMP used prosthetic limbs less often than those with more distal AMP ($p < 0.001$, chi-squared test, Table 4-2).

4.4.3 Quality of life

The mean overall QoL-CS score was 5.1 (SD 1.8) (Table 4-2). Mean subdomain scores for physical, social, spiritual and psychological domains were 6.7 (SD 2.2), 4.9 (SD 2.2), 4.01 (SD 2.0) and 4.7 (SD 2.1), respectively. There was no significant difference in total QoL-CS and sub-domain scores between AMP levels or by diagnostic category (Table 4-2, Figure 4-2).

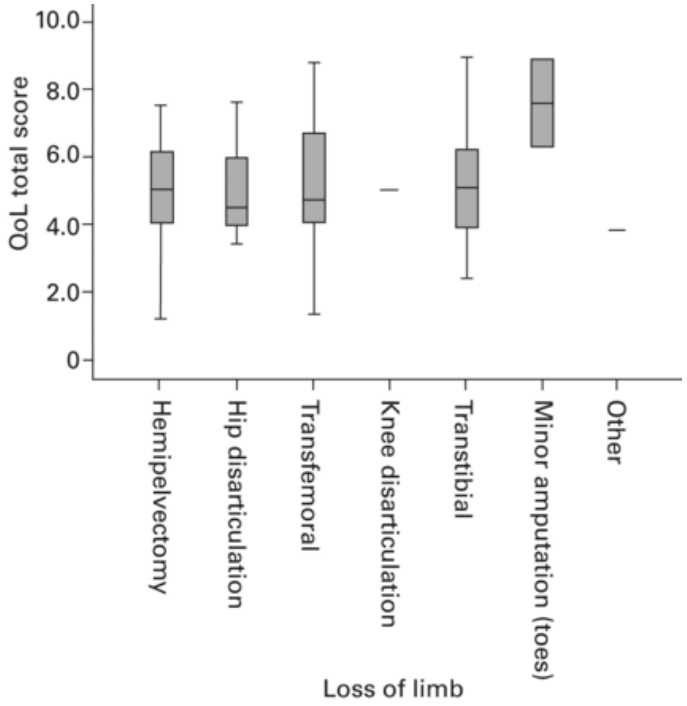


Figure 4-2: QoL-CS by AMP level (p>0.05)
Box and whisker plot showing the total Quality of Life – Cancer Survivors (QoL-CS) scale by AMP level (n = 100; one way analysis of variance p = 0.555). (Plot shows median value, box limits represent first and third quartile limits. Whiskers represent data range).

4.4.4 Pain scores

The mean pain severity score was 3.6 (SD 2.3), and the mean pain interference score was 3.4 (SD 2.9). These did not vary significantly by level or by diagnostic category (Table 4-2, Figure 4-3 and 4-4). Of 95 respondents to this item, pain was reported as mild in 46 (48.4%), moderate in 32 (33.9%), and severe in nine (9.5%). A total of eight (8.4%) had no pain. Patients with severe pain had undergone hemipelvectomy in one, hip disarticulation in two, transfemoral AMP in four and transtibial AMP in two.

The interference of pain on ADL was mild in 46 of 94 (48.9%) respondents, moderate in 18 (19.1%), severe in 17 (18.1%), but did not interfere in 13 (13.8%). The AMP level of patients who reported 'pain affected their ADLs severely' was hemipelvectomy in one, hip disarticulation in three, transfemoral in seven, transtibial in five and rotationplasty in one. Respondents described their pain as phantom limb pain (including dysaesthetic symptoms such as tingling) or stump pain.

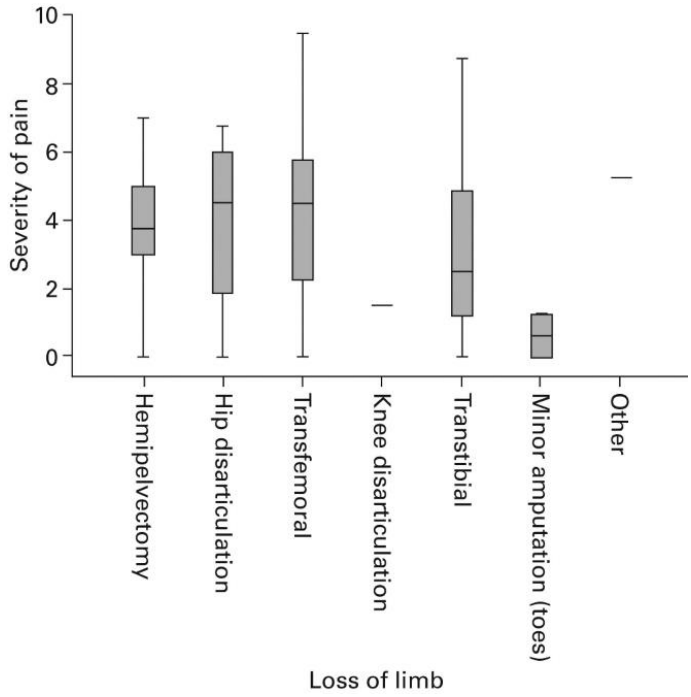


Figure 4-3: Severity of Pain by AMP Level (p>0.05)
Box and whisker plot showing the severity of pain in daily activities by AMP level (n = 100; one way analysis of variance; p = 0.215). (Plot shows median value, box limits represent first and third quartile limits. Whiskers represent data range).

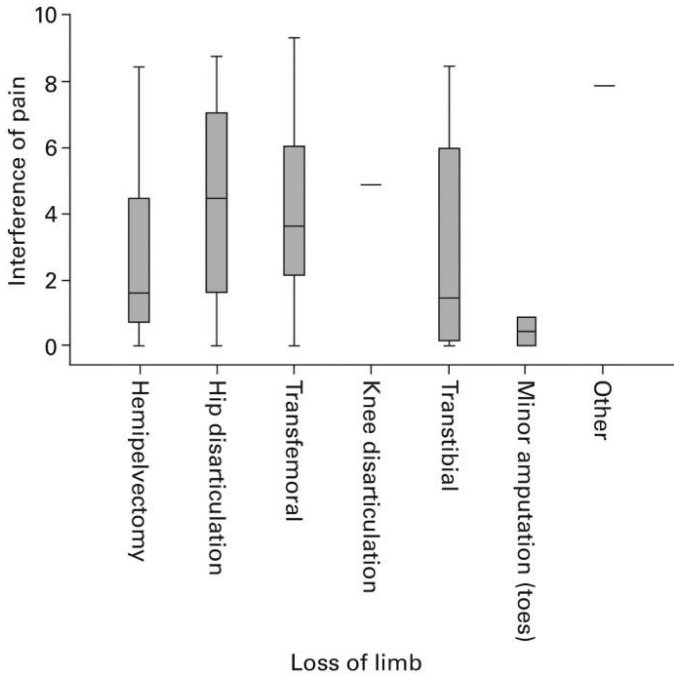


Figure 4-4: Interference of Pain by AMP Level (p>0.05).
Box and whisker plot showing the pain interference in daily activities by AMP level (n = 100; one way analysis of variance; p = 0.215). (Plot shows median value, box limits represent first and third quartile limits. Whiskers represent data range).

4.4.5 Interaction between scores

Regression analysis with TESS as the dependent variable revealed a positive correlation between TESS and more distal AMP. There was a negative correlation between TESS and increasing age, diagnostic category, pain severity and pain interference scores (Table 4-3). In the regression model, pain interference, age and limb loss were significant predictors of TESS (Table 4-3). Regression with QoL-CS as the dependent variable demonstrated a positive correlation between QoL-CS and TESS, and a negative correlation with pain severity and pain interference scores (Table 4-4). In the regression model, TESS was the only significant predictor of QoL-CS (Table 4-4). In the MANCOVA model with TESS and QoL-CS as dependent variables, pain interference was the only variable to reach significance (Wilks' lambda, $p < 0.001$, F-statistic = 11.82).

Table 4-3: Regression model - TESS as dependent variable

Independent Variables	Unstandardized Coefficients	Standard Error	Standardized Regression Coefficients (Beta)	t-statistic	P value (Significance)
Constant	79.666	7.083		11.247	<0.001*
Pain interference	-4.903	0.585	-0.615	-8.373	<0.001*
Age	-0.327	0.089	-0.281	-3.677	<0.001*
AMP Level	3.372	1.067	0.242	3.160	0.002*

Significant predictors in Regression Model: Age, Level of AMP and Pain interference.

Regression Model Summary: R square = 0.542, Adjusted R square = 0.526, Sig. F Change = 0.002*, Significance of Regression Model – p<0.001*

Table 4-4: Regression model - QoL-CS as dependent variable

Independent Variables	Unstandardized Coefficients	Standard Error	Standardized Regression Coefficients (Beta)	t-statistic	P value (Significance)
(Constant)	3.595	0.457		7.871	<0.001*
TESS	0.026	0.007	0.351	3.494	0.001*

Significant predictors in Regression Model: TESS

Regression Model Summary: R square = 0.123, Adjusted R square = 0.113, Sig. F Change = 0.001*, Significance of Regression Model - P = 0.001*

4.5 Discussion

4.5.1 Overview of study findings

This survey represents an unprecedented national collaboration to investigate patient outcomes after lower extremity AMP for bone and soft-tissue tumours in England. We have demonstrated a substantial number of patients living after AMP for tumours, whose survivorship experience is characterised by reduced levels of physical function, the need for walking aids and pain. We have shown more proximal AMP, increasing age and pain interference are associated with lower TESS scores. We have also shown that although TESS appeared to be the only significant independent predictor of QoL scores in our regression model, this was likely driven by pain interference scores. The clinical implications of this work have been discussed under the sub-headings of individual outcomes.

4.5.2 Physical function

We have shown that AMP level has a major impact on the level of disability, the use of prosthetic limbs and the use of walking aids. Although this is not a novel finding (Aksnes *et al.*, 2008; Grimer *et al.*, 2013), this is the first multicentre study in the NHS to show this. The greatest difference in TESS was between those with AMP above the knee and those below the knee. There was less difference between AMP at transfemoral and more proximal levels, in keeping with the series from Aksnes et al (Aksnes *et al.*, 2008) Although AMP level was not clearly related to QoL, disability influences many domains of survivorship, including social and psychological status, independent living, education, employment and financial status. Patients who have an AMP for a primary BT may be less likely to have a job (Nagarajan *et al.*, 2003). It is therefore important to improve and/or develop specialised rehabilitation programmes to reduce disability and minimise the impact of treatment on other aspects of life. Poor responses to item scores including gardening and yard work, sports, stairs, walking outdoors and leisure activities provides some insight into areas where targeted rehabilitation might be most helpful, particularly for those with more proximal AMP.

4.5.3 Pain scores

Our study confirms that almost all patients experience pain (91.6% reported some pain: mild in 48.4%, moderate in 33.9% and severe in 9.5%) and that this interferes with ADL (86.2% reported some interference: mild in 48.9%, moderate in 19.1% and severe in 18.1%). Furthermore, pain interference appeared to be a significant influence on TESS and QoL-CS in

the MANCOVA analysis. The causes of pain are multifactorial, for example from the use of a prosthesis, phantom pain or tumour recurrence (Tabone *et al.*, 2005; Daigeler *et al.*, 2009), and may be higher after AMP than LSS (Aksnes *et al.*, 2008; Grimer *et al.*, 2013). Good pain management is therefore an essential part of after care for these patients, and may lead to improvements in QoL and physical functioning.

4.5.4 Quality of life

In terms of QoL, Nagarajan et al (Nagarajan *et al.*, 2004a) reported mean QoL-CS scores of 6.8 (SD 1.3), compared with 5.1 (SD 1.8) in our study. The mean QoL-CS psychological and social subscales were also lower in our study (6.4, SD 1.6 *vs* 4.75, SD 2.14: 7.3, SD 1.9 *vs* 4.98, SD 2.25). Although we have only looked at outcomes following AMP, there may be no difference in QoL between these patients and those who have LSS, although limb sparing procedures are associated with better daily competence and less use of walking aids. Regardless of local treatment, body image and daily competence are associated with a better QoL (Eiser *et al.*, 2001).

4.5.5 Comparison to published studies

Comparison of our results with published series is difficult in this heterogeneous population. However, our results appear to indicate poorer outcomes than international comparators in TESS and QoL-CS measures. In the series from the Scandinavian Sarcoma Group, Aksnes et al (Aksnes *et al.*, 2008) reported a median TESS of 88 (minimum to maximum 43 to 100) after lower extremity AMP, compared with a median of 55.8 (minimum to maximum 8 to 100) in our series. These differences are seen at every level; hip disarticulation, transfemoral and transtibial. In a matched series of Canadian patients treated with limb sparing or AMP, mean TESS after AMP (mean age 34.4 years, SD 11.6) was 74.5 (SD 19.7) (Davis *et al.*, 1999a), and in Nagarajan et al's (Nagarajan *et al.*, 2004a) series of childhood bone and soft-tissue cancer survivors, mean TESS was 83.8 (SD 13.1) for patients with a mean age at diagnosis of 13.5 years (1 to 20) and 34.8 (SD 19.5) at questionnaire completion. The older age of our population (mean 56.6 years, 19 to 91) may explain some of the difference as TESS declines with increasing age, but this difference merits further investigation.

4.5.6 Strengths

This collaborative study may better represent the experience of patients across the NHS in England, rather than a single centre series. The co-operation in this project strengthens the foundation for further collaborative research in this and allied areas. Another strength of this

study, is the use of evidence based tools to assess outcomes.

4.5.7 Limitations

Despite sending a reminder, the response rate for this survey was not as high as we would have wished, and there may therefore be a response bias. Completion and return of the survey tool was dependent on input from local centres, with the co-ordinating centre unable to identify and/or contact individual patients. Despite enthusiasm, centres differed in their recruitment and we did not have data about non-respondents. However, the distribution of patient demographics, diagnoses and AMP level appears reasonable for this population. Although we accept the TESS measure was developed for patients who have LSS (Davis *et al.*, 1996), it has been used widely in assessing disability after AMP (Davis *et al.*, 1999a; Aksnes *et al.*, 2008; Barrera *et al.*, 2012).

4.5.8 Recommendations for future work

The measures used in this study are subjective and patient reported, therefore face limitations of recall bias. Objective tools can overcome these inherent limitations and give an accurate indication of physical function. Future studies could involve the use of these objective tools in the clinic to identify underlying mechanisms for poor function. Whereas, remote monitoring of physical function using objective tools could reflect the true picture of activity limitations.

4.6 Conclusion

In conclusion, this national survey confirms that after AMP for bone or soft-tissue tumours patients report a wide range of functional disabilities and participation restrictions. Importantly this study shows the outcomes that can be anticipated after AMP when advising patients about treatment for a musculoskeletal tumour. Patients with more proximal AMP have poorer levels of physical function, use their prosthetic limb less and are more reliant on walking aids, but have similar QoL and pain scores. Pain is a major feature of the survivorship experience in this population and has a negative impact on physical function and QoL scores. The outcomes we have identified appear worse than in published series (Davis *et al.*, 1999a; Nagarajan *et al.*, 2004a; Aksnes *et al.*, 2008), and need investigation for underlying mechanisms, which has been described in subsequent chapters. Specialised rehabilitation, pain management and psychological support services are needed if these patients are to achieve the best outcomes

Chapter 5: Objective clinical measurement of physical functioning after treatment for lower extremity sarcoma – A systematic review.

This work has been published in the European Journal of Surgical Oncology (reference below).
Furtado, S., et al., Objective clinical measurement of physical functioning after treatment for lower extremity sarcoma; A systematic review. European Journal of Surgical Oncology, 2016. 43(6): p. 968-993.

5.1 Introduction

Although traditional measures of physical functioning in sarcoma survivors, the TESS (Davis *et al.*, 1996), and the MSTS (Enneking *et al.*, 1993) measure disability and impairments like joint range of movement, muscle strength, joint stability, pain, deformity, functional activity and emotional acceptance, they do not capture objective information about balance, gait and PA. Moreover, TESS relies on subjective recall and does not relate to objective data about gait and PA (Rosenbaum *et al.*, 2008b), making it difficult to understand underlying interactions. Although an advance in the use of laboratory systems has been seen to assess balance and gait impairments for decades (Hillmann *et al.*, 2000; Donati *et al.*, 2012), they do not seem to easily translate into the clinical setting. Common challenges encountered could be the lack of simple, cost-effective and accurate devices, and the lack of training support to staff to use these systems.

Cost-effective clinically useful accurate, valid and reliable outcome measures are urgently needed to support effective clinical management. (MacDermid *et al.*, 2009). Useful measures would accurately detect differences between distinct treatment groups (LSS vs AMP), shed light on interactions with important clinical factors (for example: joint range, muscle strength), measure the impact of treatments (chemotherapy, surgery, rehabilitation strategies) over time and show reliability in repeat measurements (Schuck and Zwingmann, 2003; Roach, 2006). Therefore, the aim of this study was to systematically review the literature to identify studies quantifying balance, gait and PA in patients treated for lower extremity sarcoma, using methods which are likely to be easily translated into routine clinical practice.

5.2 Specific objectives

1. To identify methods used to quantify balance, gait or PA in patients after treatment for sarcoma, with the potential for translation into busy clinic settings.
2. To investigate whether these measures have been tested for validity, reliability and sensitivity to change.

5.3 Methods

5.3.1 Search strategy

We identified relevant studies by searching four electronic databases, Medline, Embase, Scopus, and Web of Science up to February 2016. An initial search combined four main search terms using the Boolean "AND" operator: 1) Bone neoplasms OR Soft tissue neoplasms 2) Physical functioning 3) Extremities 4) Measurement (Appendix 6.0: Search Strategy A). After reviewing eligible articles, additional search terms covering the three physical functioning domains of balance, gait and PA were identified, and a second (updated) search implementing these terms was undertaken to ensure no relevant articles were missed. (Appendix 6.0: Search Strategy B).

5.3.2 Selection of studies

Search results from each database were imported into EndNote bibliographic management software (Thomson Reuters, Endnote version X7). The titles and abstracts of these references were screened by two independent reviewers (SF and CG) and appropriate articles selected. Differences in opinion were resolved by consensus. Additional hand searching of reference lists of included articles and excluded reviews identified further studies for inclusion (Figure 5-1).

Studies were selected using the eligibility criteria outlined.

Inclusion Criteria:

1. Primary research investigating objective measures of postural balance, gait and PA in patients treated for lower extremity bone or soft tissue tumours.
2. Devices which have the potential to be used in routine busy clinical settings (advantages such as rapid to measure, portable depending on outcome measured)

Exclusion Criteria:

1. Conference proceedings or non-journal articles such as commentaries whose methodology is not clear.
2. Non-English articles
3. Including purely upper extremity tumours.
4. Case report/case reports
5. Full text not available.
6. Cumbersome laboratory systems such as a Gait laboratory, EMG systems etc.
7. Review articles (secondary research)

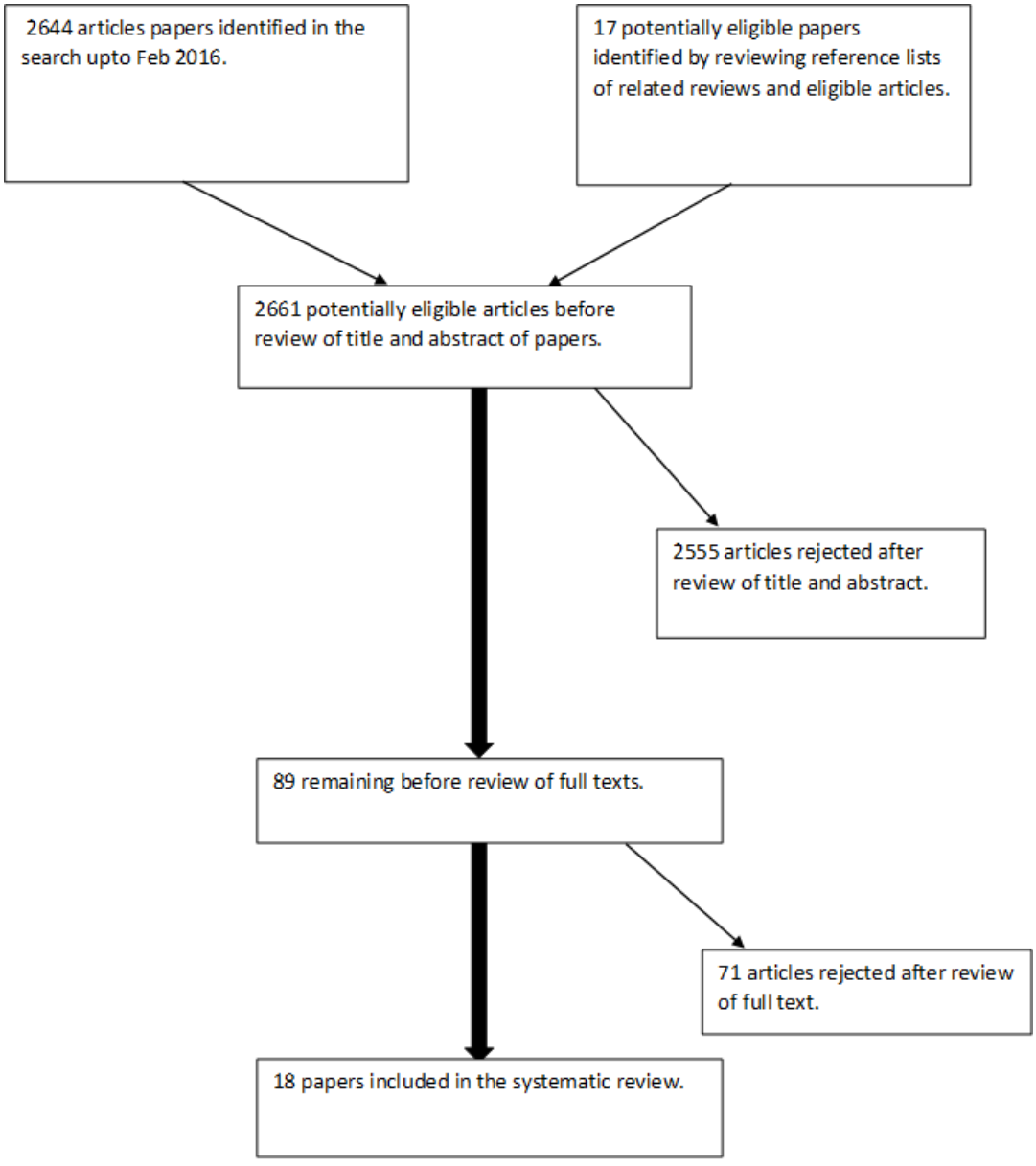


Figure 5-1: Selection of Papers for this review

5.3.3 Data extraction

The data extraction tool was prepared by the 2 independent reviewers, based on clinical information, and the psychometric properties of outcome measures in the study. The tool consisted of 2 tables. The first table comprised the patient population, demographics, treatments, instruments used to capture outcomes, objective measures used and main results/conclusions of the study. The second table comprised psychometric properties, including validity, reliability and sensitivity of change of balance, gait and PA measures in these studies. Data were extracted by the first independent reviewer (SF) using the tool and were reviewed, by a second independent reviewer (CG), to ensure accuracy and rigour.

5.3.4 Quality assessment tool

As no standardised quality assessment tool is available for this topic (Sanderson *et al.*, 2007), a checklist (Table 5-1) was developed, including both methodological and patient criteria. This comprised a comprehensive list of criteria from the Critical Appraisals Skills Programme (CASP) (CASP, 2014) and Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) (Elm *et al.*, 2007) for methodological issues; criteria related to patient specific issues were selected from a checklist developed in a previous study (Kwong *et al.*, 2014) [which was adapted from (Borghouts *et al.*, 1998; Kuijpers *et al.*, 2004; Mols *et al.*, 2005)]. The rater scored yes /no (+/-) for each criterion of the checklist (Table 5-1). The maximum score was calculated by adding the number of 'yes (+)' scores and a final percentage of this was worked out. A higher percentage indicated a higher quality of the study. The maximum score achievable was 18 (100%): studies achieving a score of greater than 70% were defined as "high quality", 50-70% were "moderate quality" and less than 50% were "low quality" (Den Oudsten *et al.*, 2007). A quality assessment of selected papers was conducted but was not used as a selection criterion. The development of the quality assessment checklist and assessment of studies against the checklist was performed by SF to ascertain quality of the studies.

Table 5-1: Quality assessment of articles: Criteria for assessing the quality of studies.

A.	The study mentions a clear scientific background and rationale for conducting the investigation.
B.	The study mentions clear aim/objectives and/or including hypothesis.
C.	Use of an appropriate study design to address the aim/objectives - Prospective study design (also positive in studies where previously unknown outcomes are measured in a historical cohort, case series or cross-sectional patient group)
D.	The study size calculation is explained – to ensure appropriately powered.
E.	Study population was well defined and types of sarcoma described.
F.	Socio-demographic data mentioned.
G.	Time since diagnosis reported.
H.	Participant eligibility criteria outlined and the methods and sources of selection/recruitment.
I.	Data collection process has been described.
J.	Type of sarcoma interventions has been reported.
K.	Presence of a control group for relevant studies (no score if study data was compared to literature)
L.	Participation rate (score given if rate of participation > 75%).
M.	Use of a standardised and valid assessment tool (internal validity)
N.	Precision of result reported.
O.	Mention of efforts to reduce any potential sources of bias (example: selection bias, performance bias).
P.	The impact of confounding factors on outcome was clearly mentioned (example: age, time since surgery, level of surgery, rehabilitation interventions etc).
Q.	Use of an appropriate statistical analysis tests to answer meet the aim/objectives.
R.	Generalisability (external validity) of the results to a local population (for example: results when patients are receiving treatments in hospitals or outpatient departments).

Adapted from following sources: (Kwong *et al.*, 2014), CASP [Critical Appraisal Skills Programme (CASP) 2014], STROBE (Elm *et al.*, 2007). CASP [Critical Appraisal Skills Programme (CASP) 2014], CASP Checklists, Oxford. CASP

5.4 Results

A total of 2661 papers were identified, of which 18 were included (Figure 5-1, Table 5-2) published between 1998 and 2013. Of the 18 studies, 5 were case series (De Visser *et al.*, 1998; De Visser *et al.*, 2000; de Visser *et al.*, 2001; de Visser *et al.*, 2003; Beebe *et al.*, 2009), 7 cross-sectional studies (Zohman *et al.*, 1997; Kawai *et al.*, 2000; Sugiura *et al.*, 2001; Tsauo *et al.*, 2006; Rosenbaum *et al.*, 2008b; Bekkering *et al.*, 2011; Sheiko *et al.*, 2012), 2 prospective longitudinal studies (assessment at multiple time points) (Bekkering *et al.*, 2012a; Winter *et al.*, 2012), 1 retrospective cohort study (Hopyan *et al.*, 2006) and 1 validity and reliability (van Dam *et al.*, 2001). 11 were high quality studies (>70% rating) and 7 moderate quality (50-70% rating) (Table 5-3). Of these 18 studies, 1 was about balance (de Visser *et al.*, 2001), 7 gait (Zohman *et al.*, 1997; De Visser *et al.*, 1998; De Visser *et al.*, 2000; Kawai *et al.*, 2000; de Visser *et al.*, 2003; Tsauo *et al.*, 2006; Beebe *et al.*, 2009) and 10 PA (Sugiura *et al.*, 2001; van Dam *et al.*, 2001; Hopyan *et al.*, 2006; Rosenbaum *et al.*, 2008b; Winter *et al.*, 2009; Bekkering *et al.*, 2011; Bekkering *et al.*, 2012a; Sheiko *et al.*, 2012; Winter *et al.*, 2012; van der Geest *et al.*, 2013). The sample size in the studies ranged from 4 to 82.

Table 5-2: Numbers of articles identified by database

Database	References found following automated de-duplication to April 2014	References found following automated de-duplication May 2014-Dec 2015	Updated terms added Feb 2016 (articles found by previous searches have been removed)
Medline (Ovid)	132	17	29
Embase (Ovid)	285	63	117
Scopus	1412	293	43
Web of Science	154	33	66
TOTAL	1983	406	255
GRAND TOTAL			2644

15 were conducted in patients with BT only and 3 in a mixed group of BT and STS. In 12 studies, patients had LSS and in 6 LSS+AMP. The age of patients ranged from 9 to 85 years and time since surgery from 6 weeks to 39 years. In longitudinal cohorts, patients were assessed pre-operatively and at several time points up to a maximum of 24 months. 7 were childhood cancer survivors (CS), 5 adult cancer survivors (AS), 4 CS+AS and 2 not specified.

Table 5-3: Quality scoring of articles.

S.No	Article	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	Score (%)	Quality Rating
1.	De Visser et al, 2001	+	+	+	-	+	+	-	-	+	+	+	-	+	+	-	-	+	-	11(61)	Moderate
2.	De Visser et al, 1998	+	+	+	-	+	+	+	-	+	+	+	-	+	+	-	-	+	-	12(67)	Moderate
3.	De Visser et al, 2000	+	+	+	-	+	+	+	-	+	+	+	-	+	+	-	-	+	-	12(67)	Moderate
4.	Kawai et al, 2000	-	+	-	-	+	+	+	-	+	+	+	-	+	+	-	-	+	-	10(56)	Moderate
5.	De Visser et al, 2003	+	+	+	-	+	+	+	-	+	+	-	-	+	+	-	-	+	-	11(61)	Moderate
6.	Tsauo et al, 2006	+	+	+	-	+	+	+	+	+	+	+	+ (80% participation rate as 20 out of 25 participated)	+	+	-	-	+	+	15(83)	High
7.	Beebe et al, 2009	+	+	-	-	+	+	+	+	+	+	n/a	-	+	+	-	-	+	-	11(65)	Moderate
8.	Zohman et al, 1997	+	+	+	-	+	+	+	-	+	+	+	- (34% as 10 out of 29 patients participated)	+	+	-	-	+	-	12(67)	Moderate
9.	Rosenbaum et al, 2008	+	+	+	-	+	+	+	+	+	+	+	-	+	+	-	-	+	+	14(78)	High
10.	Sheiko et al, 2012	+	+	+	-	+	+	+	+	+	+	+	-	+	+	-	-	+	+	14(78)	High
11.	Van deer Geest et al, 2012	+	+	+	-	+	+	+	+	+	+	+	-	+	+	-	-	+	+	14(78)	High
12.	Winter et al, 2012	+	+	+	-	+	+	+	+	+	+	+	+ (80% participation rate as 20 out of 25 participated)	+	+	-	-	+	+	15(83)	High
13.	Sugiura et al, 2001	+	+	+	-	+	+	+	-	+	+	+	-	+	+	-	-	+	+	13(72)	High
14.	Van Dam et al, 2001	+	+	+	-	+	+	+	+	+	+	-	-	+	+	-	-	+	+	13(72)	High
15.	Hopyan et al, 2006	+	+	+	-	+	+	+	+	+	+	-	- (37% as 45 out of 123 patients participated)	+	+	-	-	+	+	13(72)	High
16.	Winter et al, 2009	+	+	+	-	+	+	+	+	+	+	+	- (65% as 80 out of 123 patients participated)	+	+	-	-	+	+	14(78)	High
17.	Bekkering et al, 2011	+	+	+	-	+	+	+	+	+	+	-	+ (75% as 82 out of 110 participated)	+	+	-	+	+	+	15(83)	High
18.	Bekkering et al, 2012	+	+	+	-	+	+	+	+	+	+	-	- (90% 44 out of 49 recruited, participated in initial assessment) and 49% , 24 out of 49 completed the study at 2 years)	+	+	-	+	+	+	14(78)	High

5.4.1 Methods used to quantify balance, gait and PA outcomes

A wide range of outcome measures were used to quantify balance, gait and PA. These included amplitude of the center of pressure (ACP), velocity of the center of pressure (VCP), step velocity, walking speed, stride length, step cycle duration, gait symmetry, double support time, swing time, stride time, steps/day, time spent walking, gait cycles (gcs)/day, strides/day, and movement intensity. 10 instruments were used to capture outcomes included force platforms, foot switches such as VA Rancho - Footswitch Stride Analyser ®, gaitmats such as GaitMatTMII and GaitRite ®, pedometer and activity monitors such as Dynaport ® ADL, StepWatch™ Activity Monitor, Step Activity Monitor ® (SAM), Uptimer device ® and Actilog ® V3.0 (Table 5-4). In most studies assessing PA in this cancer group, activity monitors were attached to the ankle (Winter *et al.*, 2009; Bekkering *et al.*, 2011; Bekkering *et al.*, 2012b; Winter *et al.*, 2012; van der Geest *et al.*, 2013), in two studies to both the waist and thigh (van Dam *et al.*, 2001; Rosenbaum *et al.*, 2008a; Lewis *et al.*, 2009) and in one study to the thigh (Hopyan *et al.*, 2006). In two other studies, the location of attachment of the monitors were not mentioned (Sugiura *et al.*, 2001; Sheiko *et al.*, 2012).

Table 5-4: Objective measures of balance, gait and PA.

No	Author, Year and Type of study	No of patients	Age (in years)	CS/AS	Type of tumour	Procedure [Limb Sparing Surgery (LSS)/ Amputation/ (AMP)]	Follow Up	Control group	Device/Instrument used	Parameters measured	Main Results/Conclusion
Impairment – Balance *Patient group - LSS*											
1.	De Visser et al, 2001 – A case series.	N= 11	Mean age (±SD) 41.45 ±17.42 years.	CS+AS	10 patients with a PMBT in the lower extremity (ilium, proximal and distal femur) and one with a STS in the gluteal region.	LSS (Resection with or without reconstruction)	N/A	10 healthy controls.	Force Platform: wooden plate on four force transducers and recorded vertical ground reaction forces.	Balance measures: Measure of ACP (in millimetre (mm)) and the VCP (millimetre/second (mm/sec) in normal standing and standing on balance board, with eyes open, eyes closed and a task demanding attention.	After LSS for lower extremity sarcoma, patients demonstrated no significant differences in balance (ACP and VCP) compared to healthy controls, in upright standing. However, upright standing in more challenging conditions such as visual and cognitive loads is associated with significantly higher ACP and VCP compared to normal standing. This suggests that postural automatism is affected in patients treated for lower extremity sarcoma.
Impairment – Balance *Patient group – LSS+AMP or AMP – No articles*											
Impairment – Gait *Patient group: LSS*											
2.	De Visser et al, 1998 – A case series	N =12	Mean age 38 years	AS	PMBT or locally aggressive primary BT of lower extremity (osteosarcoma (n=3), chondrosarcoma (n=6), ewing's	LSS (Excision+ reconstruction or arthrodesis)	Mean time since surgery (±SD) 34±21.63 (range, 13 to 59) months.	10 age-matched healthy controls, mean age 37.5 years	Foot switches: Treadmill walking - At patient preferred speed. Footswitches in shoe insoles to record heel strike and heel off.	Gait measures: Spatio-temporal parameters of gait including walking speed, stride time and co-efficient of variation.	Restoration of walking after LSS is good in normal walking conditions, but patients exhibit lower preferred walking speed and higher coefficient of variation during normal walking. Complex walking with visual and cognitive load demonstrated a significant decrease in stride time in

					sarcoma (n=2) and aggressive osteoblastoma (n=1))						patients, but not in controls. Therefore, suggesting gait reautomatisation is not complete 2 to 5 years post-surgery.
3.	De Visser et al, 2000 – A case series.	N=19	Mean age 45 (range 21 to 80) years	AS	Malignant BT of the lower extremity.	LSS Group 1: Knee surgery: (n=9). Group 2: Hip surgery. (n=10)	12 to 24 months post surgery.	10 healthy controls, mean age 37 (range, 22 to 61) years.	Foot switches: Treadmill walking, with footswitches in insole of shoes. Electro goniometers to measure knee flexion angles.	Gait measures: Spatio-temporal parameters of gait including preferred walking speed, stride time, stance time, swing time, double-limb support time, and joint angles.	Mean preferred walking speed lower in patients compared to controls (0.7 m/s vs 1.1m/s). Mean stride duration longer in patients compared to controls (1.5 seconds (s) vs 1.1 seconds (s)). Stance phase shorter in the affected leg (57% of cycle compared to 62%). No difference between hip and knee groups in these parameters. Range of motion is lower in the knee in patients compared with controls in the stance phase. Therefore, patient's gait is significantly affected compared to healthy control demonstrating an incomplete re-organisation of gait.
4.	Kawai et al, 2000 – A cross-sectional study.	N=15	Median age 24 (range 16 to 47) years.	AS	PMBT of the proximal femur. Tumours included osteosarcoma (n=6), ewing's sarcoma, (n=4), chondrosarcoma (n=4) and malignant fibrous histiocytoma (n=1).	LSS - Patients underwent an intra-articular resection of the hip. The median length of femoral resection was 21 (8-28) centimetres (cms). Reconstruction consisted of 1 THR and 14 Bipolar implants.	Median time since surgery was 27 (range, 12 to 76) months.	20 healthy controls (n=20) and 6 patients after hip disarticulation (n=6)	Foot switches: VA Rancho - Footswitch Stride Analyser ® (Rancho Los Amigos Medical Centre , California)	Gait measures: Gait stride characteristics including Free-walking velocity, stride length, cadence, gait cycle time, double-limb support time, and single-limb support time.	Patients had significantly lower free walking velocity and cadence than controls, but higher than after hip disarticulation (walking velocity 63.9 m/min vs 80.6 and 50.6 respectively; cadence 101 steps/min vs 111 and 81.6 respectively). Asymmetry of single-limb support time significantly correlated negatively with gait velocity and positively with net energy cost. Use of a walking aid led to less asymmetry but did not change velocity because cadence was reduced and stride length increased.

											Asymmetry of single-limb support time negatively correlated with the strength of hip abductors. Walking performance of LSS patients was better than those who had hip disarticulation.
5.	De Visser et al, 2003 –A case series.	N= 11	Mean age at time of surgery 43 (range 19 to 66) years.	AS	PMBT of the lower extremity. Tumours included osteosarcoma, ewing's sarcoma, or chondrosarcoma.	LSS (Distal femoral knee prosthesis (n=4), proximal femoral hip prosthesis (n=4), and a saddle prosthesis) (n=3)	Gait analysis at 5 months postoperatively, repeated at 7, 9, 12, and 15 months	No control group. Affected and unaffected sides compared	Foot switches: Treadmill walking - at patient preferred speed. Footswitches in the insoles of the shoes were used to record heel strike and heel off.	Gait measures: Preferred walking velocity, stance duration, swing duration, step-cycle duration, stride time.	Improvement in walking speed and asymmetry is seen during recovery up to 15 months post operatively. However even after the recovery period gait control is not optimal, which could be attributed to the sensory motor losses as a result of treatment of the cancer. Patients with knee prosthesis had a preferred walking speed of 3.9 km/hr and a stride time of 1.15 s, those with a hip prosthesis with 3.4 km/hr and 1.21 s and those with a saddle prosthesis 2.2 km/hr and 1.50 s respectively.
6.	Tsauo et al, 2006 - A cross-sectional survey	N = 20	Mean age (±SD) 21.7±7.3 (range 13 to 40) years	CS+ AS	PMBT (Osteosarcoma) around knee, located in the distal femur (n=13) and proximal tibia (n=7).	LSS – Wide resection and endoprosthetic knee reconstruction (TKR)	Mean±SD of follow-up was 3.0±1.6 (range, 1 – 5) years post-operatively.	20 age sex-matched healthy control, mean age 21.8±7.3 years.	Gaitmat: GaitMatTMII; (Gait MatII E.Q. Inc., Philadelphia, USA), 3.6m in length.	Gait measures: Step velocity, step length, duration of stance phase and swing phase.	Walking velocity of patients was significantly lower than controls' (54 ± 12m/min vs 72 ± 6m/min, $p<0.05$). The step length of the unaffected side was significantly shorter than that of controls and the affected side ($p<0.05$). The stance phase of the affected leg was significantly shorter than that of controls and the unaffected side ($p<0.05$). Conversely, swing phase of the affected leg, was significantly longer than that of the unaffected sides. Patients have

											achieved an acceptable recovery in gait outcomes, with some functional limitations.
7.	Beebe et al, 2009 – A report of 4 cases.	N=4	Skeletally immature patients. At time of surgery – 9 , 9, 10, 11 years.	CS	PMBT in the distal femur and proximal tibia. Tumours included osteosarcoma (n=3) and ewing's sarcoma (n=1).	4 LSS - Wide resection of bone sarcoma and Repiphysisexpandable endoprosthesis.	Mean time since surgery 31.5 months.	No control group.	Gaitmat: GaitRite ®; CIR Systems Inc, 60 Garlor Dr, Havertown, PA, 19083	Gait measures: Gait velocity, stride time, cadence, double limb support, stance phase, swing phase, step time, step length.	Surgery with a non-invasive expandable endoprosthesis produces acceptable functional outcomes in children with PMBT. Patients had certain functional limitations including reduced ROM and muscle strength. Patients also demonstrated altered walking and sit-to-stand patterns, yet demonstrating a good level of coping and emotional acceptance after treatments for sarcoma.
8.	Zohman et al, 1997 – A cross-sectional study.	N = 10	Mean age 23.8 (range, 18 to 41) years	N/A	PMBT (Osteosarcoma) of the proximal tibia.	LSS - Intra-articular proximal tibial replacement.	Mean time since surgery 6.5 years.	A control group (n=5) of above knee amputees including trauma (n=4) and musculoskeletal cancer (n=1). Mean age of controls was 43.6 years and time since surgery 24.1 years	Foot switches: Stride Analyser ®; (B&L Engineering, Santa Fe Springs, CA) has foot pads worn inside shoes, containing foot switches.	Gait measures: Gait velocity, stride length, cadence, and stance time symmetry	Significant difference was only seen between cadence after intraarticular proximal tibial replacement (112.4 ± 10.6 steps/minute) vs control group of AMP (110.1 ± 2.4 steps/ minute) (p=0.03). No statistical significance was seen between mean step velocity after intraarticular proximal tibial replacement (79.2 ± 7.6 m/minute) and control group of AMP (71.4 ± 5.4 m/minute) (p=0.06). No significant differences were seen between length of stride (1.41 ± 0.13 m vs 1.43 ± 0.12 m) and the symmetry of stance time (0.90 ± 0.07 vs 0.87 ± 0.11) for proximal tibial replacement vs control group of AMP. The results suggest that LSS for proximal tibia leads to a

											gait comparable with that after above knee AMP with a prosthesis.
Impairment – Gait *Patient group – LSS+AMP or AMP – No articles*											
Participation Restrictions – Physical Activity (PA) *Patient group – LSS*											
9.	Rosenbaum et al, 2008 – A cross-sectional study.	N=22	Mean age (±SD) at diagnosis 26.2±18.4 (range,10 to 73) years. Mean age (±SD) at assessment 34.5±18.4 (range, 16 to 76) years.	CS+AS	PMBT in distal femur (n=18) and proximal tibia (n=4). Tumours included osteosarcoma(n=14) chondrosarcoma (n=4), ewing's sarcoma (n=3), and malignant fibrous histiocytoma (n=1).	LSS - Intraarticular resection of tumour + reconstruction including knee replacement (rotating hinge (mutars), n=20; or fixed hinge (Kotz), n=2).	Mean (±SD) of follow-up 7.8±7.9 (range, 2 to 39) years	No control data for dynaport. 26 age matched healthy control from which SAM data was collected.	Activity monitors: The DynaPort ® ADL monitor;(McRoberts, Den Haag, The Netherlands) worn for 24 hours SAM ® Step Activity Monitor; (Cyma Inc., Seattle, OR): SAM was worn for a week in community.	Ambulatory (walking) and sedentary PA in 24 hours Time spent in different activities Movement intensity. Ambulatory PA *Volume:* Daily number of gcs. *Intensity* as step cycles/minute.	The highest percentage of PA was sitting (54 ±18%) of the total time recorded, followed by standing as second highest (27±16%), walking (10±6%), and lying position (8±6%). During walking, the average ambulatory daily PA accumulated to 4,786±1,770 (range 2,045–8,135) step cycles, which corresponds to a yearly 1.75 million steps. No significant correlation was seen in between clinical scores and ambulatory PA measures. The ambulatory PA in patients was lower than normal healthy adults, however it was comparable to the level of activity for other patients, for example, after hip arthroplasty reported in previous research.
10.	Sheiko et al, 2012 – A cross sectional study	N=20	Mean age 15.8 (range, 11.7 to 20.8) years	CS	PMBT in distal tibia (n=1), proximal tibia(n=8), distal femur (n=9) and proximal femur (n=2). Tumours	LSS – Implants (n=12) and Allografts (n=8)	Mean time since surgery 1.79 (range, 0.39 to 3.82) years.	20 age- and sex-matched healthy controls	Activity monitor: StepWatch ™ activity monitor (2-dimensional accelerometer	Ambulatory PA: *Volume:* Total stride/day, average walking minutes/ day *Intensity:* Time spent/day at high activity levels *Others:* endurance,	Patients who had undergone LSS had significantly poorer PA sub-scores compared to controls. Significant differences were seen between LSS patients and healthy controls in total PA/day (43% vs 48% of total time active; P = 0.03), median number of

					included osteosarcoma (n=13), ewing's (n=5), and other malignancy not specified (n=2).				r). Monitored for 7 consecutive days.	accumulated peak effort, cardio-vascular score, burst score, and peak score.	total strides/day (4487 vs 7671 strides; p = 0.001), and time spent/day at high activity levels (20 minutes vs 47 minutes; p = 0.001). This demonstrates patients undergoing LSS for a PMBT exhibit decreased PA compared to healthy age-matched controls. Self reported PA questionnaire Activity Scale for Kids, Activity scale for kids (ASKp-38) summary score significantly correlated with ambulatory PA recorded by the SAM.
11.	Van deer Geest et al, 2013 – A prospective study	Tumour (N= 43),	Mean age 41.5 (range, 19 to 67) years.	AS	Benign or lowgrade- malign ant bone and soft tissue tumours.	LSS - Local excision or curettage and cryosurgery.	Patients were assessed before surgery and at 6 months after surgery.	Controls were Knee arthroscopy patients (n=24) Mean age of control group was 43.1 (range, 23‑68) years.	Activity Monitor: An actometer (Actilog V3.0 ®); a device which senses motion and attached at the ankle for 12 consectutive days	PA: GPA score defined as the average number of accelerations in a 5 minute duration through the day. Higher GPA scores mean a high PA.	In tumour patients, 35% of patients were severely fatigued before their surgery and 33% post-surgery. Significantly higher levels of anxiety were reported by tumour patients. No significant differences between tumour patients and controls were seen in pain, physical limitations, self-efficacy or PA scored captured by actometer. Higher pain scores, higher anxiety and lower self-efficacy were significantly associated with fatigue severity. In controls the percentage of severely fatigued patients decreased from 38% before surgery to 29% 6 months post-surgery. A high number of patients were severely fatigued in both the tumour and the knee arthroscopy groups. Pain, anxiety and self-efficacy were seen to be the most important factors linked to fatigue

											severity in tumour patients prior to surgery.
12.	Winter et al, 2012 – A longitudinal study	N=20	Mean age (± SD) 14.4±2.6 years	CS	PMBT in the lower extremity. Tumours included osteosarcoma (n=15) and ewing's sarcoma (n=5).	LSS - Endoprosthetic replacement of the affected bone (proximal femur 3, distal femur 12, proximal tibia 5)	6 weeks, 3 months, 6 months, 12 months, and 18 months after surgery.	20 healthy age- and gender-matched controls.	Activity monitor: StepWatch ™ Activity Monitor SAM ; (Ortho-Care Innovations) attached to ankle and worn for seven days.	Ambulatory PA: a. *Volume* in the form of the number of gcs (one gait cycle is two steps) b. *Intensity* measured as gcs/minute.	Patients with a PMBT in the lower limb demonstrated significantly lower ambulatory PA during the course of active treatments. However these patients recover markedly after cessation of treatments; reaching 71.9% of control group volume of gcs at 18 months. Patients with complications were slower to recover with some limitations seeming to persist at 18 months post operatively.
Participation Restrictions - Physical activity (PA) *Patient group – LSS+AMP*											
13.	Sugiura et al, 2001 – A cross-sectional study	N=56 Tumours included PMBT (n=20) and malignant soft-tissue tumours (n=36).	Mean age 45.3 (range, 14 to 85) years.	CS+AS	Primary musculoskeletal tumours (n=56), PMBT in the distal femur (n=9), proximal tibia (n=5), proximal femur (n=3), proximal fibula (n=2), femoral shaft (n=1) and STS were located in thigh (n=16), hip (n=8), knee (n=5), calf (n=5),	All cases of BS were widely resected (n=20) and cases of STS were either widely resected (n=34) or marginally resected (n=2).	Mean period of follow-up was 4.3 ± 2.1 years,	20 healthy controls of mean age 30.4 years.	Pedometer: Omron Health Counter HJ-5 pedometer®; (Accuracy was 95%): Pedometer worn for 2 weeks	Ambulatory PA: *Volume* in the form of number of steps/day.	Patients achieved an average daily count of 7119 ± 3563 steps (69.8% of controls 10,206 ± 1388). BT group achieved smaller number of steps/day than soft-tissue tumours. Average daily step count scores were not correlated with ROM. However they were correlated with MSTS scores (coefficient 0.52). Kotz TKR and semiconstrained THR groups had lower numbers of steps than other groups. Proximal BT nearer to the trunk tended to be lower than those with tumours in other locations. The daily number of steps obtained by a pedometer and ADL score appear to

					pelvis (n=1), foot (n=1).						be clinically as useful as the MSTS outcome measure. Thus the pedometer is a cost-effective and useful objective assessment tool for measuring walking ability in sarcoma.
14.	Van Dam et al, 2001 – A reliability and validity study.	N=20	Median age 49 (range, 18 to 69) years.	N/A	Malignant BT in the leg, including tumours located in femur (n=12) and tibia (n=8).	LSS (n=12) included allograft (n=1), allograft+ endoprosthesis (knee) (n=5), Kotz prosthesis (n=5) and mutars prosthesis (n=1) or AMP (n=8) which included Above knee AMP (n=3), Knee disarticulation(n=3) and Van Nes rotationplasty (n=2).	Median time since surgery 2 (range, 1 to 13) years.	No control group.	Activity monitor: Dynaport monitor ®; (McRoberts BV, The Hague, The Netherlands) – Uniaxial accelerometer.	PA: Seven aspects were measured over a period of 24 hours which were time spent walking, standing and sitting (as a percentage of 24 hours), the movement intensity, and also sum of the movement Intensities.	The reliability of the monitor was satisfactory, with an Intraclass correlation coefficient (ICC) from 0.65 to 0.91 over the function measured. There was a significant correlation seen between 'time spent walking' and the MSTS scores and also the Rand-36 scores. A significant association was also seen between 'movement intensity during walking' and MSTS. Results demonstrate promising reliability and validity of the monitor to clinically measure PA objectively in patients treated for a lower extremity malignant BT.
15.	Hopyan et al, 2006 – A retrospective cohort study	N = 54 (45 completed study and 9 lost to follow-up)	Mean age of patients who completed the study (n=45) 26±7 (range, 10 to 39) years.	CS - Mean age of these patients at diagnosis 11.9 ±4.2 (range, 1-19)	PMBT of the lower extremity.	LSS (n=20) and Above knee AMP (n=19), Rotationplasty (n=5) and below knee AMP (n=1).	Mean follow-up time of study patients (n =45) was 13.9±5.7 (5-26) years	No control group.	Activity monitor: Uptimer device ®; (National Aging Research Unit, Victoria, Australia), an activity monitor.	PA: PA was measured using the uptime device "amount/percentage of time an individual spends in the upright position (standing or walking)" also termed as "uptime	SF-36 (36-Item Short Form Survey) and uptime measured by the activity monitor, were similar between groups. Uptime had higher values in patients with rotationplasty, although statistical comparisons were not feasible.

				years							
16.	Winter et al, 2009 – A prospective study.	N= 23 lower extremity BT (Total 29 patients with BT in upper extremity (n=6) and lower extremity (n=23)	Median age (± SD) of all BT patient (n=29) 15.1±3.2 years.	CS	80 patients including BT (n=29), leukaemia (n=20), lymphoma (n=15), brain tumours (n=12), germ cell tumours (n=3), and neuroblastoma (n=1).	LSS+AMP 13 out of 23 lower extremity BT patients were operated as follows: Prosthetic limb replacement (n=7), AMP (n=3), and excision (n=3)	2 groups of BT patients: 16 patients were measured pre-operatively 13 patients on an average of 12 weeks post-operatively.	45 healthy controls who were age and gender matched to patients for distribution and body mass index (BMI), height and weight comparable to patients.	Activity monitor: StepWatch ™ Activity Monitor SAM; (OrthoCare Innovations, Seattle, WA) - A uniaxial accelerometer. worn on ankle	Ambulatory PA: *Volume* measured as gcs/ day. *Intensity* measured as gcs/ minute.	Pediatric cancer patients (2,787 gcs/day) scored significantly lower than healthy controls (8,096 gcs). Patients were more physically activity at home (3,185 gcs, 40% of controls) rather than inpatient stays (1,830 gcs, 23% of controls). Patients with BT exhibited lower PA scores than those with leukemia with respect to the volume (1,849 gcs vs. 2,992 gcs) and also the intensity of PA. Patients with BT exhibited 16% of the PA when compared to controls during inpatient stay and 27% of the PA compared to controls during their home stay. Patients with leukaemia achieved higher percentage of PA in both inpatients and home when compared to BT, however this difference was not significant. Patients with BT seem to be at a substantially high risk of reduced PA. This indicates individualised rehabilitation interventions need to be delivered during treatment to improve outcomes.
17.	Bekkering et al, 2011 – A cross - sectional study	N = 82	Mean age (± SD) at time of surgery 14.2±4.1 years.	CS	PMBT around knee, located in the proximal femur (n=54) and distal tibia (n=28). Tumours included osteosarcoma and	LSS (n=39) consisting of allograft (n=24), endoprosthesis (n=15) Ablative surgery (n=43) consisting	Mean time since surgery was 2.8± 1.6 years.	No control group	Activity monitor: Actilog ® V3.0; Radboud University Nijmegen	PA: a. GPA score defined as the average number of accelerations in a 5 minute duration through the day, and b. Average peak amplitude	Significantly better scores were seen in the LSS group for the timed up and down stairs (TUDS) and various walking activities test (VWA) as compared to the AMP group. No significant differences were seen between LSS and AMP for any of the

			Mean age (± SD) at assessment was 16.9 ±4.2 years.		ewing's sarcoma.	of AMP (n=27) and Rotationplasty (n=16)			Medical Centre, Nijmegen, The Netherlands) – Placed on ankle of non-affected limb and worn for 7 consecutive days.	and duration (average peaks is the number of high peak accelerations in a 5 mins duration, during the day and is a reflection of intensity of PA) of accelerations	Actilog PA measures. In long term (from 1 to 5 years), post-surgery due to a bone cancer in paediatric population and adolescents, there is no significant difference seen between patients having a LSS and AMP with respect to overall physical functioning and PA, apart from going up and down stairs and few walking activities.
18.	Bekkering et al, 2012 – A prospective longitudinal study	N=44 44 patients were recruited into study, out of which 24 patients completed study	Mean age (± SD) at time of surgery 14.9± 4.8 years	CS	PMBT around knee, located in distal femur (n=32) and proximal tibia (n=12). Tumours included osteosarcoma (n=41) and ewing's sarcoma (n=3).	LSS (n=27) including allografts (n=8), prosthesis (n=19), Ablative surgery (n=17) including AMP (n=10) and Rotationplasty (n=7)	At 3, 6, 9, 12, 18, and 24 months post-surgery.	No control group.	Activity monitor: Actilog ® V3.0; Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands) .– Placed on ankle of non-affected limb and worn for 7 consecutive days.	PA: a. GPA score defined as the average number of accelerations in a 5 minute duration through the day, and b. Average peak amplitude and duration of accelerations	Over the first year post-operatively, patients demonstrated significant improvements in QoL, physical ability and activity levels as measured by Baecke questionnaire. Over the second year after surgery, the improvements were present but less pronounced. No difference in PA was detected by the Actilog activity monitor.

5.4.2 Validity, Reliability and Responsiveness to change over time

Indicators of validity including outcomes in different clinical groups and the impact of clinical factors:

Patients demonstrated significantly diminished balance, gait and ambulatory (walking) PA compared to healthy controls in the short and long term (de Visser *et al.*, 2001; de Visser *et al.*, 2003; Winter *et al.*, 2012):patients spent most of their time sitting (54±18% of the time)(Sugiura *et al.*, 2001; Rosenbaum *et al.*, 2008b) . LSS and AMP are distinct clinical groups, and most studies demonstrated no significant differences in ambulatory PA between LSS and AMP (van Dam *et al.*, 2001; Hopyan *et al.*, 2006; Bekkering *et al.*, 2011). However, one study showed patients with above knee AMP, resection alone cases (simple LSS) and autoclaved bone reconstructions achieved a higher number of steps than patients who underwent complex LSS such as the Kotz modular reconstruction system, including total knee replacement (TKR) or semiconstrained total hip replacement (THR) (Sugiura *et al.*, 2001). BT patients (6001 ± 2684 gcs)) demonstrated lower average daily step counts than STS patients (7758 ± 3835 gcs) ($p < 0.05$) (Sugiura *et al.*, 2001). Patients with complications such as wound-healing problems, superficial or deep infection demonstrated significantly lower intensity of PA at 18 months, than those without complications (Winter *et al.*, 2012).

In terms of correlations with existing measures, contrasting results were seen, for example: in one study the number of step cycles or percentage of ambulatory time were not correlated with TESS or MSTS (Rosenbaum *et al.*, 2008b), but in others, MSTS correlated with "time spent walking"(van Dam *et al.*, 2001) and with steps/day (number of steps = 0.001 X MSTS score ± 14.499) (Sugiura *et al.*, 2001). In addition, although instruments assessing similar outcomes (for example: Various walking activities (VWA) and Timed Up and Down Stairs (TUDS)), detected differences between LSS and AMP, the general physical activity (GPA) from the Actilog activity monitor did not detect differences between these groups (Bekkering *et al.*, 2011). Interestingly, age did not relate to PA, but body mass index (BMI) was negatively correlated with duration of data collection ($p<0.01$) (Rosenbaum *et al.*, 2008b). In addition, although time since surgery, length of bone resected and ROM did not correlate with PA, muscle strength was significantly positively correlated with PA (Sugiura *et al.*, 2001).

Sensitivity or responsiveness to change:

Only 4 studies investigated change in outcomes over time. Of these, step-cycle duration, walking speed, and gait symmetry recorded by footswitches were sensitive to change over time, as at the end of rehabilitation gait improved compared to baseline ($p<0.05$) (de Visser *et al.*, 2003). Similarly PA captured by the StepWatch™ Activity Monitor was sensitive to change from 6 weeks to 18 months post-surgery (Winter *et al.*, 2012). However, contrasting results in another study revealed GPA from the Actilog monitor was not sensitive to change over time from 3 to 12 months post-surgery, although there was a change in PA detected by the Baecke questionnaire. (Bekkering *et al.*, 2012a).

Reliability:

Only 1 reliability study was undertaken, with good Intraclass correlation coefficient (ICC) from 0.65 to 0.91. ICC values for PA volume in walking time were 0.65, standing time were 0.83, sitting time were 0.75. ICC values for movement intensity (m/s^2) was 0.91 in walking, 0.69 in standing, 0.79 in sitting and a total of 0.91 in walking, standing or sitting (van Dam *et al.*, 2001). These indicators of validity are represented in Table 5-5 and 5-6.

Table 5-5: Summary table of validity and reliability of measures

Study	*Outcome*	*Comparison to controls/ unaffected side.*	*Sub-group comparison or relation with demographics, clinical parameter*	*Comparison between different testing conditions*	*Association with established validated measures in Sarcoma*	*Comparison with a gold standard*	*Reliability*	*Sensitivity /Responsiveness to change*
Balance								
De Visser et al, 2001	Amplitude of the centre of pressure (ACP) and velocity of the centre of pressure (VCP)	✓	X	✓	X	X	X	X
Gait								
De Visser et al, 1998	Walking speed, stride time and co-efficient of variation.	✓	✓	✓	X	X	X	X
De Visser et al, 2000	Walking speed, stance time, swing time, double-support time, swing time, stride time and joint angles during gait in both legs.	✓	✓	X	X	X	X	X
Kawai et al, 2000	Free-walking velocity, stride length, cadence, time to complete gait cycle, double-limb support time, and single-limb support time.	✓	✓	✓	✓	X	X	X
De Visser et al, 2003	Step-cycle duration, walking speed, gait symmetry.	X	✓	✓	X	X	X	✓
Tsauo et al, 2006	Step velocity, step length, duration of stance phase and swing phase.	✓	X	X	✓	X	X	X
Beebe et al, 2009	Gait velocity, stride time, cadence, double limb support, stance phase, swing phase, step time, step length.	✓	X	X	X	X	X	X
Zohman et al, 1997	Gait velocity, stride length, cadence, and stance time symmetry	X	✓	X	X	X	X	X
Physical Activity (PA)								
Rosenbaum et al, 2008	Time spent in different activities. Movement intensity. Volume: Daily number of gait cycles. Intensity as step cycles/minute.	✓	✓	✓	✓	X	X	X

Sheiko et al, 2012	Volume: Total stride/day, Average walking minutes/day Intensity: Time spent/day at high activity levels Others: endurance, accumulated peak effort, cardio-vascular score, burst score, and peak score.	✓	X	X	✓	X	X	X
Van deer Geest et al, 2013	General physical activity (GPA) score defined as the average number of accelerations in a 5 minute duration through the day	✓	X	X	✓	X	X	✓
Winter et al, 2012	a. Volume in the form of the number of gait cycles (one gait cycle is two steps) b. Intensity measured as gait cycles per minute	✓	✓	✓	X	X	X	✓
Sugiura et al, 2001	Volume in the form of number of steps/day.	✓	✓	X	✓	X	X	X
Van Dam et al, 2001	Time spent walking, standing and sitting (as a percentage of 24 hours), the movement intensity (m/s^2), and also sum of the movement Intensities.	X	✓	X	✓	X	✓	X
Hopyan et al, 2006	"Amount/percentage of time an individual spends in the upright position" also termed as "uptime	X	✓	X	✓	X	X	X
Winter et al, 2009	Volume measured as gait cycles/day. Intensity measured as gait cycles per minute.	✓	✓	✓	X	X	X	X
Bekkering e al, 2011	General physical activity (GPA) Average peak amplitude and duration	X	✓	X	✓	X	X	X
Bekkering e al, 2012	GPA Average peak amplitude and duration	X	X	X	✓	X	X	✓

Table 5-6: Validity and reliability of measures in the literature: Reference Values for patients treated for Musculoskeletal cancer

Sr No.	Article	Comparison to controls (Form of construct validity – divergent validity)	Comparison between sub-groups of patients (Divergent validity) or relations between demographics, clinical characteristics and outcome Convergent validity)	Comparison between different testing conditions (Form of construct validity)	Association with established validated measures in Sarcoma (Form of construct validity – convergent validity)	Comparison with a gold standard (Criterion validity)	Reliability (Test-retest validity or intra-tester or inter-tester reliability)	Sensitivity /Responsiveness to change
Balance – LSS								
1.	De Visser et al, 2001	Upright Standing: Eyes-open: No significant differences in ACP and VCP measures between patients and controls ($p>0.05$). Eye-closed: Both patients and controls have an increased VCP with eyes closed, in comparison to eyes open ($p<0.05$). However, displacement of CP in eyes closed condition, was smaller for patients than controls ($p<0.05$). Dual-Task: Only patients showed a significantly higher ACP (4.5±0.8 mm) when compared to normal standing (2.9±0.4 mm) and VCP (18.6± 3.0 mm/sec) when compared to normal standing (11.9±1.0 mm/sec) when the auditory stroop task was performed, however patients and		Upright Standing: Eyes-open: No significant differences in ACP and VCP measures between patients and controls ($p>0.05$). Eyes-closed: Closing the eyes increases ACP and VCP in patients in the anterior-posterior direction, when compared to eyes-open normal standing. Dual-Task: When the auditory stroop task was performed, only patients showed a significantly higher ACP (4.5±0.8 mm) when compared to eyes-open normal standing (2.9±0.4 mm) and VCP (18.6± 3.0 mm/sec) when compared to eyes-open normal standing (11.9±1.0 mm/sec).				

		controls were not significantly different. Standing on balance board: Eyes open: No significant differences were seen between patients and controls. Eyes-closed and Dual-task: A significant difference in VCP was seen for both groups with eyes closed condition and also under dual-task conditions (controls, 23.2±3.3 and 14.9±2.9 mm/sec; patients, 80.1±12.9 and 23.6± 3.4 mm/sec).		Standing on balance board: Eyes-Closed and Dual-task: A significant difference in VCP was seen in patients with eyes closed condition and also under dual-task conditions; (patients, 80.1±12.9 and 23.6± 3.4 mm/sec).
Gait – LSS				
2.	De Visser et al, 1998	Patients walked with a lower preferred walking speed (2.4 km/hr) than controls (3.8 km/hr) and showed a higher co-efficient of variation of stride time than the normal subjects, in normal and complex walking. When walking with constraints, a significant reduction in stride time was seen in patients, but not in normal subjects, ($p<0.05$). Controls did not show any significant differences in the three conditions.	There was no relation between sub-groups such as tumour type, surgery type and location of tumour with the level of visual and cognitive dependency.	In complex walking such as dual task or visual restrictions, patients showed a significant reduction in stride time compared to normal walking conditions. ($p<0.05$).
3.	De Visser et al, 2000	The preferred speed of walking in LSS patients (0.7±0.3 m/s) was lower than that in controls	There were no significant differences between gait parameters in hip and	

		(1.1±0.08 m/s). The mean stride duration in patients (1.5±0.6 s) was longer than controls (1.1±0.06 s)($p<0.05$). The stance phase of affected leg was shorter and of non-affected leg was longer. The stance phase of non-operated kegs in patients was longer than controls. All patients treated for LSS showed a reduced knee flexion during stance phase in the operated leg.	knee group ($p<0.05$).		
4.	Kawai et al, 2000	The patients walked with a significantly less cadence and stride time compared to controls ($p<0.05$). Patients had a significantly shorter single limb support time on the affected side (0.42 ± 0.06), compared to the unaffected side (0.52 ± 0.07) ($p<0.05$). The asymmetry difference was 0.09 s (0.01 to 0.22).	Patients with proximal femoral replacement had a superior gait than patients with hip disarticulation in characteristics listed below. Patients with proximal femoral replacement had a significantly higher walking velocity and asymmetry than patients with hip disarticulation ($p<0.05$). In addition, energy cost and asymmetry of walking was higher in patients with hip disarticulation compared to those who had a proximal femoral replacement.	Patients who used a cane, walked with less cadence longer stride length, and with walking velocity not significantly changed. The single-limb support times were prolonged and asymmetry was significantly decreased.	Free-walking velocity was negatively correlated with the net energy cost ($r = -0.55$, $p = 0.05$). Free-walking velocity and asymmetry of the single-limb support time demonstrated a significant negative co-relation ($r = -0.67$, $p = 0.006$). Asymmetry of single-limb support time and strength of abductor muscles demonstrated a

				weak negative correlation (r = -0.62, p = 0.05). No significant correlation was seen between gait outcomes in patients and length of the proximal femur resected.	
5.	De Visser et al, 2003	Patients treated with a knee prosthesis walked at a speed of 3.9± 0.15 km/hr and stride time of 1.15±0.05 sec. Patients with a hip prosthesis walked with a preferred speed of 3.4± 0.23 km/hr and a step-cycle duration of 1.21±0.07 sec after 15 months. Patients with saddle prosthesis walked at a speed of 2.2 ± 1.1 km/hr and a stride time of 1.50±0.33 sec.	During the recovery period, patients step cycle duration were reduced by complex add-ons such as dual task and visual restriction while walking.		Patients have an improvement in the gait outcome such as step-cycle duration, walking speed, gait symmetry over time and with rehabilitation: Walking speed was seen to increase from 2.1±0.9km/hr to 3.5±0.3 km/hr during the end of rehabilitation. Step-cycle duration 2 ±1.04 sec was significantly decreased to 1.18± 0.106 sec at end of rehabilitation. A slight improvement of gait symmetry was observed, with some

				gait asymmetry still persistent after 15 months.
6.	Tsauo et al, 2006	Patients walking velocity were 54±12m/min, and controls' was 72±6m/min ($p<0.05$). The step length of patient's unaffected side is significantly shorter than controls and affected side (Affected side was 115.8+22.2% of unaffected limbs') ($p<0.05$). The stance phase of patients' affected leg was significantly shorter than that of controls and unaffected side (88.2+5.9% of unaffected limbs')($p<0.05$). Conversely, swing phase of patients' affected leg, was significantly longer than that of their unaffected sides (127.3+22.1% of unaffected limbs') ($p<0.05$).	The ratio of quadriceps strength of operated by normal knee, and isometric strength of hamstring by quadriceps ratio of operated knee was correlated significantly to the difference of stance-phase duration of both sides ($p<0.05$).	
7.	Beebe et al, 2009	Aspects of gait reduced were: Gait velocity (range, 86.8 – 108.4cm/s; controls from literature 128cm/s), Stride length (range, 101.68–120.04cm in the affected limb; 102.07–114.19cm in the unaffected limb; controls from literature 128cm), and Cadence (range, 87.9 –113.5 steps/min; controls from literature	MSTS gait sub-component were reported as 3/5 and total MSTS score as 23.5/30) Only scores were stated. No formal comparisons have been made therefore no testing of validity in this section.	

		is 117 steps/min). Double-limb support was higher in patients (range, 26.0–32.3% Gait Cycle (GC) in the affected limb, 26.8–32.4% GC compared to unaffected limb; values for controls from literature is 20% GC). Stance phase was greater in all patients in the unaffected limb (range, 59.8–67.7% GC; values for controls from literature is 60% GC) but only in half of the patients in the affected limb (range, 58.1–67.8% GC, values for controls from literature is 60% GC). Swing phase, step length, and step time were higher in the affected limb compared to unaffected limb	
8.	Zohman et al, 1997		No statistical significance was seen between mean step velocity after intraarticular proximal tibial replacement (79.2 ± 7.6 m/min) and control group of amputees (71.4 ± 5.4 m/min) (p=0.06) Significant difference was seen between cadence after intraarticular proximal tibial replacement (112.4

			± 10.6 steps/minute) vs control group of amputees (100.1 ± 2.4 steps/minute) (p=0.03). No significant differences were seen between length of stride (1.41 ± 0.13 m vs 1.43 ± 0.12 m) and the symmetry of stance time (0.90 ± 0.07 vs 0.87 ± 0.11) for proximal tibial replacement vs control group of amputees.		
Physical Activity – LSS					
9.	Rosenbaum et al, 2008	Ambulatory (walking) and sedentary PA: Volume: Patients performed the predominant daily activity of sitting (54±18% of the time recorded) compared to control(42%), then followed by upright standing (27±16%) compared to controls (41%), followed by ambulation (10±6%) compared to controls (11%), and lying (8±6%) compared to controls (4%). The ambulatory activity level in patients was significantly lower (4,786±1,770 cycles/day) than normal healthy adults	Volume: Data collection duration was negatively correlated with Body mass index (BMI) ($p<0.01$). No correlations were seen between PA and the duration of follow-up. The gcs did not correlate with patient's age but demonstrated marked subject differences (range 2,045–8,135). The mean movement intensity during walking activity was 2.4±0.4 m/s^2 . This did not correlate with the age, weight or	Volume: On weekends, patients walked only 95% of the steps achieved during weekdays.	Volume: A low correlation was observed between SAM and MSTS (p=0.2). A poor correlation coefficients for locomotion vs MSTS or TESS, and also between SAM and TESS score. No significant relations between gait analysis in laboratory and Activities of daily living (ADL) monitoring in a sub-group of patients.

		(6,517±1,489 cycles/day) (p=0.01), however it was comparable to the level of activity for other patients. For example, with hip arthroplasty reported in literature. Intensity: Healthy controls spent more time in higher intensity activities (absolute values). No significance testing performed.	BMI. No significant differences were seen between location of tumour in proximal vs distal femur (p>0.05).		
10	Sheiko et al, 2012	Ambulatory PA: Patients who underwent LSS had significant reduced PA levels when compared to healthy controls: Volume: There were significant differences between patients who had undergone LSS and healthy controls in total PA/ day (43% vs 48%; P = 0.03), the median value of total strides/day (4487 vs 7671 strides; p = 0.001). Average walking minutes/day in LSS patients were 370 (211 - 587) as compared to healthy controls as 438 (275-518) (p=0.05) Intensity: Time spent/day at high activity levels (20 minutes vs 47 minutes; p = 0.001).			Volume: Self-reported PA questionnaire ASKp-38 summary score significantly correlated with step watch average strides/day (r=0.50, p<0.05), ASKp-38 locomotion sub-score correlated significantly with step watch average strides/day (r= 0.63, p<0.01) and StepWatch % time active r=0.56, p<0.05). Correlations were tested using spearman's correlation.

		Others: Significant differences were also seen between patients treated for LSS and healthy controls for endurance (18 vs 28, p<0.001), accumulated peak effort (22 vs 33, p<0.001), cardio-vascular score (27 vs 39, p<0.001), burst score (41 vs 54, p<0.001) and peak score (55 vs 66, p<0.001).				
11	Van deer Geest et al, 2013	PA: No significant differences between change in PA scores between tumour patients and controls (arthroscopy patients). (No reference values mentioned)			No significant correlation between fatigue and PA scores.	Absolute values of actometer scores increased over time from pre-surgery to recovery. However significance tests were not performed due to a small sample size.
12	Winter et al, 2012	Ambulatory PA: Patients achieved significantly lesser volume (gcs/day) and time spent in moderate intensity (time spent in >50 gait cycles/min)) of PA than controls at all time points (p<0.001). Volume: Controls achieved 7,100±1,918 gcs/day, whereas patients achieved 770±793gcs/day at 6 weeks, 1,847±1,047 at 3 months, 2,351±1,842 at 6 months, 3,917±1,703 at 12 months, 5,107±1,600 at 18 month, which was significantly different from	Volume and Intensity: Significant differences in volume and intensities were observed between patients with and without complications at various time points. Volume: Differences were observed between sub-groups such as patients with and without complications 6 months post operatively (599 vs. 2,794 gcs in a day) which continues to exist 12	Volume and Intensity: The lowest scores for volume and intensities for PA were seen at 6 weeks post-operatively. Significant increases in the volume of ambulatory activity were seen after cessation of therapy (chemotherapy) at 6 months post-operatively, however intensity showed minor and no significant changes. Increase in intensity to higher levels was seen in longer term follow-up. 12 months post-operatively		Volume and Intensity: A continuous increase in absolute values of volume and intensity of PA was observed at each follow-up However significant increases were only seen when comparing the first measurement after surgery to the 12 month and 18-month follow-ups (p<0.003). No significant differences observed between other

		controls at each time point (p<0.001). Intensity: Controls spent 27.6±14.5 minutes at moderate intensity (time >50 gait cycles/min), whereas patients spent 1.1±2.1 minutes at 6 weeks , 2.2±5.9 at 3 months, 3.1±7.0 at 6 months, 10.5±13.5 at 12 months and 15.2±16.1 at 18 months, which was significantly different from controls at each time point (p<0.001). Therefore patients did not reach level of healthy controls even at 18 months post-operatively.	months post-operatively, with 3,279 vs. 3,826 gcs/ day. At 18 months post-operatively, no significant differences were present with regards to volume of PA. Intensity: Patients with complications did not perform any moderate intensity activities at 12 months, whereas patients with complications achieved 4 minutes/ day. At this moderate level differences were more pronounced at 12 months (0.3 – 12.6 minutes), 18 months (3.7 vs 18.9 minutes) post-operatively.	patients significantly improved volume of activity compared to the treatment phase, with no major improvements in moderate intensity levels of PA.		measurements.
Physical Activity – LSS + AMP						
13	Sugiura et al, 2001	Ambulatory PA: Volume: 56 patients achieved an average daily step count of 7119 ± 3563 which as 69.8% of controls (10,206 ± 1388)	Volume: Average daily step count of the BT and soft-tissue tumour clinical groups were 6001 ± 2684 and 7758 ± 3835 steps (which was 58.8% and 76.0% of the controls, respectively). The BT group	Volume: Average daily step count was not correlated with ROM. Average daily step count was significantly correlated with MSTS (coefficient 0.52, P<0.001). A relation		

		demonstrated a significantly lower average daily step count compared to the soft-tissue tumour ($p < 0.05$) Kotz TKR and semiconstrained THR groups, achieved significantly lower number of steps than other groups such as resection without reconstruction of bone (n = 30), above-knee AMP (n = 4), total femur autoclaved bone (n = 5), autograft (n = 2),heat-treated bone (n = 5), replacement (n = 1). (No values for each group, only represented graphically) For patients with a tumour more proximally (closer to the trunk) tended to achieve lower steps than those with tumours in other locations, and this was mainly seen in BT group.	value was also determined as The number of steps = 0.001 X MSTS score ± 14.499 The hip abductors and hip flexors strength were more closely correlated (measured by correlation rate) with daily step count than with knee extensors and knee flexors strength.

14	Van Dam et al, 2001.	PA: Volume: The LSS (n=12) and AMP (n=8) group were both similar on MSTS, TESS, Baecke, Euro-QoL and Rand-36 scores. Percentage of time spent walking (in 24 hours) in whole group was 5.1(2.37)%. In LSS group was 5.6 (2.02)% and in AMP was 4.3 (2.78). Intensity: Walking intensities were 2.1 (0.39) m/s^2 in whole group. LSS patients scored 2.26(0.43) m/s^2 and AMP group scored 1.9 (0.15) m/s^2. However no significant differences were seen between the LSS and AMP groups with respect to 'time spent in certain activities' and 'movement intensities' ($p>0.05$).	Volume: There was a significant correlation seen between 'time spent walking' and the MSTS scores and also the Rand-36 scores. Intensity: A significant association was also seen between 'movement intensity during walking' and MSTS.	The test-retest reliability (n=17) of the monitor was satisfactory, with an ICC from 0.65 to 0.91 over the function measured. ICC for individual aspects of function were as follows: Volume: Time spent in walking task ICC = 0.65, Time in standing = 0.83, Time in sitting = 0.75. Intensity: Movement intensity (m/s^2) Walking = 0.91 Standing = 0.69 Sitting = 0.79 Total (walking, standing or sitting) 0.91

15	Hopyan et al, 2006		PA: Volume: Uptime (expressed in percentage) in LSS group (n=15) was 24.0±9.2 (range, 10-40), Above-knee AMP group (n=15) was 26.7±7.3 (range, 18-40), rotationpstlasty group (n=5) was 30.1±9.2 (18-43) and below knee AMP was 26 (n=1) Uptime measured by the activity monitor, were similar between groups. Uptime had higher values in patients with rotationplasty, although statistical comparisons were not feasible.	Volume: Significant differences were seen between LSS and AMP groups, using TESS (p=0.06) and MSTS (p<0.0001). However no significant differences were seen between LSS and AMP in uptime (p=0.39)
16	Winter et al, 2009	Ambulatory PA: Volume: Patients with BT exhibited 1275±1105, median 943 gcs/day, which was 16% of the PA when compared to controls (8096±2951, median 7438 gcs/day) during inpatient stay and achieve 2145±1422 median 1490 gcs/day which is 27% of the PA compared to controls during their home stay (p<0.001). Intensity:	Volume: Patients with BT exhibited lower volume of PA scores than those with leukemia (1,849 gcs vs. 2,992 gcs) However no statistical significant differences seen in both settings. Intensity: Percentage of time on high intensity activities were 6.1±3.7, median 5.7	Volume: Significant differences between inpatient (1275±1105, median 943 gcs/day) and home stays (2145±1422 median 1490 gcs/day) were seen in BT patients. During in stay patients achieved 59% of the PA, they achieved at home (p<0.001).

		Patients in the BT group spent a lesser percentage of time at high intensity activities during in patient stay (3.5±4.7, median 2.1) when compared to controls (14.7±7.2, median 12) ($p<0.001$) and 4.2±5.5, median 2.9 during home stay, which was significantly lower than controls (14.7±7.2, median 12) ($p<0.05$)	compared to BT patients (3.5±4.7, median 2.1). However though clearly reduced intensities of activities in bone cancer patients, there were no statistically significant differences seen between the leukaemia's and BT patients.		
17	Bekkering et al, 2011		PA: GPA values for LSS (n=30) group was 93.9 (25.4) and for AMP (n=36) group was 94.8 (29.7). No significant differences between groups. Average peaks were 142.3 (14.7) for LSS and 143.8 (21.9) for AMP. No significant differences between groups.		Significantly better scores were seen in the LSS group for the timed up and down stairs (TUDS) and various walking activities (VWA) test as compared to the AMP group. However no significant differences were seen between LSS and AMP for any of the PA measures

18	Bekkering et al, 2012		PA: PA was measured using Baecke questionnaire and Actilog activity monitor. A significant increase in activity levels between 3 to 12 months ($p < 0.01$) was detected by the Baecke questionnaire. However the GPA and average peak of accelerations measured with Actilog activity monitor did not show statistical significant differences at various time points	GPA and average peak of accelerations measured with Actilog activity monitor did not show statistical significant differences at various time points. GPA scores: At 3 months 81±6.8, 6 months 87±6.8, 12 months 92±7.3, 18 months 98±7.8, and 24 months was 93± 8.2. Average peaks: 3 months 121±4.9, 6 months 125±5.0, 12 months 127±5.4, 18 months 126±5.7, and 24 months 127±6.1.

5.5 Discussion

5.5.1 Overview of study findings

We have reviewed the literature and identified 18 relevant articles quantifying balance, gait and PA in patients treated for musculoskeletal tumours of the lower extremity. Studies were highly variable, and used a wide range of outcome measures, investigated different age groups, clinical sub-groups, ranged from case series to longitudinal studies, publication year from 1996 to 2013. 11 were high quality and 7 moderate quality, posing a difficulty in synthesizing results.

5.5.2 Indicators of validity

Very few studies investigated aspects of the validity of outcome measures raising questions about the accuracy of measures and trustworthiness of results obtained. Only one study investigated reliability and four sensitivity to change over time. Furthermore, it was perhaps surprising that some gait and PA measures were unable to distinguish between distinct clinical groups, such as LSS and AMP (van Dam *et al.*, 2001; Hopyan *et al.*, 2006; Bekkering *et al.*, 2011). In contrast, in another study, patients who had above knee AMP achieved a higher number of steps than complex LSS patients (Kotz TKR and Semiconstrained THR), and complex LSS were significantly different from simple LSS groups (resection alone) (Sugiura *et al.*, 2001). The inability to distinguish between LSS and AMP groups might therefore be due to the wide variation in the level and complexity of surgery in each group, as well as the inaccuracy or inapplicability of measures to the clinical scenario. It was interesting that GPA from Actilog could not detect differences between LSS and AMP, whilst TUDS and VWA did. (Bekkering *et al.*, 2011). Although it could be argued that this is because GPA, TUDS, VWA measure different attributes of physical functioning it is of note that in another study, the Baecke questionnaire measuring PA, was sensitive to changes in PA from 3 to 12 months ($p < 0.01$), but the GPA was not. (Bekkering *et al.*, 2012a). Therefore clearly GPA is not sensitive to change of PA over time. This could be attributed to non-linear methods of data analysis being more sensitive than linear methods, for PA data from activity monitors (Del Din *et al.*, 2016d). For example: Pattern of PA (Distribution of activity also referred to as alpha (α)) was found to be more sensitive than volume (percentage of time spent in an activity) in other clinical groups (Chastin *et al.*, 2010).

Although few studies demonstrated that established measures such as TESS/MSTS were related to total steps/day (van Dam *et al.*, 2001; Rosenbaum *et al.*, 2008b), these measures

alone do not provide a complete clinical picture of a patient's impairment, disability and activity restrictions. This may prevent clinicians from planning holistic management strategies which may contribute to poorer outcomes. It is clear that balance, gait and PA measures identified in this review provide new objective clinical information, completely different from TESS/MSTS, re-emphasizing the need to collect novel measures in conjunction with established measures in routine clinical practice. This is useful in planning clinical and cost-effective management strategies with a view to improving outcomes. However, a significant barrier to clinical use is the lack of validity and reliability testing of measures. This could mean clinicians have potentially inaccurate information and may increase the risk that clinically important information is missed. In addition, costly or heavy devices pose added difficulties to clinical translation.

The ideal device for use in a clinical setting would be valid and reliable, cost-effective (Sugiura *et al.*, 2001), portable and light-weight and able to be used for self-monitoring. Mounting such a device on the lower back using a belt, seems to be a suitable and pragmatic approach and avoids problems with limb mounting, such as the effects of major surgery, scars and AMP. Modern accelerometers have been used to improve balance and gait rehabilitation, by providing immediate biofeedback (Barclay-Goddard *et al.*, 2004; Wai *et al.*, 2014; Horak *et al.*, 2015b). For example: audio biofeedback from an accelerometer has been used to improve balance (Dozza *et al.*, 2005). Similarly simple inexpensive activity monitors have been used to monitor and guide PA rehabilitation strategies in home settings. (Culhane *et al.*, 2005; Napolitano *et al.*, 2010).

The studies identified showed that balance, gait and PA were significantly poorer in patients than healthy controls in both the short and long term, (De Visser *et al.*, 1998; De Visser *et al.*, 2000; de Visser *et al.*, 2001; Winter *et al.*, 2012). This clearly has clinical implications, emphasizing the importance of rehabilitation in both acute and chronic phases. Furthermore, the long-term rehabilitation of patients with complications requires a focus on intensity training, as intensity of PA continued to remain affected at 18 months post-surgery (Winter *et al.*, 2012). Other approaches which need to become a part of rehabilitation include reducing dependency on visual cues during progressive balance training (de Visser *et al.*, 2001). In addition, clinical factors such as proximal muscle strength and BMI significantly correlated with gait and PA ($p<0.05$), but not length of the bone resected or ROM (Kawai *et al.*, 2000; Sugiura *et al.*, 2001), stressing the importance of prioritising proximal muscle strengthening and weight reduction during physiotherapy. Rehabilitation of the unaffected extremity is also

important as there may be bilateral hip muscle weakness (Beebe *et al.*, 2009), possibly because of over-compensation for the affected extremity.

5.5.3 Strengths

This is the first systematic review investigating the measurement of balance, gait and PA in patients treated for lower extremity sarcoma. The main strengths of the review are a robust search strategy and a quality assessment tool specifically developed for this heterogenous patient group.

5.5.4 Weakness

Weaknesses of the review include sample size was low in some studies, presenting difficulty in generalizability of results. Another weakness is that TESS was originally developed in a canadian cohort of patients, therefore terms such as 'yard work' in the questionnaire could be interpreted very differently in Canada compared to elsewhere. 'Yard work' in Canada refers to work undertaken to maintain a lawn or activities related to landscaping (high intensity activities), compared to other countries such as UK, where it means work done in one's garden or outside their house (low intensity activities).Therefore the study findings across countries need to be interpreted with caution. Some papers were older, and patients were treated at a time when primary AMP rates were higher, leading to a higher number of patients presenting with poorer physical function and is a potential source of bias. Although one paper showed contrasting results, the real reason could be that this sample is from an older study and may be significantly different to that seen in the clinic in the modern era. Other findings which would be important to account for in future studies are that balance and gait were significantly affected in unbalanced tasks (de Visser *et al.*, 2001; de Visser *et al.*, 2003), arguing for the collection of outcomes in real life challenging situations. It is also important to account for differences in ambulatory PA at weekends, as a study demonstrated that LSS patients walked only 95% of the steps achieved during weekdays (Rosenbaum *et al.*, 2008b).

5.6 Conclusion

There is a deficit in studies quantifying balance, gait and PA in patients treated for lower extremity sarcoma. Of the available studies, the majority did not use consistent, valid and reliable instruments developed specifically for sarcoma patients. Novel cost-effective, portable, valid and reliable instruments specific to assessing balance, gait and PA are important to develop, to gain accurate information, in patients treated for lower extremity sarcoma. Better measures of physical functioning are important when considering the impact of treatment and are essential if clinical management is to be improved. Wearable, portable and cost-effective tools such as activity monitors could be possible solutions, as are easy to apply and have a good potential for clinical translation. In the final phase of the PhD we have piloted portable small body worn triaxial accelerometers, which can capture a wide range of important clinical information and could possibly bridge these gaps.

Chapter 6: Evaluation of physical functioning after treatment for lower extremity musculoskeletal tumours – A feasibility study of accelerometer-based body worn monitors: Objectives, methods and research participants

6.1 Summary

This chapter contains the methods for the study 'Evaluation of physical functioning after treatment for lower extremity musculoskeletal tumours – A feasibility study of accelerometer-based body worn monitors'. These methods are relevant to chapters 7 and 8, which include the specific results and discussion for BWM outcomes obtained in the laboratory (clinic) and community environment respectively. In addition to general methods, this chapter includes a description of specific protocols and data processing techniques for obtaining clinical outcomes in the laboratory and community. This chapter also describes the demographic, clinical and functional characteristics of patients recruited to the study. The data collected from patients as a part of this study was used for the results in chapters 7 and 8.

6.2 Specific objectives of the study

1. To investigate the feasibility of quantifying balance, gait and TUG outcomes in patients treated for lower extremity musculoskeletal tumours using a fifth lumbar vertebrae (L5) BWM in the clinic setting.
2. To investigate indicators of validity of BWM clinic outcomes by comparing:
   i. balance, gait and iTUG outcomes between patients and healthy controls, and major clinical groups such as BT vs STS and LSS vs AMP groups (to assess discriminant validity)
   ii. balance, gait and iTUG measures against established disease-specific clinical scales such as TESS, MSTS, 3 metre-TUG time and QoL-CS (to assess convergent validity)
   iii. balance, gait and iTUG outcomes against standard manual techniques such as stopwatch and video used in clinics (to assess concurrent validity), and
   iv. agreement between two consecutive BWM measurements (to assess repeatability).

3. To investigate the feasibility and acceptability of free-living monitoring of ambulatory PA in patients treated for lower extremity musculoskeletal tumours; using a thigh-worn accelerometer-based BWM in the community setting.
4. To investigate indicators of validity of BWM community outcomes by comparing:
   i. Ambulatory PA outcomes between major clinical groups such as BT vs STS and LSS vs AMP groups (to assess discriminant validity)
   ii. Ambulatory PA measures against established disease-specific clinical scales such as TESS, MSTS, 3 metre-TUG time and QoL-CS (to assess convergent validity)

6.3 Methodological design, ethics and patients

6.3.1 Study design

This was a prospective cross-sectional pilot and feasibility study.

6.3.2 Ethical approval

The study was conducted according to the Ethical Standards of Helsinki declaration and Good clinical practice (GCP) guidelines. The study was approved by the National Research Ethics committee (NREC) (NREC Reference - 13/NE/0296 and IRAS Project Number: 138880) and the Newcastle Upon Tyne Hospitals NHS Foundation Trust, Research and Development department (R&D Number: 6801) on 16/12/2013. All patients provided written informed consent. The project manager ‘Sherron Furtado (SF)’ prepared and co-ordinated the submission of applications to regulatory bodies to obtain approvals.

6.3.3 Sampling

This was a convenience sample of patients recruited from the North of England Bone and Soft Tissue Tumour Service, situated in the Newcastle Upon Tyne Hospitals NHS Foundation Trust. This is one of the five specialist services in England funded for the investigation and surgical treatment of patients with primary bone and soft tissue tumours.

6.3.4 Patients

34 adult patients (age: ≥18 years) treated for lower extremity musculoskeletal tumours (bone or soft tissue tumours) were recruited into the study, from clinics and clinical records. Patients were included if they had undergone treatment including surgery and/or radiotherapy for a bone or soft tissue tumour located in the lower extremity (iliac crest or below). Patients were excluded if they were undergoing active treatment, had benign bone or soft tissue tumours,

were unable to take part because of cognitive or physical incapacity or refused to provide informed consent or participate.

6.3.5 Recruitment and data monitoring

Patients were mainly approached in the paediatric oncology clinics at the Great North Children's Hospital (Royal Victoria Infirmary (RVI)), orthopaedic outpatient clinics at Freeman Hospital, physiotherapy outpatient departments at the RVI and Freeman Hospital and clinical records. Eligible patients were given the appropriate Patient Information Sheet (PIS) (Appendix 7.0). Patients interested in participating in the study attended the department to provide written consent (Appendix 8.0) and completed data collection as per the NREC approved study protocol. SF independently performed screening, recruitment and data collection. For the part of the protocol in which BWM data was collected, one other research staff assisted SF, as the assessments require atleast two people to complete it. SF lead the assessments and was mainly responsible for all parts of data collection.

97 patients were screened in total, during a 9 month period from February 2014 to October 2014 to achieve the study target of 40 patients (Figure 6-1). Of 97 patients, 65 were eligible. Of 65 eligible patients, 40 (34 adults and 6 children) enrolled into the study and 25 did not. 25 patients did not enrol because; 21 declined participation into the study and 4 patients were non-contactable in the first instance. Of 21 patients declining participation, 4 were non-contactable after initial contact despite several attempts (hence recorded as declined). Of the remaining 17 patients, 10 declined participation because they lived far away from the hospital and therefore could not attend the department. 7 patients gave personal reasons such as work, other personal life commitments or did not wish to specify (Figure 6-1). The datasets from 34 adults (age: ≥18 years) were used for final analysis. The orthopaedic research department monitored and audited data collection as routine practice. Data from this study are stored in a secure office and will be kept on paper and computer for 10 years after study completion in accordance with departmental policy. Video recordings were anonymised and were used only to ensure reliability of the assessments. Video recordings were not to be seen by anyone outside of the direct research team unless express consent was obtained from the patient.

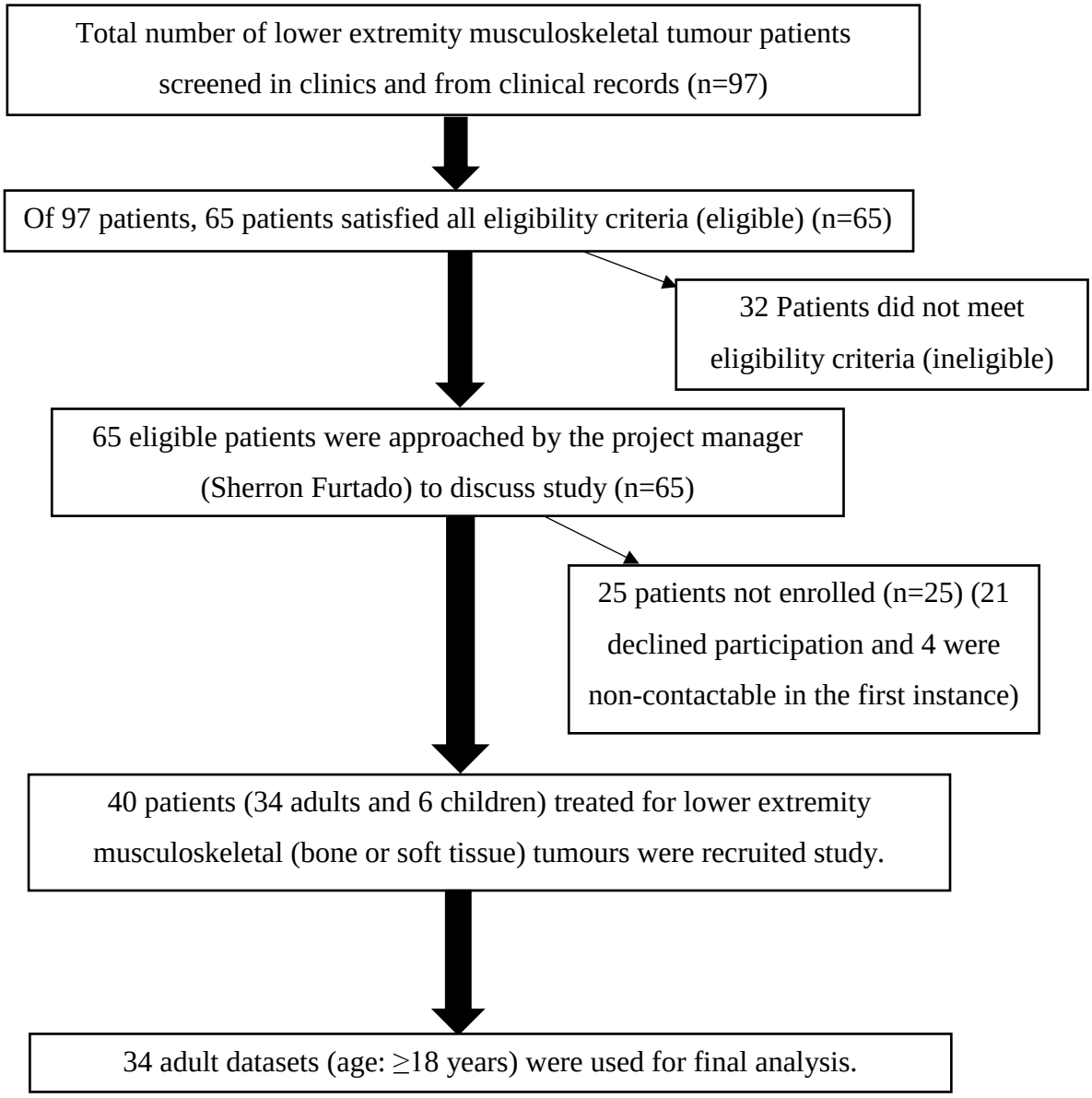


Figure 6-1: Flowchart of recruitment

6.4 Experimental protocol

Demographic data about age, gender, height, weight, BMI were noted for each patient. Height and weight were collected using a standard weight/height machine. Clinical characteristics such as diagnosis, treatments (chemotherapy and radiotherapy), surgery, time since surgery were collected on a review of clinical records form (Appendix 9.0). Patient enrollment and data collection were completed in the human movement laboratory on Level 1 at Freeman Hospital. Patients completed a musculoskeletal tumour disease-specific assessment and BWM assessments in the laboratory and community environment.

After patients completed the study, their General Practitioner (GP) was notified about their participation in the study (Appendix 10.0).

The experimental protocol is shown in Figure 6-2.

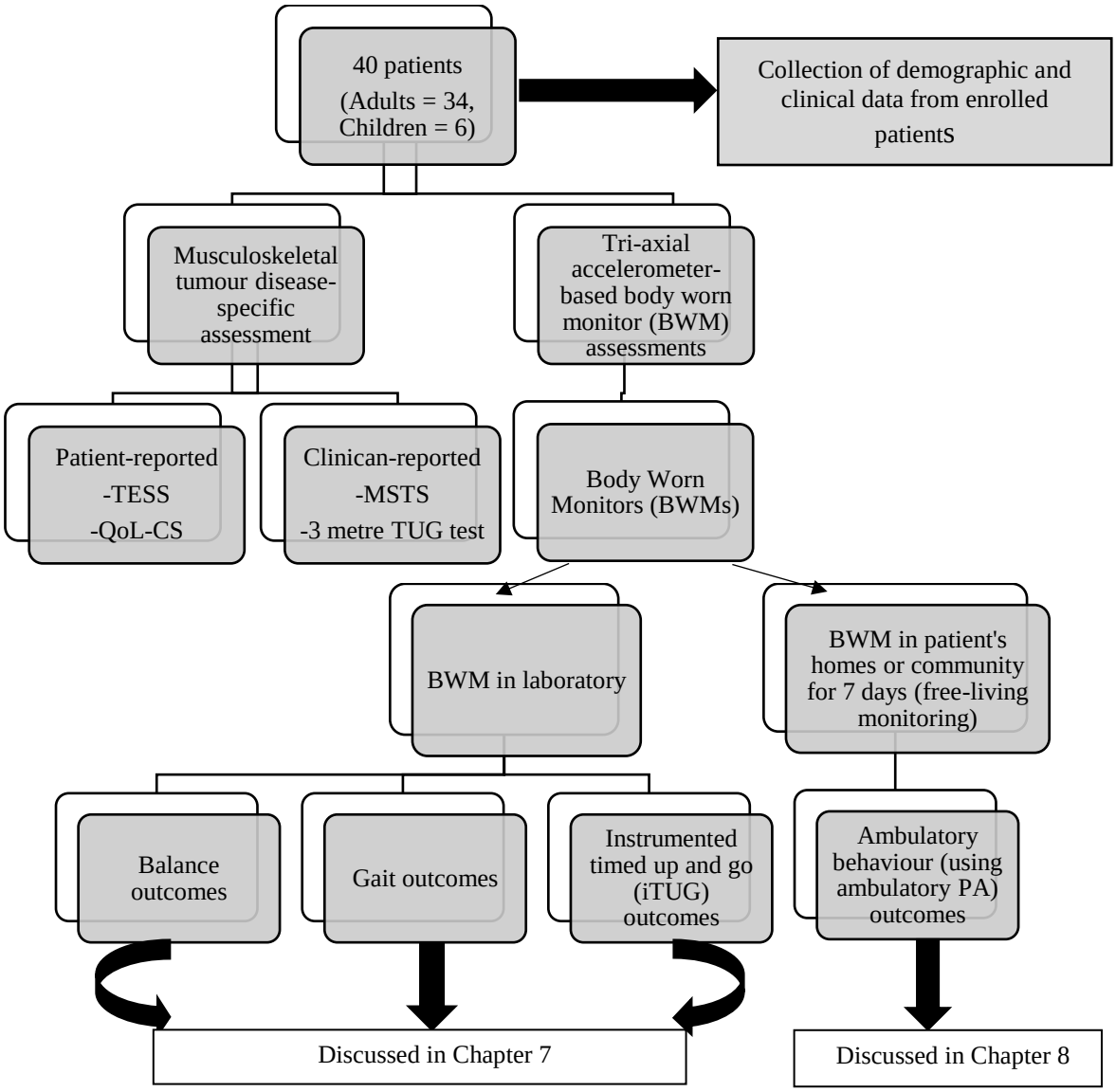


Figure 6-2: Experimental protocol

6.4.1 Musculoskeletal tumour disease-specific assessment

Patients were asked to complete disease-specific clinical scales, which included measures routinely used to assess function and QoL, in patients treated for musculoskeletal tumours. These consisted of questionnaires or patient-reported outcome measures (PROMs) (completed in the laboratory or at home) and clinician reported measures (completed in the laboratory) (Table 6-1) and are described below:

Table 6-1: Specific outcome measures for patients treated for Musculoskeletal tumours.

S.No	Disease-specific clinical scales	Sub-domains	Outcomes	Scores
Patient (Self)reported Outcome measures				
1.	Toronto Extremity Salvage Score (TESS) (Davis *et al.*, 1996)	30 self-reported items	Physical disability	Scores range from 0 to 100 (worst to best outcomes)
2.	Quality of Life for Cancer Survivors (QoL-CS) (Ferrell *et al.*, 1995)	41-item questionnaire	QoL	Scores range from 0 to 100 (worst to best outcomes)
Clinician-reported Outcome measures				
3.	Musculoskeletal Tumour Society score (MSTS) version developed in 1987 (MSTS-1987) for the Lower Limb (Enneking, 1987)	7 sub-domains range of motion, stability, deformity, pain, muscle strength, functional activity and emotional acceptance	Impairment	The MSTS total score is expressed from 0-35 (worst to best physical functioning). Individual sub-domain score is 0-5
4.	3-metre Timed Up and Go (TUG) test (Williams *et al.*, 2005)	TUG test of 3 metres	Physical capability	Less than 10 s = normal, 10-19 s = good mobility, can go out alone, mobile without a gait aid, 20-29 s = problems, cannot go outside alone, requires a gait aid

Patient-reported outcome measures (questionnaires)

i. Toronto Extremity Salvage Score (TESS)

TESS, a patient reported measure (Davis *et al.*, 1996; Davis *et al.*, 1999b), detailed in Chapter 2 was used in this study to assess disability. Scores range from 0 to 100 (worst to no disability) (Appendix 11.0).

ii. Quality of Life for Cancer Survivors (QoL-CS)

QoL-CS is a 41-item questionnaire used to assess quality of life in cancer survivors (Ferrell *et al.*, 1995) (Appendix 12.0). It comprises four QoL sub-domains; physical, psychological, social and spiritual. It is valid and has been previously used in patients after surgery for musculoskeletal tumours. QoL-CS scores are expressed as a percentage from 0 to 100 (worst to best QoL) (Ferrell *et al.*, 1995; Nagarajan *et al.*, 2004a).

Clinician-reported outcome measures

i. Musculoskeletal Tumour Society score (MSTS) version developed in 1987 (MSTS-1987) for the Lower Limb

MSTS-1987 a clinician completed tool (Enneking, 1987), detailed in Chapter 2 was used in this study to measure impairments. The MSTS total score is expressed from 0-35 (worst impairment to no impairment) (Appendix 13.0).

ii. 3-metre Timed Up and Go (TUG) test

The 3-metre TUG test was assessed by a clinician using a stopwatch (Williams *et al.*, 2005) (Appendix 14.0) (Figure 6-3). The TUG test starts with the patient sitting upright on a chair and includes 5 components of standing up, walking for 3 metres, turning around, walking back for 3 metres and sitting back in the chair. The subject wore their usual footwear, and could use their usual walking aids if required, but could not be assisted by another person. The time taken to complete this test is referred to as '3-metre TUG time' and is validated as an indicator of physical capability (Podsiadlo and Richardson, 1991). A longer time taken to complete the test is an indication of worse physical capability, and a shorter time of better physical capability. For example: in older adults, less than 10 s = normal, 10-19 s = good mobility, can go out alone, mobile without a gait aid, 20-29 s = problems, cannot go outside alone, requires a gait aid (Podsiadlo and Richardson, 1991). A score of more than or equal to fourteen seconds has been associated with a high risk of falls (Barry *et al.*, 2014). The score has been shown to be reliable, correlates well with clinical balance scores (for example: Bergs balance scale) and also appears to predict the patient's ability to move outside their home alone safely (Yelnik and Bonan, 2008).

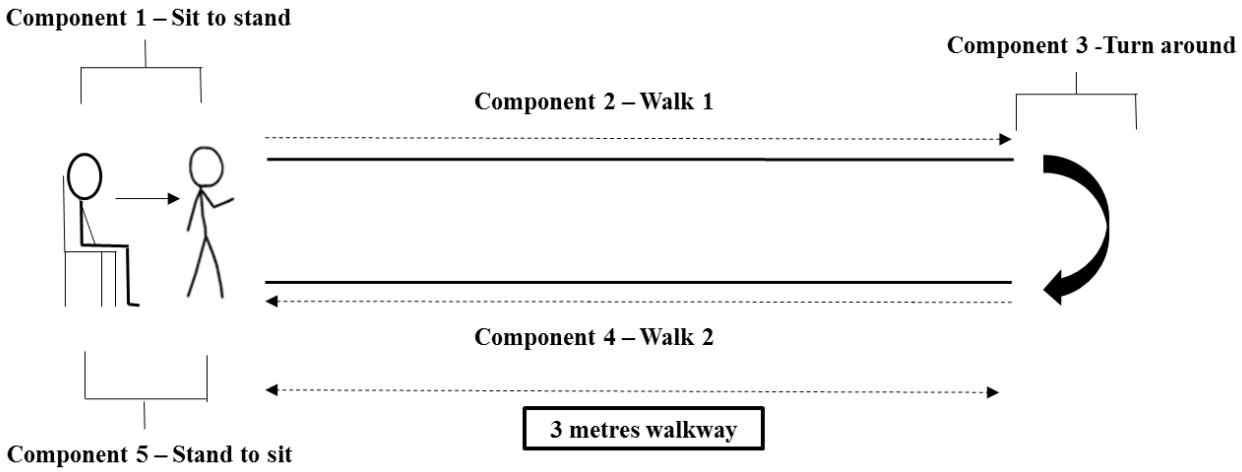


Figure 6-3: 3-metre timed up and go (TUG) test

6.4.2 Body worn monitor (BWM) assessment

The instrument used to quantify physical functioning in the laboratory and community in our study, was a tri-axial accelerometer-based BWM (Axivity AX3 dimensions 23.0, 32.5 and 7.6 mm, weight: 11.0 g). This BWM is essentially a generic movement sensor containing a triaxial accelerometer (Figure 6-4), which measures acceleration in the vertical (X axis), medio-lateral (Y axis) and anterior-posterior directions (Z axis), due to gravity and movement of the patient. The BWM was programmed to capture information at a sampling frequency of 100 Hz (16-bit resolution) and a range of ± 8 g and has been validated for its suitability to capture high-resolution data for human movement analysis (Ladha C, 2013).

(a) (b)

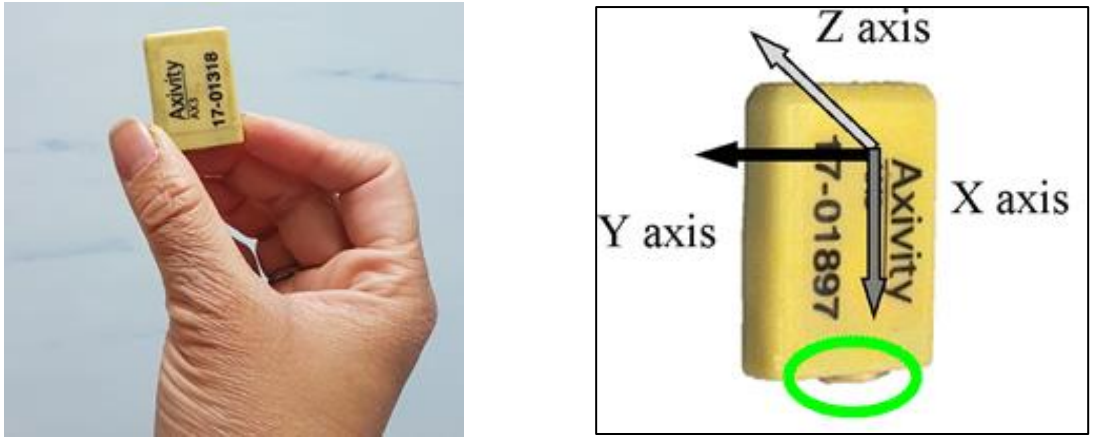


Figure 6-4: Body Worn Monitor (BWM) device
(a) and (b): Photograph of BWM device – Axivity AX3, A triaxial accelerometer capturing acceleration in vertical (X axis), medio-lateral (Y axis) and anterior-posterior (Z axis) directions.

BWM in the laboratory: Balance, Gait and Instrumented Timed Up and Go (iTUG) assessment

A BWM was used in the laboratory to capture balance, fast walk and instrumented timed up and go (iTUG) outcomes. The raw data collected by the fifth lumbar vertebrae (L5) sensor were processed to obtain balance, gait and iTUG outcomes (Figure 6-5). The L5 sensor was inserted into the pocket of a lumbar belt, with port facing downwards. This site was selected for BWM attachment, as it is in close proximity to the centre of mass (COM). In addition, balance, gait and TUG outcomes obtained from a BWM in this location are valid in healthy controls and patients with other clinical conditions (such as Parkinson's disease) (Godfrey *et al.*, 2015; Del Din *et al.*, 2016a).

Figure 6-5: BWM on low back at fifth lumbar vertebra, (L5) level for laboratory testing

Three tests of standing, intermittent fast walks and iTUG were performed in the clinic. These activities were also video recorded. The three tests are as follows:

i. Standing (balance) test

This was a test of quiet standing measured for 120 s, to assess standing balance (Mancini *et al.*, 2012). Patients were asked to start from a position of quiet standing on a level surface, with feet positioned slightly apart, hands by their side and eyes open (Figure 6-6). Patients were instructed to look straight ahead and maintain an upright standing posture for 120 s. During the test, patients wore their shoes and were not restricted to placement of their feet (Moghadam *et al.*, 2011). Each patient completed one repetition, which was in line with previous research (Whitney *et al.*, 2011), and also to avoid practice effect and fatigue.

(a)

(b)

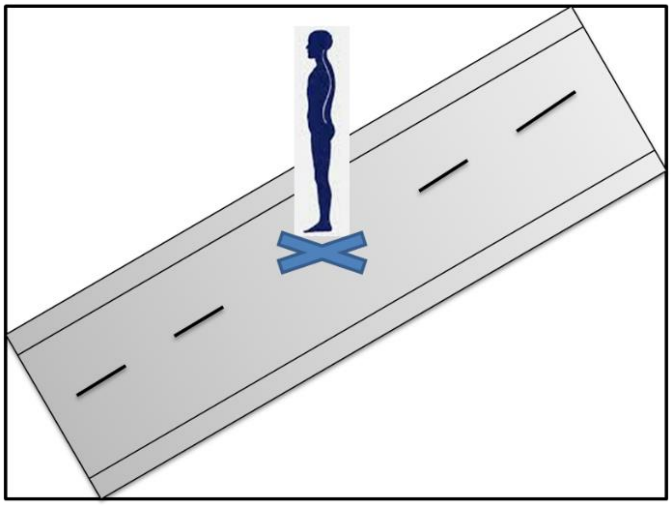


Figure 6-6: Standing (balance) test
(a) Standing test with eyes open on a flat surface using a BWM
(b) Patient position at a set point in the laboratory during the Standing (balance) test

ii. Intermittent fast walk (gait) test

This was a test of three intermittent fast walks to assess spatio-temporal parameters of gait (Figure 6-7). During the test, patients were instructed to walk as fast as they could along a 7-metre walkway without running. Following each fast walk, the patient was asked to stop walking, turn around, and then initiate the next walk. Fast walks were used instead of self-selected speed walks, as these are more sensitive than self-selected speed walks in assessing relationships with clinical scales (Fitzpatrick *et al.*, 2007).

(a)

(b)

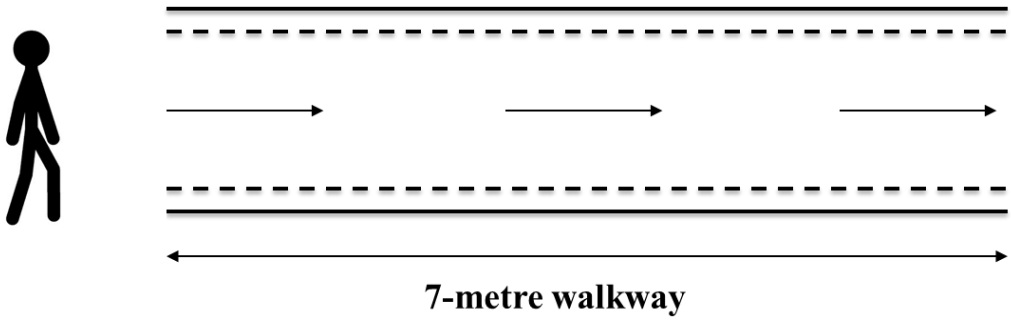


Figure 6-7: Intermittent fast walk (gait) test

(a) Intermittent fast walk test using a BWM

(b) Patient's walkway for 7 metre fast walk test

iii. 7-metre instrumented timed up and go (iTUG time) test

This was an instrumented timed up and go (iTUG) test, using a BWM, on a 7-metre walkway. Instructions were similar to the 3-metre TUG test (described in Chapter 6, Section 6.3). This test also involved 5 components listed in the 3-metre TUG test; standing up from the chair (component 1), walking for 7 meters at a regular pace (walk 1 - component 2), turning around (component 3), walking back for 7 meters to the chair (walk 2 - component 4) and sitting back in the chair (component 5). (Figure 6-8). A stopwatch was used to simultaneously record the time taken to complete the test to assess concurrent validity.

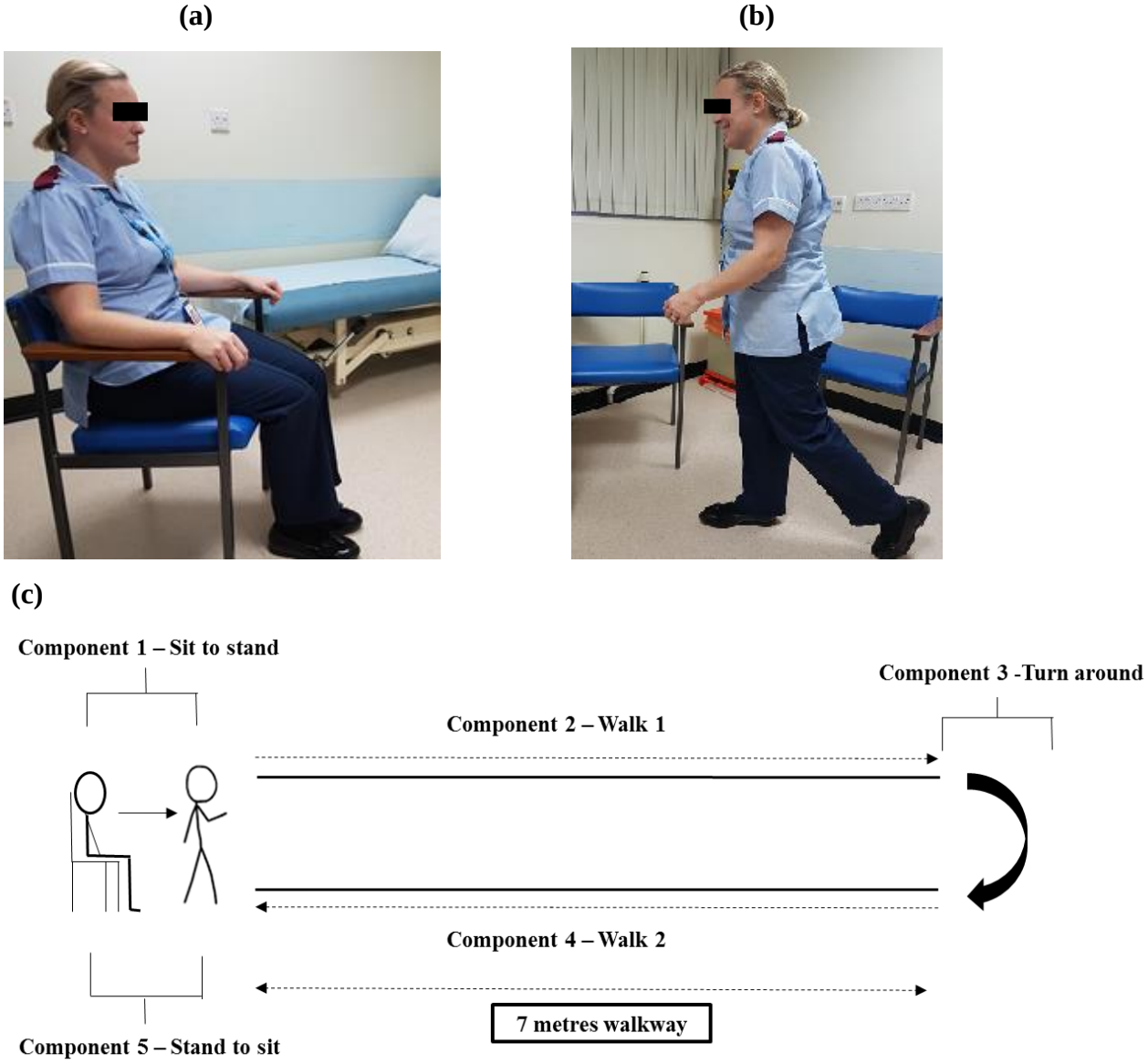


Figure 6-8: iTUG test (iTUG time)

(a) Starting position of the iTUG test using a BWM (b) Walk component of the iTUG test (c) Patient's walkway for 7 metre iTUG test.

BWM in the community environment: Ambulatory PA assessment

Following laboratory assessment, the BWM was used for monitoring of the patient's ambulatory behaviour over 7 days in their normal home or community environments (also known as the "free-living" environment). The BWM was attached to the mid-thigh as shown in Figure 6-9. Monitors in this location have been shown to give valid ambulatory PA outcomes in patients treated for lower extremity musculoskeletal tumours (Rosenbaum *et al.*, 2008b).

(a) **(b)**

Figure 6-9: BWM on mid-thigh for community testing
(a) Attachment of BWM on mid-thigh (port facing downwards) for measuring ambulatory PA
(b) Participant walking with a BWM on mid-thigh

Patients were asked to wear the BWM in their homes for 7 days and were free to perform their usual ADLs during this period (van Schooten *et al.*, 2015). The patient was given instructions about attaching the monitor on the mid-thigh of the dominant limb (Velotta *et al.*, 2011), directly against the skin, using adhesive tapes and with the port facing downwards. Patients were also asked to complete an activity diary (Appendix 15.0) for the 7 days, which included entries for the type and duration of activities and the wearability of monitors. Upon completion of the 7 day monitoring, patients returned the monitor and activity diary by post in a pre-paid envelope to the research team (Godfrey *et al.*, 2014). If monitors or forms were not received, two reminder calls were made to prompt non-responders to post back the monitors or forms.

Feedback about BWMs in the laboratory and community environment

After completion of the laboratory and community monitoring and receipt of the BWM, a letter of thanks (Appendix 16.0), and a feedback form (Appendix 17.0) were posted to patients. The latter asked questions about the acceptability of BWMs to patients and their families, in both the laboratory and community environment.

6.5 Data Processing

BWM outcomes obtained from laboratory testing

The BWM captures raw acceleration signals as a patient performs physical activities. However the raw data are not clinically meaningful. Therefore data processing of raw signals is required to obtain clinically relevant outcomes. Data processing was carried out by SF using the MATLAB® (R2012a) program working with collaborators based at the Institute of Neuroscience (IoN), Clinical Ageing Research Unit (CARU), Newcastle University.

Raw data were processed to obtain clinical outcomes in 3 steps as follows:

Step 1: Downloading of BWM raw data

Raw data (logged in a binary format) were downloaded from the BWM as Continuous Wave Accelerometer (CWA) files using the OMGUI 1.0 (open movement software informers) software.

Step 2: Activity classification (segmentation)

Next the raw acceleration data stream was classified (segmented) into specific activities of standing, fast walking and iTUG test using time stamping, and analysed in the MATLAB® (R2012a) program (Godfrey *et al.*, 2015). The accelerometer signals were then transformed into a horizontal–vertical coordinate system using the technique described by Moe-Nilssen in 1998 (Moe-Nilssen, 1998a).

Step 3: Derivation of BWM outcomes

Subsequent to activity classification, specific established algorithms (Del Din *et al.*, 2015; Godfrey *et al.*, 2015; Del Din *et al.*, 2016a) were applied to the raw data to derive balance, gait and iTUG outcomes using a MATLAB® (R2012a) program.

6.5.1 Derivation of balance outcomes

The raw acceleration signals obtained during standing in the antero-posterior (AP) and medio-lateral (ML) planes (Appendix 18.0) reflect standing balance in these directions (Mancini *et al.*, 2011; Mancini *et al.*, 2012; Del Din *et al.*, 2016a), which were of particular interest and therefore investigated in this study. We used the technique suggested by Horak 2006 and Mancini 2011 to process the raw acceleration signals to obtain balance outcomes, as this was found to be valid in healthy controls and other clinical conditions (such as Parkinson's

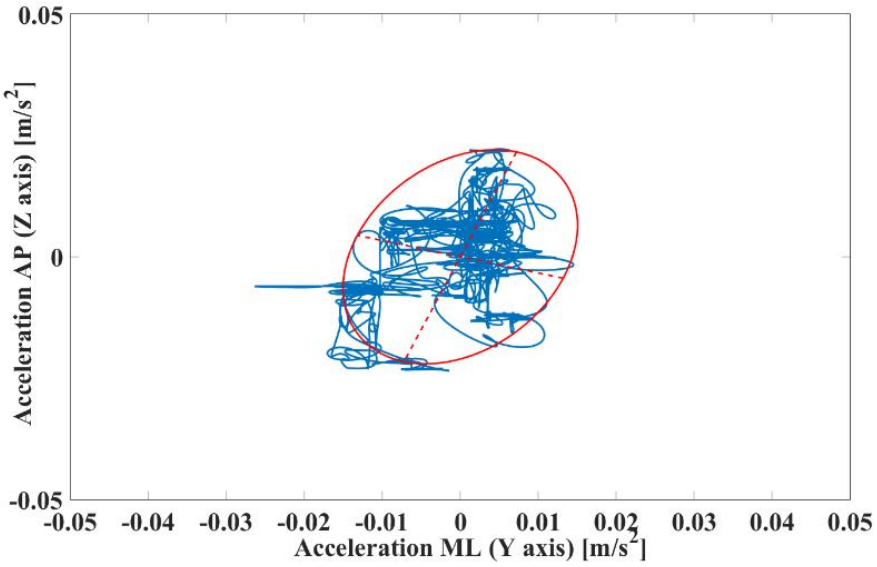
disease) (Horak, 2006; Mancini *et al.*, 2011; Del Din *et al.*, 2016a).

The following balance variables were extracted:

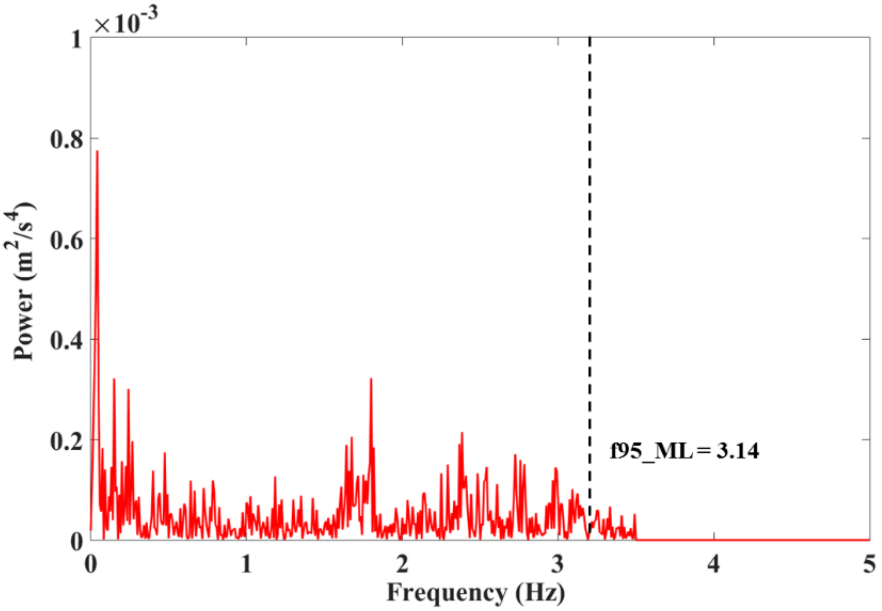
i. **Ellipsis (m^2/s^4):** Ellipsis is defined as the area of postural sway during standing, including 95 % AP and ML direction of the acceleration trajectories (Figure 6-10a). Ellipsis is calculated as the product of acceleration (in AP and ML directions), in the elliptical area of postural sway, therefore the unit of ellipsis is m^2/s^4 ($m/s^2 * m/s^2$).
ii. **Frequency (Hertz) (f95):** The frequency below which 95% of power of acceleration power spectrum is observed (f95%) (Mancini *et al.*, 2011) (Figure 6-10b). f95_AP is the frequency obtained in the antero-posterior direction, and f95_ML is the frequency in the medio-lateral direction.
iii. **Jerk (m^2/s^5):** Jerk is defined as the rate of change of acceleration signals over time, essentially a time derivative of acceleration. Jerk was found to be valid and the most discriminatory measure in other clinical conditions (Mancini *et al.*, 2011). Jerk_AP is jerk measured in the antero-posterior direction and Jerk_ML in medio-lateral direction.
iv. **Root mean square (RMS) (m/s^2):** The root mean square (RMS) of the acceleration signal represents the magnitude of acceleration. RMS was observed to be a discriminative measure in other clinical conditions (Mancini *et al.*, 2011). RMS_AP is RMS measured in the antero-posterior direction and RMS_ML in medio-lateral direction.

Balance data obtained were normalised over length of test (120 s), to compare with datasets from healthy controls.

(a)



(b)



Figures 6-10: Derivation of Balance outcomes from the Standing (balance) test in a tumour patient

(a) Ellipsis derived from an accelerometer signal: On the y–z [(ML)-(AP)] axis plane, the blue lines are the acceleration signal from BWM and red is the elliptical area which includes 95 % acceleration trajectories in the AP and ML directions. The area of sway was assessed using MATLAB® (R2012a) functions.

(b) Frequency in medio-lateral direction (f95_ML) derived from an accelerometer signal. The power spectrum is represented in red and final result below which 95% of the accelerations are present are represented by the black dotted line.

6.5.2 Derivation of gait outcomes

The process of deriving gait outcomes from the raw BWM signals (Appendix 19.0: Figure 1) obtained during the intermittent fast walk test using a L5 sensor was performed using established methods (Del Din *et al.*, 2015).

Derivatives of ICs and FCs

A continuous wavelet transform (CWT, i.e mother wavelet) of BWM data (Figure 6-11a) was used to estimate initial contact (IC)/final contact (FC) events from the vertical acceleration (Appendix 19.0: Figure 2). The point of IC, FC, temporal (step time, stride time, stance time, swing time) and spatial estimates (step length) were obtained from the raw signal using algorithms developed by McCamley (McCamley *et al.*, 2012) and Zijlstra and Hof (Zijlstra and Hof, 2003) respectively as these are specifically developed for sensors on the lower back. A zoomshot of the IC and FC events is shown in Figure 6-11b. Step velocity was calculated using step time and step length. The total steps taken were derived from the accelerometer data during the intermittent fast walk test using established methods (Del Din *et al.*, 2015).

The gait measures derived are described below:

i. Temporal characteristics

Using the sequence of IC and FC events, the left and right (opposite) events were recognised, allowing estimation of step, stride and ultimately stance and swing time (Appendix 19.0: Figure 3). Total time to complete each fast walk was termed as 'total time'. This was obtained by calculating the time between the first IC and last FC of the fast walk.

ii. Spatial characteristic

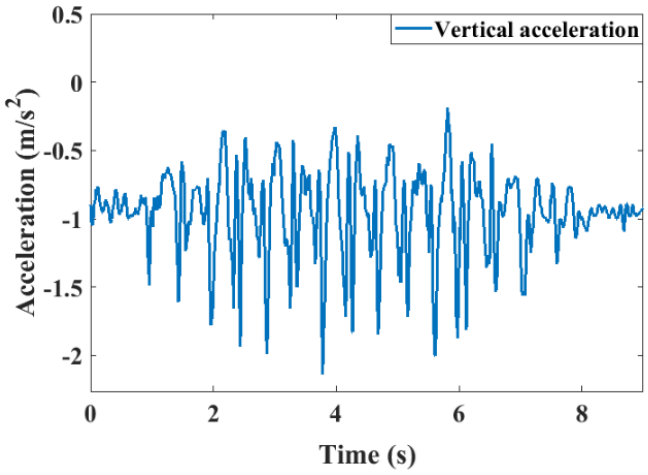
Step length was estimated using the vertical displacement of COM, using the inverted pendulum model described by Zijlstra and Hof (Zijlstra and Hof, 2003). During every single support phase of each fast walk; the vertical movement of COM has a circular trajectory in the form of an inverted pendulum (Zijlstra and Hof, 2003). If a change in height of COM (*h*) is measured and the height of sensor from the ground to L5 sensor (l) is known (reflecting the pendulum length), step length can be calculated using equation 1 (Figure 6-11c).

Equation 1: Step Length = $2\sqrt{2lh - h^2}$, h=ΔCOM, l=height of sensor

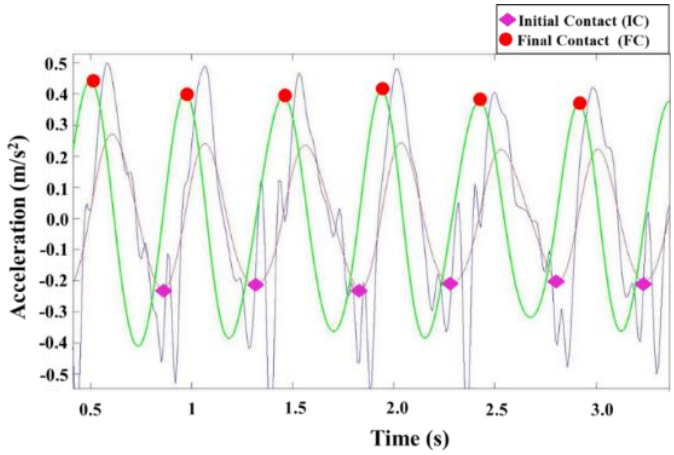
iii. Spatio-temporal characteristic

Step velocity was measured using the relationship between step time and step length (Equation 2). Equation 2: Step velocity = Step length/Step time

(a)



(b)



(c)

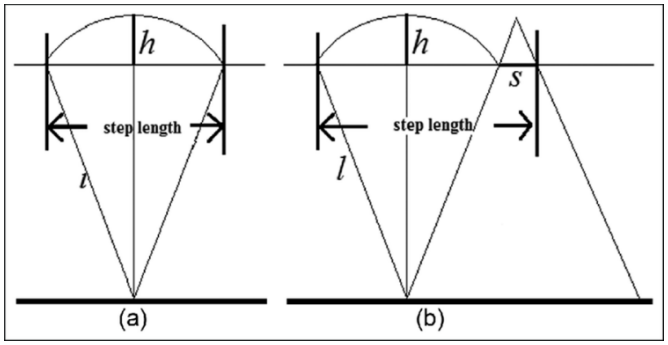


Figure 6-11: Derivation of gait outcomes from the intermittent fast walk test in a tumour patient
(a) Raw vertical acceleration signal during a fast walk trial: Represented by blue lines were used for data processing (b) Zoomshot of Initial Contact (IC) and Final Contact (FC) events: The pink diamond dots represent the initial contact and the red dots represent the final contact. (c) Inverted Pendulum Model to derive step length. The leg movement reflects an inverted pendulum model, where l denotes the leg length, h denotes the vertical displacement of L5 level, and step length is calculated. Figure taken and referenced from Improved method of step length estimation based on inverted pendulum model. By Zhao, Qi, Zhang, Boxue, Wang, Jingjing, Feng, Wenquan Jia, Wenyan, Sun, Mingui. 'International Journal of Distributed Sensor Networks', Volume 13, Issue 4 (Zhao *et al.*, 2017)

6.5.3 Derivation of iTUG outcome

Raw acceleration signals obtained from a BWM during the iTUG test (Figure 6-12) were analysed to derive the iTUG time (Figure 6-12), the main outcome of this test. The iTUG time is calculated as the time from initiation of standing from a chair to the time when the patient's back touches the backrest of the chair at the end of the task. The iTUG time was estimated from a discrete wavelet transform (DWT, utilising a fifth-order approximation and Meyer wavelet) of the signal vector magnitude (SVM) obtained from the X, Y and Z axes of the accelerometer (Bidargaddi *et al.*, 2007). This algorithm (Bidargaddi *et al.*, 2007) was mainly applied to the vertical acceleration to identify the types of transition and calculate the time between the first trough ('standing from the chair' component) to the final peak ('sitting down in the chair' component) (iTUG time) (Figure 6-12). The period of walking between the movement transitions was supressed, allowing the accurate estimation of iTUG time.

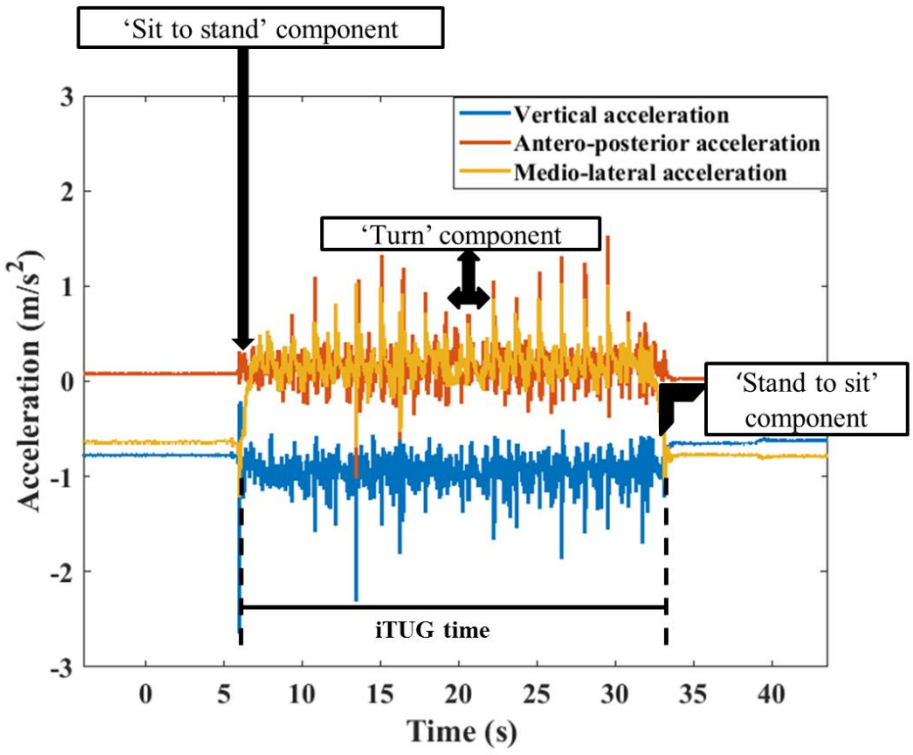


Figure 6-12: Derivation of iTUG time from the iTUG test in a tumour patient.
Method of calculation of iTUG time. Algorithm uses the vertical acceleration to detect the first crest representing 'sit to stand component' and last crest representing 'stand to sit' component. Duration taken to complete iTUG test, also termed as iTUG time was calculated as the time between two crests.

BWM outcomes obtained from community testing

6.5.4 Derivation of ambulatory PA outcomes using BWM in community

Data processing from the thigh worn monitor was conducted in 3 steps (Del Din *et al.*, 2016b), and is described below. A representation of the data processing flow is presented in Appendix 20.0)

Step 1: Downloading of BWM raw data

Once the monitor was received, data were downloaded to a computer.

Step 2: Segmentation per calendar day

Next the raw acceleration data stream (Figure 6-13) was segmented by each calendar day in MATLAB® (R2012a) program.

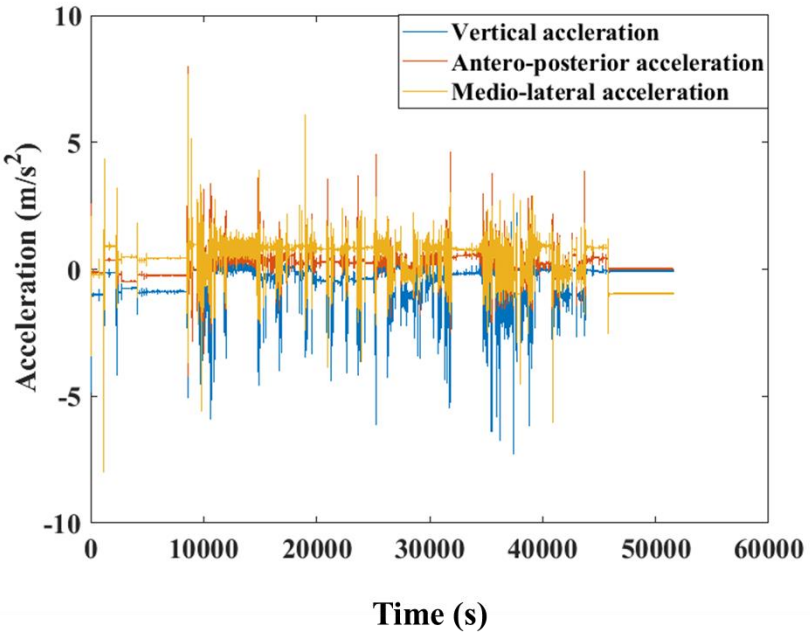


Figure 6-13: Example of a raw BWM acceleration signal during one day of physical activity from a patient who underwent LSS for a lower extremity musculoskeletal tumour .

Step 3: Derivation of BWM outcomes

For each calendar day, ambulatory bouts were extracted using the MATLAB® program (Figure 6-14). In this study, a threshold of at least three steps (which represents the minimum ambulatory bout length) was selected to define an ambulatory bout (de Bruin *et al.*, 2007; Schwenk *et al.*, 2014; Brodie *et al.*, 2015; Brodie *et al.*, 2016). The raw data were processed in phases which included importing raw data, identifying upright positions (standing/stepping

or walking) from sitting/lying (sedentary) positions and classifying standing from stepping/walking (Figure 6-14). Subsequent to identification and classification of ambulatory bouts, established algorithms (Godfrey *et al.*, 2016), were applied to derive ambulatory PA outcomes of volume, pattern and variability using MATLAB® (R2012a) program.

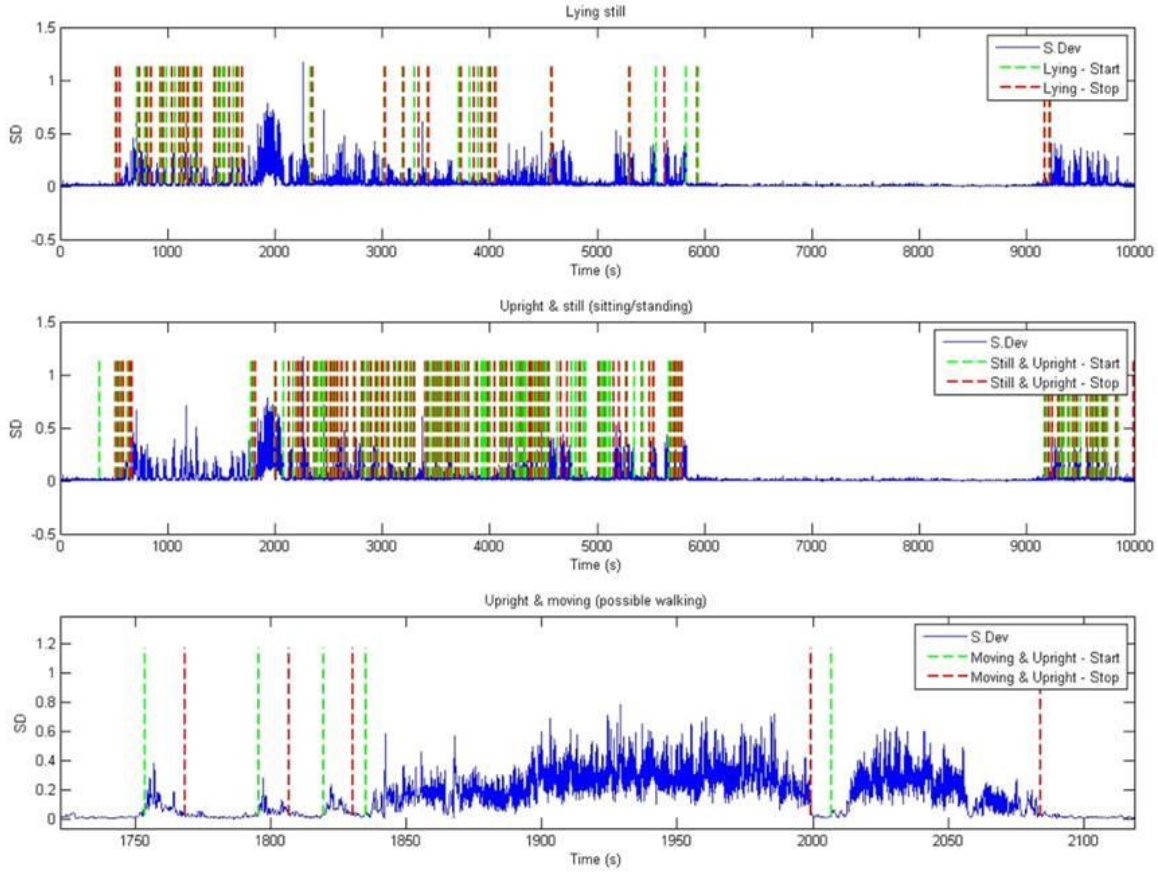


Figure 6-14: Reflection of general physical activity (PA) and ambulatory PA outcomes in the community.
Example of BWM acceleration output from a participant in the community. Segmentation of activities into lying still and upright (sitting/standing) and moving and upright - analysed in MATLAB® (R2012a) program.

Ambulatory PA outcomes derived were volume, pattern and variability of ambulatory PA and were as follows:

Volume of PA

Volume of PA is defined as the total amount of activity accumulated by an individual (Godfrey *et al.*, 2014; Del Din *et al.*, 2016d). In order to ensure consistency of measurement across all patients, volume of PA was divided by the number of days recorded.

i. Total steps/day

The total number of steps taken over a 7 day period was divided by the number of days

recorded.

ii. Total ambulatory bouts/day

The total number of ambulatory bouts (continuous periods of walking >3 steps) over 7 days was divided by the number of days recorded.

iii. Total ambulatory hours/day

The total number of hours spent walking was measured over a period of 7 days was divided by the number of days recorded.

Pattern/distribution of ambulatory bouts

i. Alpha (α)

The pattern outcomes described by the distribution of ambulatory bouts was quantified using the power law distribution exponent alpha (*α)*. Alpha (*α)* is defined as the accumulation (by bout length) of walking time (Myung, 2003). A low alpha indicates a greater accumulation of longer bouts and a high alpha of shorter bouts (Lord *et al.*, 2013).

ii. Mean walk time/bout (seconds (s))

Mean walk time/bout is defined as the mean length of walking time in seconds (s), over a 7 day period. Mean walk time/bout is calculated using the maximum likelihood ratio technique, as the data were log normally distributed, which has been described in previous literature (Godfrey *et al.*, 2014). A higher mean walk time/bout reflects higher periods of continuous walking, whereas a low mean walk time/bout reflects shorter periods of pottering around.

Variability of ambulatory bouts (measured using variability (S_2))

Variability is defined as the 'within person' variability of ambulatory bout length and examines the dispersion of ambulatory bout lengths in the same patient. This was also measured using the maximum likelihood method, as the data were log normally distributed (Godfrey *et al.*, 2014). A higher variability indicates a greater variation in the pattern of walking, whereas a lower variability indicates a smaller variation of ambulatory bouts (Lord *et al.*, 2013).

Patients with gait data ≥ 2 days were included in the final data analysis, to maximise the use of representative data (van Schooten *et al.*, 2015). An initial inspection of ambulatory PA outcomes of total steps/day of individual cases was undertaken to investigate if ambulatory activity outcomes were reflective of patient's physical status. Cases were excluded if values were distant from patient's known physical status.

6.6 General data considerations

In order to test the feasibility and validity of the BWM the following analysis approaches were used consistently in Chapter 7 and 8:

6.6.1 Approach to investigate feasibility and acceptability of using BWM

In order to investigate 'feasibility', the possibility of use of the monitors to assess function in these patients and problems encountered during assessments and data processing (including data loss) were investigated. 'Acceptability' of BWM was assessed by analysing the data from feedback forms and activity diaries on acceptability, comfort and user-friendliness of monitors.

6.6.2 Approach to investigate indicators of validity

The four indicators of validity, discriminant validity, convergent validity, concurrent validity and repeatability were investigated using steps in Table 6-2. For assessing discriminant validity, BWM outcomes from patients were compared with those of healthy controls and between major clinical groups. Furthermore, relationships were investigated between BWM measures and disease-specific clinical scales to measure convergent validity. BWM outcomes were also compared with standard methods to measure concurrent validity and consistency between repetitions of tests was investigated to measure repeatability.

Table 6-2: Steps to test indicators of validity

Types of Validity	Steps to test indicators of validity
Discriminant	BWM outcomes from patients were compared with those of healthy controls and between major clinical groups.
Convergent	Relationships were investigated between BWM measures and disease-specific clinical scales.
Concurrent	BWM outcomes were compared with standard methods.
Repeatability	BWM outcomes obtained during consecutive BWM tests were compared.

i. Discriminant validity – comparison with healthy controls and between major clinical groups

Comparison with healthy controls

BWM outcomes from patients were compared with those from healthy control data, to assess if the BWM could discriminate between these groups. Healthy control data were collected in other parallel studies including:

1. Pilot work exploring the potential use of the XSens and Open Movement Sensor Device for the Assessment of Osteoarthritis" (Osteoarthritis study) which included young healthy control data (age: 19-35 years) (for balance and gait outcomes).
2. Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation—GAIT (ICICLE-GAIT) study. This study is a collaborative project with ICICLE-PD, an incident cohort study (Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation — Parkinson's disease) which was conducted between June 2009 and December 2011 (Khoo *et al.*, 2013; Yarnall *et al.*, 2014). This included middle-aged and elderly healthy control data (age: 36-90 years) (for balance and gait outcomes).
3. Healthy control data were not available for ambulatory PA outcomes, due to methodological differences between our study and other parallel studies.

In order to ensure unbiased comparisons, the healthy controls were randomly selected from the control datasets. In addition, the same tri-axial accelerometer (AX3, Axivity), protocol and data processing techniques were followed in both studies, ascertaining robust comparisons. Prior to comparing BWM outcomes between patients and controls, these groups were examined to ensure there were no significant differences in demographics (i.e. age, gender and BMI) between groups. This was performed to eliminate the confounding effect of demographics on outcomes.

Comparison between Major clinical sub-groups

Major clinical groups, such as BT vs STS and LSS vs AMP were compared for BWM outcomes to assess if the BWM could discriminate between these groups.

ii. Convergent validity with musculoskeletal tumour disease-specific clinical scales

The relationships between BWM measures and musculoskeletal tumour disease-specific clinical scales were assessed to investigate if they were clinically sensible. For example: BWM measures were compared with MSTS, TESS, and QoL-CS. The investigation of these relationships was guided by the ICF model (Bornbaum *et al.*, 2013).

iii. **Concurrent validity with standard manual techniques**

Physical activities in clinic measured using both BWM and standard methods (stopwatch or video) were selected to assess if agreement was present between techniques.

iv. **Repeatability**

The consistency of measurement between two consecutive BWM tests, Test 1 vs Test 2 (performed under identical conditions) were assessed.

6.6.3 Approach to deal with heterogeneity of the sample and outlier cases

The major clinical groups (BT, STS, LSS or AMP) were further combined to form homogenous clinical groups of patients who had a similar tumour type, surgery type and location of tumour. The six homogenous clinical groups were as follows: patients treated with; an above knee LSS for a BT, abbreviated as 'BT above knee LSS'; below knee LSS for a BT, abbreviated as 'BT below knee LSS'; an above knee LSS for a STS, abbreviated as 'STS above knee LSS'; a below knee LSS for a STS, abbreviated as 'STS below knee LSS'; an above knee AMP for either a BT or a STS, abbreviated as 'above knee AMP'; a below knee AMP for either a BT or a STS, abbreviated as 'below knee AMP'.

For the purpose of analysis, outlier cases were defined as those with observations that are numerically distant from other data points (Grubbs, 1969). Boxplots in SPSS software version 21 (IBM Corp., Armonk, New York) were used to identify outliers. For this study purpose, we defined outliers as those with a data point situated outside the "whiskers" or fences of a boxplot (The fences are the horizontal line at the top and bottom of the box which represents minimum and maximum value, when the data points are within 1.5 times of the inter-quartile range (IQR, the difference between the 75th percentile of data and 25th percentile of data) mark from either end of the box) (Peat, 2005). Even if accurate, outlying data points may still skew the results, (Grubbs, 1969). Therefore, where appropriate, statistical tests were repeated with and without outlying data points. If tests showed statistical significant differences both with and without the outliers, the results were considered robust and trustworthy.

6.7 Statistical analysis

Statistical analysis was conducted at the orthopaedic research unit at Freeman hospital with SPSS software version 21 (IBM Corp., Armonk, New York).

The Shapiro-Wilk test for Normality was used as this study had a small sample size (below 50) (Ghasemi and Zahediasl, 2012). $p<0.05$ was defined as not normally distributed, non-parametric data for the purpose of statistical analysis. A series of non-parametric tests were mainly used to deal with outliers skewing distributions, to ensure rigour. Parametric data were expressed using means ± SDs (min – max) and non-parametric data were expressed using medians with interquartile ranges (IQR or 25th - 75th percentile of the data). Independent t-tests for parametric data and Mann-Whitney U test for non-parametric data were used to study differences in BWM outcome between patients and heathy controls, and different clinical sub-groups (to assess discriminant validity). Pearson correlations were calculated to examine relationships between parametric variables and Spearman's rho correlations for non-parametric data (to assess convergent validity). Strength of correlations were classified as, -1.0 to -0.5 or 0.5 to 1.0 as a strong correlation, -0.5 to -0.3 or 0.3 to 0.5 as a moderate correlation and -0.3 to -0.1 or 0.1 to 0.3 as a weak correlation. Significance was taken at the 0.05 level. In order to perform regression analysis, the data were first tested for assumptions. If assumptions were met, regression models were run to assess the influence of BWM measures on disease-specific clinical scales and vice-versa (to assess convergent validity). Confounding factors identified, were adjusted in the regression analysis. ICC agreement and Bland Altman analysis were used to test agreement between BWM measures and standard manual techniques used in clinics (to assess concurrent validity) and also agreement between two consecutive BWM measurements (to assess repeatability). ICC agreement were interpreted as; poor for values less than 0.5, moderate for values between 0.5 and 0.75, good for values between 0.75 and 0.9 and excellent for values >0.9 (Portney LG, 2000; Koo and Li, 2016).

6.8 Study patients

6.8.1 Characteristics of tumour patients versus healthy controls

Demographics and clinical characteristics of adult patients have been listed in Table 6-3. In the soft tissue tumour group, the diagnostic group "others" included one case of each of the following: leiomyosarcoma, myxoid liposarcoma, PNET, soft tissue chondrosarcoma, and STS (high grade)). The demographics (age, gender and BMI) of patients versus healthy controls are presented in Table 6-4 for balance outcomes dataset and in Table 6-5 for gait outcomes dataset. There were no significant differences noted in age, gender and BMI between patients and healthy controls (Table 6-4, Table 6-5).

6.8.2 Assessment of physical functioning using musculoskeletal tumour disease-specific clinical scales in adults

Of 34 patients, 29 completed the TESS questionnaire. Median TESS scores were 83.6 (IQR 62.1 – 93.8) (range 8.3 – 100.0). MSTS scores were available for 34 patients. Mean MSTS scores were 24.5 (SD 7.9) (range 5.0-35.0). 33 completed the 3-metre TUG test, median TUG time was 10.8 (IQR 8.5 – 12.7) (range, 7.9 to 32.3) s. 28 completed QoL questionnaires, and median QoL-CS total score was 7.1 (IQR 6.1 – 7.8) (range 2.7 to 9.1), QoL-CS physical sub-score 8.7 (IQR 6.5 – 9.5), QoL-CS psychological sub-score 7.3 (IQR 6.2 – 8.3), QoL-CS social sub-score 8.2 (IQR 6.2 – 8.9) and QoL-CS spiritual sub-score 4.1 (IQR 3.3 – 5.0).
Of 34 adults recruited, six were dependent on walking aids. Of the six, four used one walking stick/crutch (SC02, SC13, SC16 and SC23), one used two crutches (SC11) and one a wheelchair (SC09) for mobility.

Table 6-3: Demographic and clinical factors in patients

Demographic/Clinical factors		
Age		43 ± 20 (range from 19-89)
Gender	Male	25 (73.5%)
	Female	9 (26.5%)
Height		1.8±0.10 (1.6 – 1.9) metres
Weight		78.4 (IQR 66.0 – 101.1)(49.0 to 124.7) kilograms (kgs)
BMI		25.9 (IQR 21.7 – 31.6), [range from 19.2 to 44.1]
Type of tumour	Bone tumours	21(61.8%)
	Osteosarcoma	10 (29.4%)
	Ewing's sarcoma	1 (2.9%)
	Chondrosarcoma	6 (17.6%)
	MFH	2 (5.9%)
	Malignant pilomatrixoma	1 (2.9%)
	Others (Metastatic bone cancer)	1 (2.9%)
	Soft Tissue Sarcoma	13 (38.2%)
	Myxofibrosarcoma	4 (11.8%)
	Synovial Sarcoma	4 (11.8%)
	Others	5 (14.7%)
Location of tumour	Pelvis/Hip	4 (8.8%)
	Above Knee	19 (55.9%)
	Below knee	9 (26.5%)
	Ankle/Foot	3 (8.8%)
All LSS patients		27 (79.4%)
Type of LSS	Excision only	11 (32.4%)
	Excision+Endoprosthesis	12 (35.3%)
	Other LSS (Allograft/Autograft/Flaps)	4 (11.8%)
All AMP patients		7 (20.6%)
Level of surgery	Pelvis/Hip	7 (20.06%)
	Above Knee	17 (50%)
	Through knee	---
	Below knee	9 (26.5%)
	Ankle/Foot	1(2.9%)
Number of months post-surgery		79 (33 – 108) months

Table 6-4: Demographics (age, gender and BMI) in patients versus healthy controls for the balance outcomes dataset (p>0.05)

Group	Age in years (Median (25^{th} – 75^{th}Percentile) Mann-Whitney U test	Gender (Percentage) Pearson Chi-square		BMI (Median (25^{th} – 75^{th} Percentile) Mann-Whitney U test
		Male	Female	
Patients	43 (24 – 60)	25 (73.5%)	9 (26.5%)	25.86 (21.67 – 31.57)
Controls	62 (24 – 66)	14 (56.0%)	11(44.0%)	25.68 (23.72 – 29.43)
Comparison statistical test p-value (sig*)	0.177	0.160		0.988

* = p<0.05 indicates significant differences between groups

Table 6-5: Demographics (age, gender and BMI) in patients versus healthy controls for the gait outcomes dataset (p>0.05)

Group	Age in years (Median (25th – 75th Percentile) Mann-Whitney U test	Gender (Percentage) Pearson Chi-square		BMI (Median (25th – 75th Percentile) Mann-Whitney U test
		Male	Female	
Patients	43 (24 – 60)	25 (73.5%)	9 (26.5%)	25.86 (21.67 – 31.57)
Controls	59 (25 – 69)	17 (58.6 %)	12(41.4%)	26.72 (23.99 – 29.43)
Comparison statistical test p-value (sig*)	0.053	0.211		0.783

* = p<0.05 indicates significant differences between groups

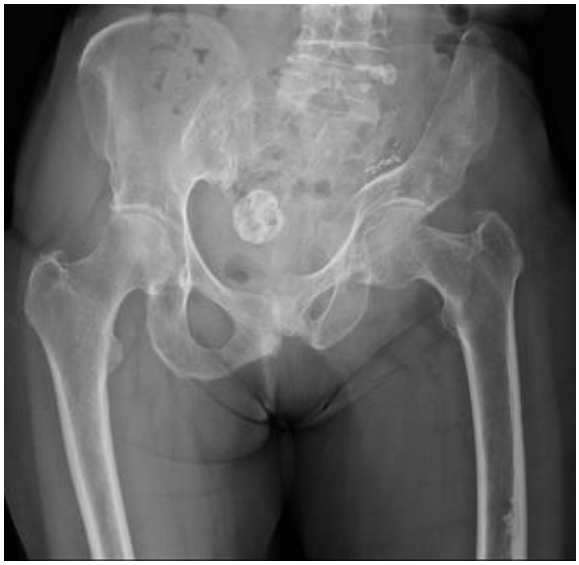
6.8.3 Radiographic images from musculoskeletal tumour patients belonging to the distinct clinical sub-groups

The radiographic images (X-rays) of different types of surgeries for a lower extremity musculoskeletal tumour are presented below in figures 6-15, 6-16, 6-17, 6-18.

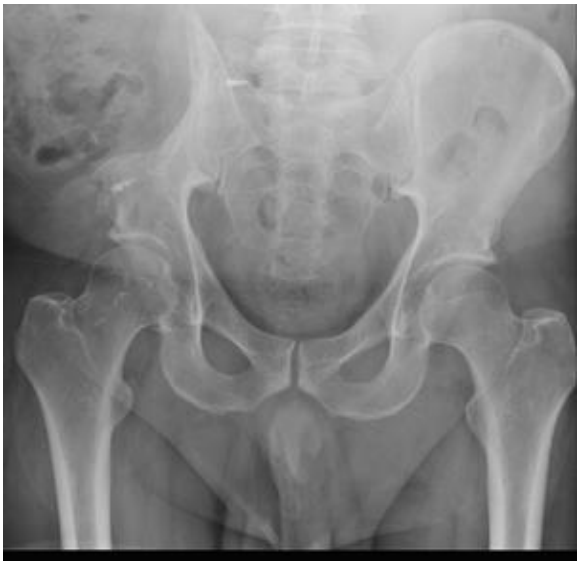
i. BT treated at pelvic/hip level: excision only cases

2 patients, SC02 (71 years old) and SC06 (43 years old) were treated with an excision for a BT at the pelvis/hip level. X-ray images of cases have been provided (Figures 6-15)

(a)



(b)



Figures 6-15: Radiographic images of BT patients treated at pelvic/hip level: Excision only cases (a) Plain X-ray of patient SC02 (71 years old) showing position of pelvis after resection of posterior iliac bone on left side. (b) Plain X-ray of patient SC06 (43 years old), showing partial resection of the iliac bone on the right side.

ii. BT treated at pelvic /hip level: excision+endoprosthesis case – proximal femoral endoprosthesis

4 patients SC08, SC16, SC18 and SC35 of age 77, 89, 19 and 23 years respectively were treated with a proximal femoral endoprosthesis for a BT at pelvis/hip level. An X-ray image of a representative case (SC08) has been provided (Figure 6-16).

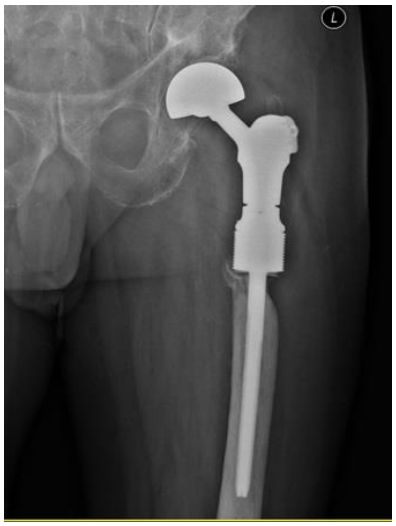


Figure 6-16: X-ray image of endoprosthesis in a patient treated with a proximal femoral endoprosthesis and hemiarthroplasty of hip for a BT at the pelvic/hip level (SC08).

iii. BT treated with a distal femoral endoprosthesis

5 patients SC04, SC11, SC20, SC26 and SC33 of age 43, 50, 51, 29, 25 years respectively were treated with a distal femoral endoprosthesis for a BT in the proximal femur. An X-ray image of a representative case (SC04) has been provided (Figure 6-17).

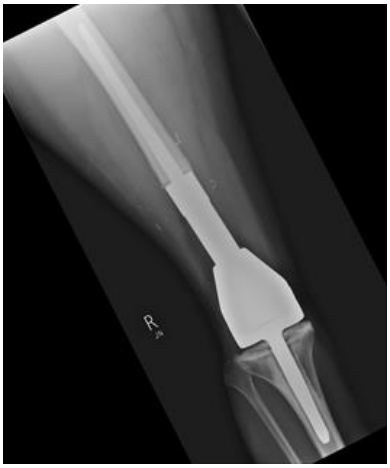


Figure 6-17: X-ray image of endoprosthesis in a patient with a BT, treated with a distal femoral endoprosthesis (SC04)

iv. BT treated with a proximal tibial endoprosthesis

3 patients SC07, SC13 and SC28 of age 19, 23 and 32 years respectively were treated with a proximal tibial endoprosthesis for a BT in the proximal tibia. An X-ray image of a representative case (SC07) has been provided (Figure 6-18).

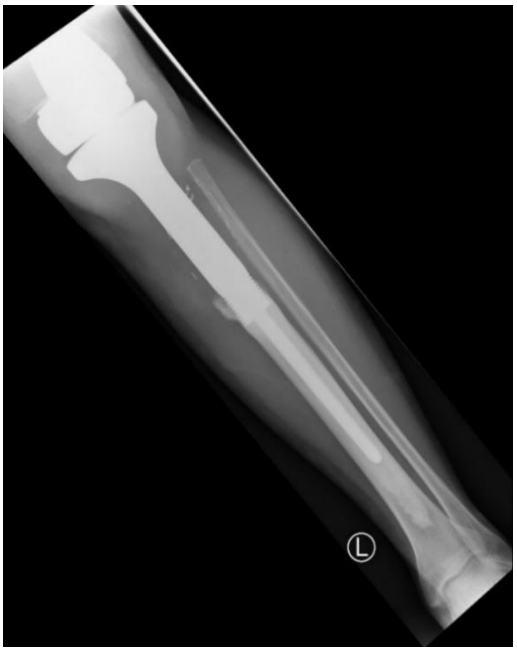


Figure 6-18: X-ray image of endoprosthesis in a patient with a BT, treated with a proximal tibial endoprosthetic reconstruction (SC07).

Chapter 7: Quantification of, gait and timed up and go outcomes using a body worn monitor in a clinic setting after treatment for lower extremity musculoskeletal tumours.

7.1 Introduction

Major surgery, chemotherapy and radiotherapy for musculoskeletal tumours in the pelvis and lower extremity have a detrimental impact on the locomotor system (Carty *et al.*, 2010a). Impaired balance and gait seen as a result (de Visser *et al.*, 2001; de Visser *et al.*, 2003) often lead to reduced mobility, lack of confidence, and loss of adaptive mechanisms to maintain the body in space, and falls (Piirtola and Era, 2006; Visser *et al.*, 2008). Yet balance and gait assessments are traditionally performed either by visual examination or subjective clinical scales (Studenski *et al.*, 2003; Ganz *et al.*, 2007). These limited assessments may not be able to detect subtle abnormalities and have the limitations of ceiling effects in highly functioning individuals (Godi *et al.*, 2013). Furthermore, the interpretation of these tests is often variable and difficult, due to their subjectivity (Godi *et al.*, 2013), hindering the standardisation of rehabilitation approaches. In recent years, therefore, objective instrumentation of tests has been advocated (Furtado *et al.*, 2016b). These include simple tests of balance, gait and timed up and go (TUG) which may give an indication of physical capability, balance and the risk of falls (Horak, 1997; Vaught, 2001; Mancini *et al.*, 2011).

The use of small portable low-cost BWMs (described in Chapter 6) to assess physical functioning has increased over recent years (Horak *et al.*, 2015b), as they overcome the inherent limitations of other clinical scales and cumbersome laboratory systems. The main advantages of using these devices for clinical assessments are: BWMs show better sensitivity to differences in test conditions than force platforms (Mayagoitia *et al.*, 2002), test-retest reliability of measures (Moe-Nilssen, 1998b) and responsiveness to change after rehabilitation treatments in comparison to performance-based tests (Horak *et al.*, 2015b). Other important advantages include the ability of BWMs to assess mild disability (Horak *et al.*, 2015b). For example: BWMs were found to be sensitive at detecting mild balance differences between patients and controls, in diabetic neuropathy (Turcot *et al.*, 2009) and untreated Parkinsonism (Mancini *et al.*, 2011). Hence these might be particularly useful in patients treated for a

musculoskeletal tumour who may only have mild abnormalities of function. BWMs are also particularly useful in providing instant biofeedback which can allow patients to focus on their impairments and improve delivery of rehabilitation interventions (Horak *et al.*, 2015b).

The human posture in upright standing demonstrates oscillatory behaviour, which is also referred to as 'postural sway'. The area of postural sway captured has been linked to the ability of the postural control system to maintain the body within limits of stability (Mancini *et al.*, 2011). However, the area of sway might not be sensitive in identifying mild balance deficits. This is because often patients with mild deficits present with a normal sway area but need to frequently correct their postural sway, by increasing the jerkiness of their sway (Mancini *et al.*, 2011). Multiple measures might therefore be needed to characterise postural sway more accurately (Prieto *et al.*, 1996; Kitabayashi *et al.*, 2003). In this study, therefore, information was also collected on the smoothness of sway, by measuring jerk, a sensitive measure of balance (Mancini *et al.*, 2011) and also the frequency of sway (Mancini *et al.*, 2012). In addition, root mean square (RMS) of acceleration was collected as it is sensitive to test conditions, age and history of falls (Moe-Nilssen and Helbostad, 2002; O'Sullivan *et al.*, 2009).

Gait is a complex phenomenon which varies between individuals, and in the same individual from step to step and in different conditions. Instrumenting gait using BWMs can rapidly quantify important temporal (step time, stance time, stride time and swing time) and spatial outcomes (step length) (Godfrey *et al.*, 2015), which have the potential to guide rehabilitation. Gait speed is also important as this is indicative of energy consumption (Schrack *et al.*, 2013). In addition, the need to remotely monitor gait in the community (Furtado *et al.*, 2016a) has also been recognised, and patients could benefit from a tool which accurately measures total steps taken and other aspects of gait. For this, we also investigated whether an accelerometer-based BWM attached to the low back counts steps accurately in the clinic. Another simple rapid valid, and reliable test 'instrumented TUG' test which provides instant information about the physical capability of an individual (Salarian *et al.*, 2010) was also collected as a part of this study.

Therefore the goal of this study was to test the feasibility and validity of a simple low-cost (approximately £100) accelerometer-based BWM system, to quantify balance, gait and iTUG outcomes in patients with musculoskeletal tumours in a clinic setting.

7.2 Feasibility and acceptability of using a BWM in a laboratory setting

Feasibility of using a BWM in the laboratory

The BWM was feasible and straightforward to use in laboratory testing, and was quick to set up. Data downloading, data processing of raw acceleration signals and derivation of BWM outcomes of balance, gait and iTUG were feasible using methods described in Chapter 6 - Section 6.4. The data processing technique was straightforward to perform taking about 10 minutes to obtain outcomes. However it took an additional 10-20 minutes to tackle problems if they were encountered during data processing.

Data loss encountered during laboratory testing and data processing

Of 34 adults who attended the laboratory assessment, one who was wheelchair bound, reported a high level of disability and was unable to participate in any of the laboratory tests, as this patient could not stand and perform transfers. The remaining 33 adult patients were able to maintain the upright standing position for up to two minutes and also completed the iTUG test successfully, leaving data from each test in 33 cases. However, three adult patients did not participate in the intermittent fast walk test due to fatigue or lack of time, leaving 30 cases for analysis.

In addition, minimal data loss was encountered during the data processing of outcomes. For example, balance outcomes were derived for all patients, except SC04 where the f95 data was lost due to the data files being corrupt. One patient's step length outcome could not be calculated as the height of the sensor from the floor was not available. For iTUG outcomes, data were obtained for all patients. This ultimately left us with 33 balance cases, 29 gait cases and 33 iTUG cases for the final analysis (Figure 7-1).

Acceptability of BWM in the laboratory

Patients found the BWM small and easy to wear in the clinic. Despite reminder calls, only 20 patients returned completed feedback forms about these devices, 19/20 (95%) patients found the BWM acceptable and comfortable in clinic. 17/20 (85%) patients found BWM user-friendly. Patients also reported that they found the whole process of clinic assessment relaxed and fascinating. Patients were hoping this would aid the technological development of methods for assessing patients treated for musculoskeletal tumours.

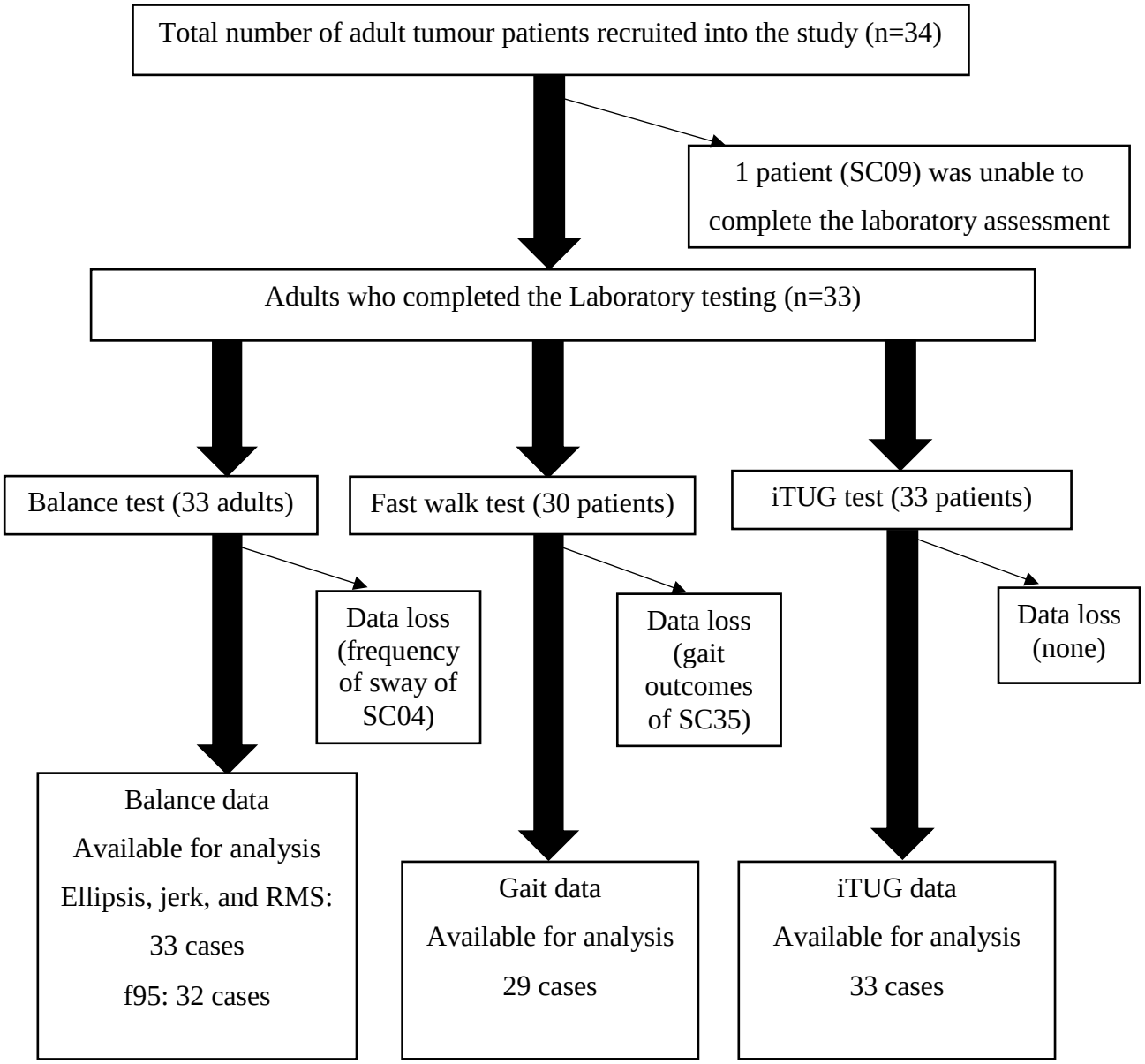


Figure 7-1: Flow chart of feasibility of BWM assessment and data loss in tumour patients

7.3 Balance

7.3.1 Summary of balance measures

A summary of balance measures described in Chapter 6 have been listed in Table 7-1.

Table 7-1: Summary of extracted balance measures

S.No	Balance measure (unit of measurement)	Outcome
1.	Ellipsis (m^2/s^4)	Area of postural sway
2.	Frequency (Hertz) (f95)	Frequency below which 95% of power of acceleration power spectrum is present.
3.	Jerk (m^2/s^5)	Rate of change of acceleration signals over time
4.	Root mean square (RMS) (m/s^2)	Magnitude of acceleration

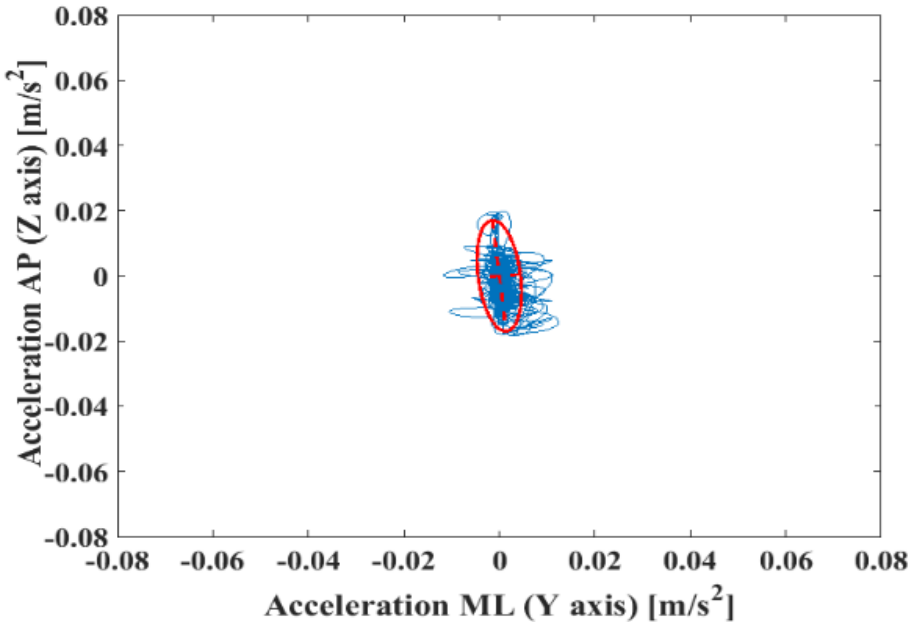
7.3.2 Examples of normal versus impaired balance outcomes

Balance outcomes are complex and therefore the interpretation of ellipsis, frequency (f95), jerk or RMS needs careful consideration in different clinical conditions (Horak, 2006; Salarian *et al.*, 2010; Mancini *et al.*, 2011; Del Din *et al.*, 2016a).

De Visser et al, 2001 showed that patients treated for lower extremity musculoskeletal tumours showed higher postural sway than healthy individuals, which represents a deterioration of balance (de Visser *et al.*, 2001). Therefore for the purposes of this study, we classified patients showing higher postural sway values compared to healthy control data as impaired, and patients with relatively low values as normal (unimpaired).

Examples of patient data are shown in Figures 7-2 and 7-3. The first patient shows low ellipsis (small area of sway) suggestive of unimpaired balance (Figure 7-2a), whereas the second patient shows high ellipsis (large area of postural sway) indicating impaired balance (Figure 7-2b). Similarly, low f95 in a patient with unimpaired balance (Figure 7-3 a), is compared with a patient with a high f95 indicating impaired outcome (Figure 7-3b).

(a)



(b)

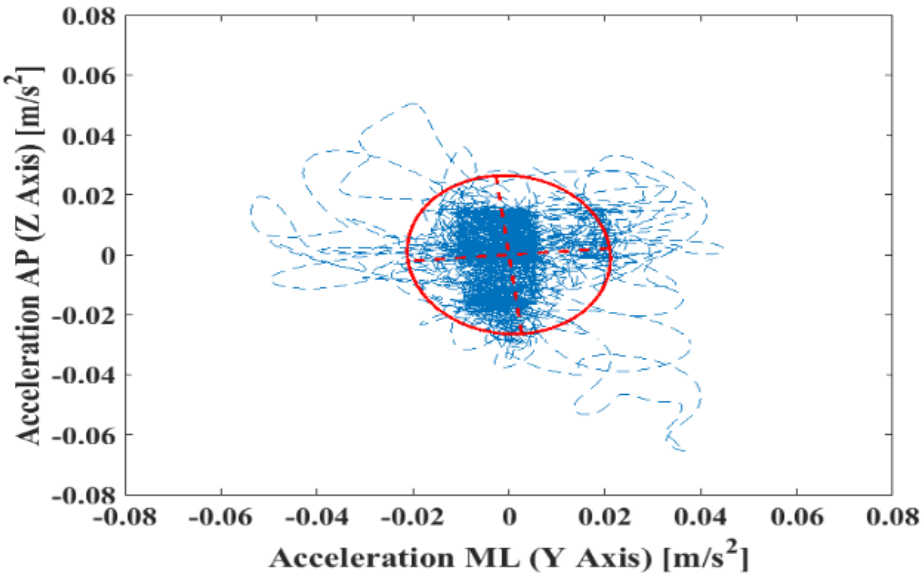
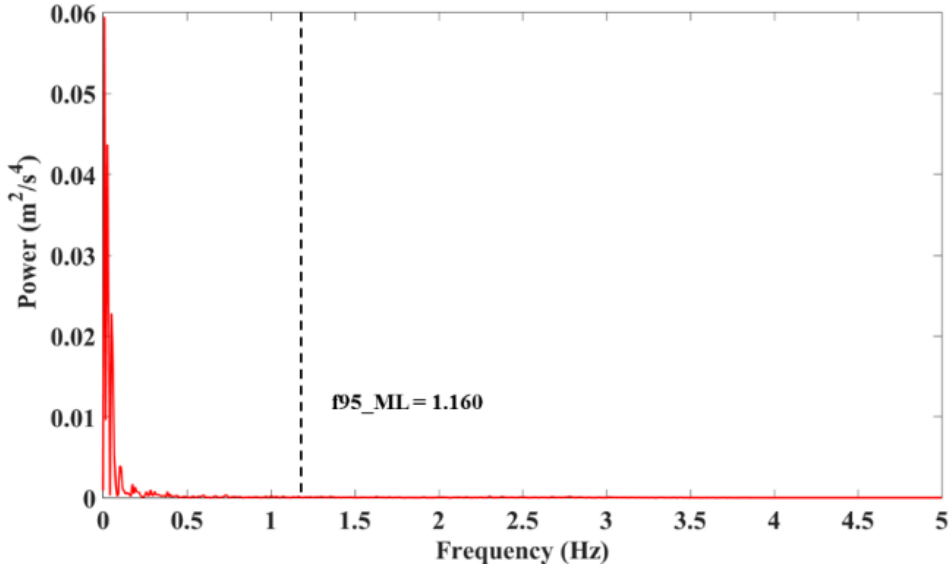


Figure 7-2: Example of normal balance outcome (low ellipsis=0.0113 m^2/s^4) vs impaired balance outcome (high ellipsis=0.5890 m^2/s^4) obtained in tumour patients.

(a) Normal outcome: 19 year old male treated with Above Knee LSS (Excision plus proximal femoral reconstruction) for a bone tumour in the thigh demonstrates a low ellipsis = 0.0113 m^2/s^4 (i.e small area of postural sway) during the standing test.

(b) Impaired outcome: 22 year old male treated with an Above Knee AMP for a bone tumour in the thigh demonstrates a high ellipsis = 0.5890 m^2/s^4 (i.e large area of postural sway) during the standing test.

(a)



(b)

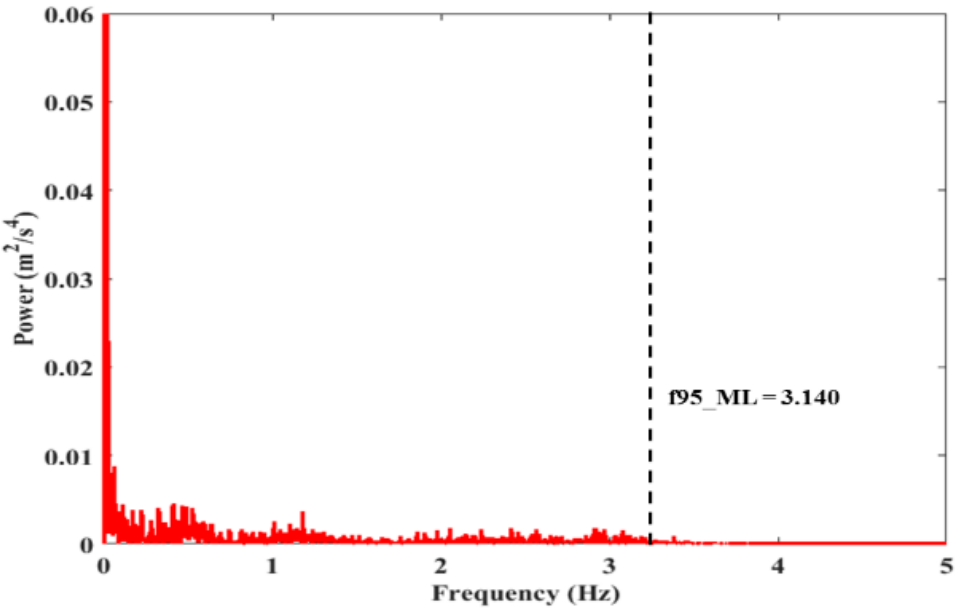


Figure 7-3: Example of normal balance outcome (low f95_ML=1.160 Hz) vs impaired balance outcome (high f95_ML== 3.140 Hz) obtained in tumour patients
(a) Normal outcome: 19 year old female in the Above Knee LSS group (Resection of adductor compartment of thigh for a soft tissue tumour) demonstrates a low frequency of sway in the ML direction = 1.160 Hz, i.e normal balance outcome during the standing test.
(b) Impaired outcome: 22 year old male treated with an Above Knee AMP for a bone tumour in the thigh demonstrates a high frequency of sway in the ML direction i.e f95_ML = 3.140 Hz i.e impaired balance outcome during standing test.

7.3.3 Balance in tumour patients vs healthy controls

Patients vs healthy controls

During the standing (balance) test, patients presented with a wide range of postural sway values compared to healthy controls (Table 7-2, Figures 7-4) and these data were not normally distributed (Appendix 21.0). There were no significant differences in age, BMI and gender distribution between patients and controls.

Patients presented with a significantly higher ellipsis, RMS and jerk (mainly in the medio-lateral direction) than healthy controls ($p<0.05$), whereas f95_AP and f95_ML were not significantly different between groups ($p>0.05$) (Table 7-2, Figures 7-4). A sub-group analysis by age revealed differences in balance control between young and middle-aged+older patients (Appendix 22.0)

A higher ellipsis and jerk in patients were seen due to cases from the 'BT above knee LSS', 'STS above knee LSS' groups and 'above knee AMP' groups (Figures 7-4 a and c). Whereas a higher RMS in patients were seen due to cases from the 'BT above knee LSS', 'STS above knee LSS' and one case each from the 'BT below knee LSS, and 'STS below knee LSS' groups (Figures 7-4b).

BT vs STS group

Although no significant differences in balance were noted between BT and STS groups ($p>0.05$), the BT group showed higher absolute RMS, jerk, f95, and a lower ellipsis when compared with patients in the STS group. A sub-group analysis on level and surgery type, showed a significantly higher RMS_ML in the 'BT above knee LSS' group (n=11) [0.0017 (0.0013 - 0.0031) m/s^2] than the 'STS above knee LSS' group (n=9) [0.0010 (0.0006 - 0.0015) m/s^2] [Mann – Whitney U test=21.000, Z= -2.171 p=0.030*).

LSS vs AMP surgery

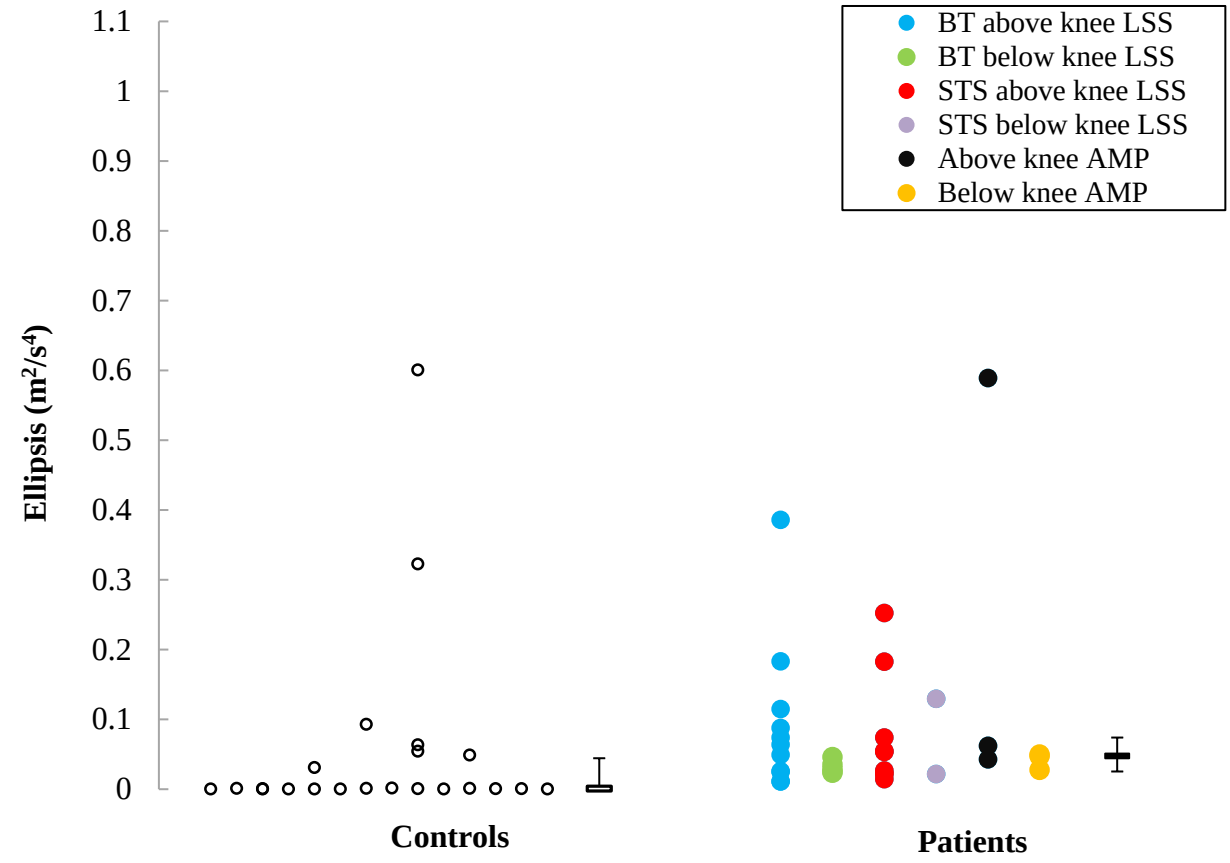
Although no significant differences in balance were noted between the LSS and AMP groups ($p>0.05$), the AMP group showed higher absolute ellipsis, jerk, jerk_AP, RMS_AP, f95_AP and f95_ML than the LSS group (Table 7-2), whereas RMS_ML, jerk_ML, were higher in the LSS group.

Table 7-2: Balance in tumour patients versus healthy controls, BT vs STS, LSS vs AMP

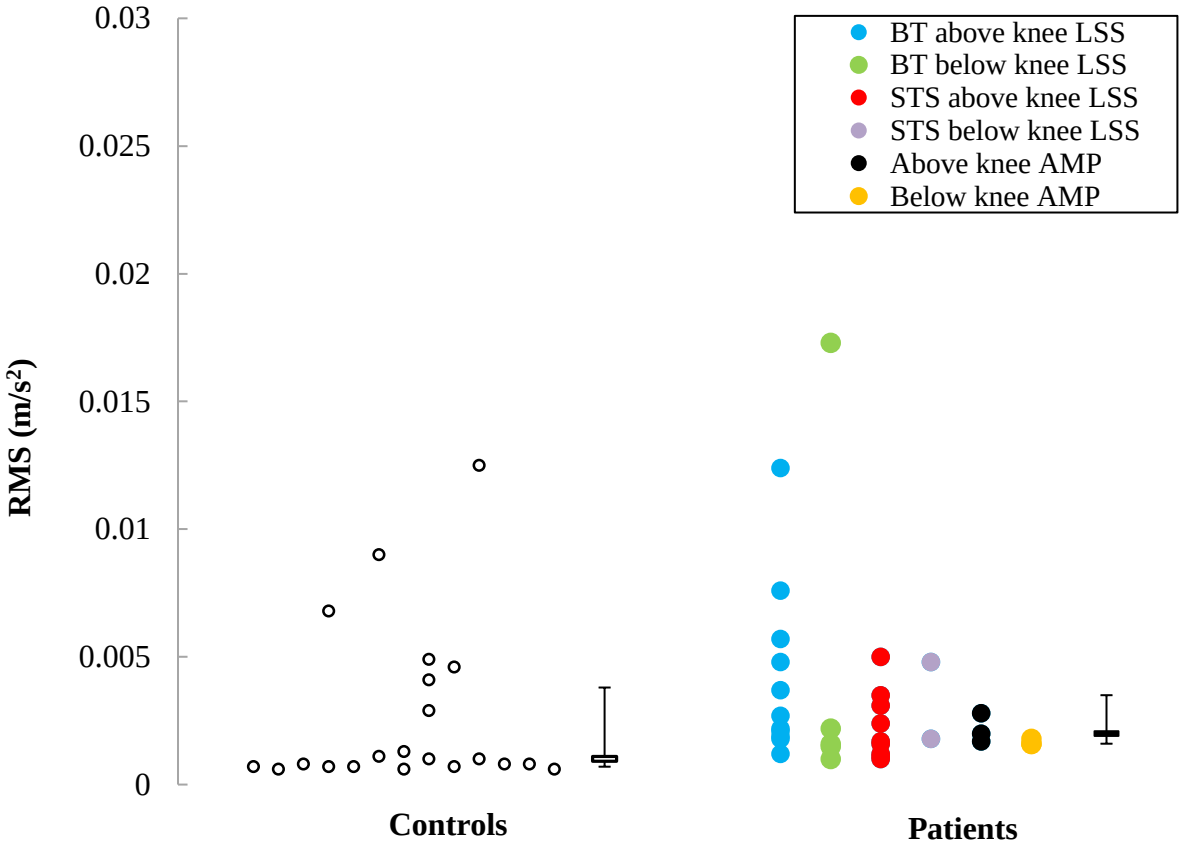
Balance measures	Healthy controls (n=22)	Tumour patients (n=33)	p-value for Patients vs controls	BT group (n=21)	STS group (n=12)	p-value for BT vs STS	LSS group (n=27)	AMP group (n=6)	p-value for LSS vs AMP
	Median Values (25^{th} – 75^{th} percentile, 1QR)	Median Values (25^{th} – 75^{th} percentile, 1QR)		Median Values (25^{th} – 75^{th} percentile, IQR)	Median Values (25^{th} – 75^{th} percentile, IQR)		Median Values (25^{th} – 75^{th} percentile, IQR)	Median Values (25^{th} – 75^{th} percentile, IQR)	
Ellipsis (m^2/s^4)	0.0007 (0.0003 - 0.0502)	0.0475 (0.0251 – 0.0810)	0.001*	0.0461 (0.0255 - 0.0808)	0.0503 (0.0220 - 0.1156)	0.881	0.0461 (0.0233 - 0.0879)	0.0486 (0.0391 – 0.1936)	0.455
RMS (m/s^2)	0.0010 (0.0007 - 0.0042)	0.0020 (0.0016 – 0.0036)	0.009*	0.0021 (0.0017 - 0.0043)	0.0018 (0.0013 - 0.0034)	0.330	0.0022 (0.0016 - 0.0048)	0.0018 (0.0016 - 0.0022)	0.362
RMS_AP (m/s^2)	0.0009 (0.0007 - 0.0051)	0.0015 (0.0013 – 0.0029)	0.034*	0.0016 (0.0013 - 0.0029)	0.0014 (0.0011 - 0.0030)	0.666	0.0015 (0.0012 - 0.0034)	0.0016 (0.0013 - 0.0019)	0.779
RMS _ML (m/s^2)	0.0004 (0.0002 - 0.0069)	0.0010 (0.0007 – 0.0017)	0.033*	0.0011 (0.0008 - 0.0018)	0.0010 (0.0006 - 0.0018)	0.329	0.0011 (0.0007 - 0.0018)	0.0009 (0.0006 - 0.0013)	0.337
Jerk (m^2/s^5)	0.0513 (0.0371 - 0.0790)	0.0910 (0.0493–0.1837)	0.004*	0.1126 (0.0575 - 0.2162)	0.0826 (0.0406 - 0.1408)	0.217	0.0870 (0.0450 - 0.2296)	0.1222 (0.0715 - 0.1571)	0.889
Jerk_AP (m^2/s^5)	0.0340 (0.0153 - 0.0483)	0.0423 (0.0239 – 0.0723)	0.073	0.0477 (0.0254 - 0.0787)	0.0382 (0.02338 - 0.0704)	0.575	0.0423 (0.0227 - 0.0751)	0.0427 (0.0348 - 0.0647)	0.815
Jerk_ML (m^2/s^5)	0.01865 (0.0163- 0.0285)	0.5180 (0.0311–0.1285)	0.0004*	0.0518 (0.0323 - 0.1379)	0.0444 (0.0261 - 0.1257)	0.500	0.0518 (0.0306 - 0.1590)	0.0499 (0.0368 –0.1168)	0.944
f95_AP (Hz)	1.2125 (0.7750 - 2.0646)	1.3500 (0.6850 – 2.0650)	0.686	1.3600 (0.7250 - 2.0650)	1.0800 (0.3150 - 2.1450)	0.572	1.2900 (0.6400 - 1.9400)	1.7200 (0.6700 - 2.1550)	0.681
f95_ML (Hz)	2.6709 (2.0562 - 2.9167)	2.6600 (2.1950 – 3.0350)	0.698	2.660 (2.3600 - 3.0350)	2.6500 (1.3750 - 3.1100)	0.697	2.6200 (2.0800 - 2.9850)	2.8300 (2.2600 -3.0800)	0.579

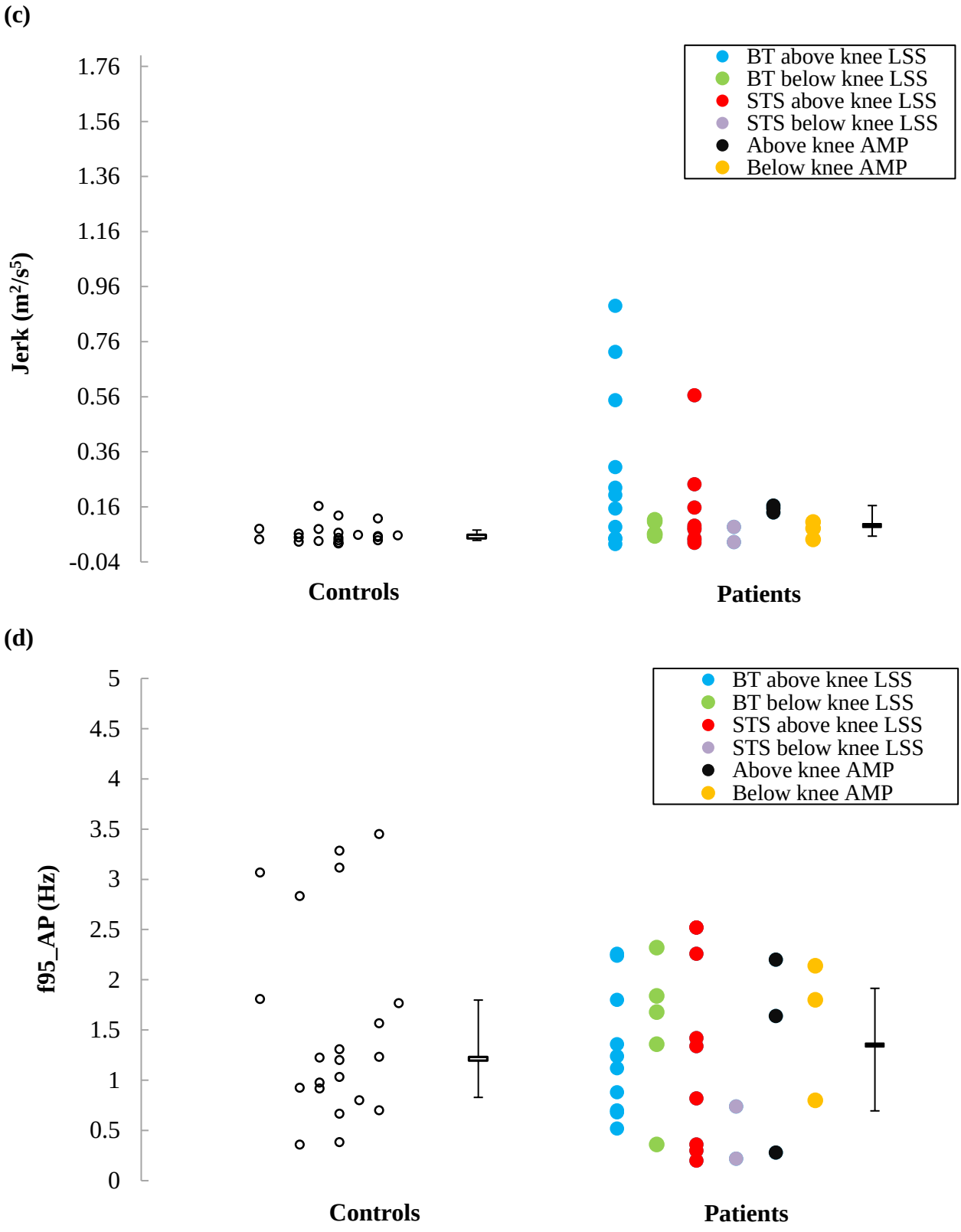
p-value – difference between groups (*=statistically significant)

(a)


BT above knee LSS
BT below knee LSS
STS above knee LSS
STS below knee LSS
Above knee AMP
Below knee AMP
Ellipsis (m²/s⁴)
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
Controls
Patients

(b)


BT above knee LSS
BT below knee LSS
STS above knee LSS
STS below knee LSS
Above knee AMP
Below knee AMP
RMS (m/s²)
0.03
0.025
0.02
0.015
0.01
0.005
0
Controls
Patients



Figures 7-4: Jitter plots to show an increased postural sway in tumour patients compared to healthy controls ($p<0.05$) (a) Significant higher ellipsis in patients compared to heathy controls (b) Significant higher RMS in patients compared to healthy controls (c) Significant higher jerk in patients compared to healthy controls (d) Higher absolute frequency of sway in AP direction in patients compared to healthy controls.

7.3.4 Balance measures versus disease-specific clinical scales

Balance vs MSTS (impairment)

Moderate negative correlations were observed between MSTS and postural sway (ellipsis, RMS, RMS_AP, RMS_ML and Jerk_AP) ($p<0.05$) (Table 7-3), indicating more impairment (low MSTS score) is related with a large area, magnitude and jerkiness of sway (poor balance).

A regression model revealed that MSTS was a negative predictor of ellipsis, indicating more impairment (low MSTS scores) predicts a large area of sway (poor balance) [Unstandardised co-efficient = -0.007, R square = 0.186, Standardised regression coefficients (Beta) = - 0.432, F-statistic = 0.012*, Significance of model p = 0.012*, n=33].

A regression model also showed that MSTS stability sub-score was a negative predictor of RMS, suggesting decreased joint stability predicts a high magnitude of sway (poor balance) [Unstandardised co-efficient = -0.001, R square = 0.215, Standardised regression coefficients (Beta) = - 0.464, F-statistic = 0.007*, Significance of model p = 0.007*, n=32].

Balance vs TESS (disability)

Moderate negative correlations were found between RMS, RMS_AP and TESS ($p<0.05$) (Table 7-3). A regression model with TESS as a dependent variable, adjusted for time since surgery, showed that RMS_AP (and not RMS) was a negative predictor of TESS ($p<0.05$) (Table 7-4). This highlights that a large magnitude of sway (poor balance) relates to and predicts high levels of disability.

Balance vs 3-metre TUG time (time taken to complete test)

Moderate positive correlations were observed between RMS and 3-metre TUG time and moderate negative correlations between f95_AP and 3-metre TUG time ($p<0.05$) (Table 7-3). This indicates a low magnitude and high frequency of sway is associated with a low 3-metre TUG time.

Balance vs QoL-CS (quality of life)

Significant negative correlations were also observed between RMS, RMS_AP and QoL-CS total score, particularly in the QoL-CS physical and social sub-domains ($p<0.05$) (Table 7-3). Regression models showed that RMS_AP was a negative predictor of QoL-CS total score,

QoL-CS physical and social sub-scores ($p<0.05$) (Table 7-4). This confirms that a large magnitude of sway (poor balance) relates to and predicts a poorer QoL, especially in physical and social domains.

In summary, MSTS total and MSTS ROM sub-scores were significant predictors of ellipsis; and MSTS stability sub-score was a significant predictor of RMS. In addition, RMS_AP was a significant predictor of TESS and QoL in patients treated for lower extremity musculoskeletal tumours.

Table 7-3: Spearman's correlations between balance and disease-specific clinical scales

Clinical scales in sarcoma	Balance Measures	All patient (n)	R value	p-value
MSTS total (impairment)	Ellipsis (m^2/s^4)	33	-0.393	0.024*
	RMS (m/s^2)	33	-0.426	0.013*
MSTS ROM	Ellipsis (m^2/s^4)	33	-0.497	0.004*
	RMS (m/s^2)	33	-0.408	0.020*
MSTS Joint Stability	Jerk_AP (m^2/s^5)	33	-0.357	0.045*
	RMS (m/s^2)	33	-0.574	0.001*
	RMS_AP (m/s^2)	33	-0.391	0.027*
	RMS_ML (m/s^2)	33	-0.361	0.042*
MSTS Functional	RMS (m/s^2)	33	-0.367	0.036*
	f95_AP (Hz)	32	-0.470	0.007*
TESS (disability)	RMS (m/s^2)	28	-0.474	0.011*
	RMS_AP (m/s^2)	28	-0.435	0.021*
3-metre TUG time (s)	f95_AP (Hz)	32	-0.470	0.007*
	RMS (m/s^2)	33	0.461	0.007*
QoL-CS total score (QoL)	RMS (m/s^2)	28	-0.453	0.015*
	RMS_AP (m/s^2)	28	-0.485	0.009*
QoL-CS Physical sub-score	RMS (m/s^2)	28	-0.493	0.008*
	RMS_AP (m/s^2)	28	-0.571	0.002*
QoL-CS Social sub-score	RMS (m/s^2)	28	-0.440	0.019*
	RMS_AP (m/s^2)	28	-0.474	0.011*

p-value – correlation between variables (*=statistically significant), n=sample number

Table 7-4: Regression Model: Balance as a significant predictor of TESS and QoL-CS total score ($p<0.05$) (n=28)

Model number	Independent variables	Unstandardised coefficients	Standardised regression coefficients (Beta)	R square	F-statistic change	Significance of regression model (p-value)	Excluded variables
Model 1: TESS as dependent variable							
	Constant	85.411		0.364	0.039*	0.003*	Age, BMI and level of tumour
	RMS_AP (m/s^2)	-7692.457	-0.455				
	Time since surgery (in months)	0.108	0.349				
Model 2: QoL-CS total score as dependent variable							
	Constant	8.295a		0.311	0.002*	0.002*	
	RMS_AP (m/s^2)	-798.252	-0.558				
Model 2: QoL-CS physical sub-score as dependent variable							Age, level of surgery and time since surgery
	Constant	10.740		0.567	0.000004*	0.000004*	
	RMS_AP (m/s^2)	-1500.789	-0.753				
Model 3: QoL-CS social sub-score as dependent variable							
	Constant	9.449		0.343	0.001*	0.001*	
	RMS_AP (m/s^2)	-1057.685	-0.586				

p-value and F-statistic (*=statistically significant). RMS_AP denotes RMS in anterior-posterior direction

7.4 Gait

7.4.1 Summary of gait measures

A summary of gait measures described in Chapter 6 has been listed in Table 7-5.

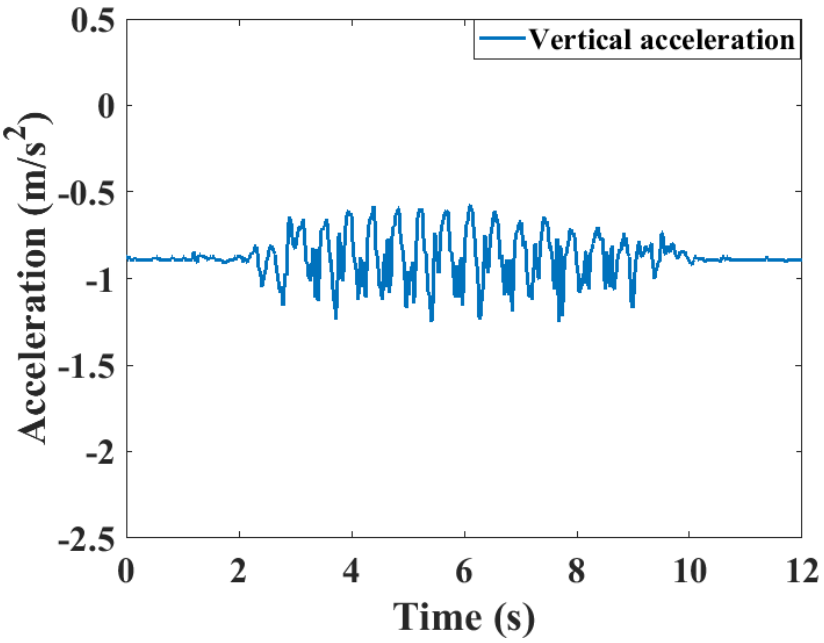
Table 7-5: Summary of extracted gait measures

S.No	Gait characteristics	Gait measure (unit of measurement)
1.	*Temporal*	Step time (s)
		Stride time (s)
		Stance time (s)
		Swing time (s)
		Total time (s)
2.	*Spatial*	Step length (m)
3.	*Spatio-temporal*	Step velocity (m/s)

7.4.2 Examples of normal versus impaired gait outcomes

Data from a patient without obvious gait deviations on video (unimpaired) shows symmetrical, sinusoidal shaped patterns of acceleration traces (Figure 7-5a) during the intermittent fast walk test, whereas data from a patient with an obviously deviated gait on video (impaired) demonstrates asymmetrical, noisy, pointed or larger acceleration waves (Figure 7-5b). Importantly, the patient with impaired gait shows higher absolute values of step time (step time = 0.801 s), compared to the patient with unimpaired gait (step time = 0.457 s).

(a)



(b)

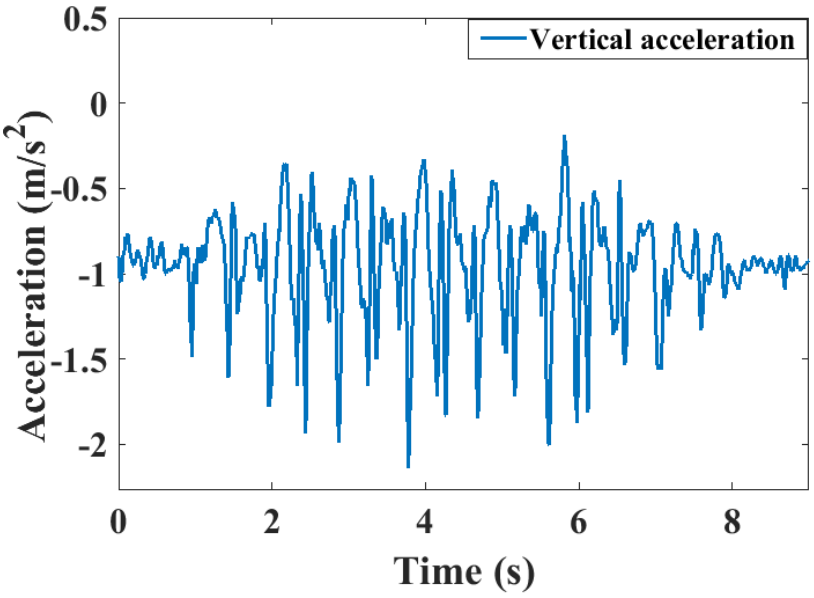


Figure 7-5: Example of normal vs impaired gait outcome in tumour patients
(a) Normal outcome: A symmetrical sinusoidal shaped acceleration signal from a LSS patient: 56 year old female treated with curettage of an intra medullary chondroid lesion right distal femoral medullary diaphysis for a bone tumour in the thigh demonstrates a near normal reference values low step time = 0.457 s). No obvious gait deviation seen in video.
(b) Impaired outcome: An asymmetrical, pointed, larger acceleration signal from an above knee amputee: 22 year old male treated with an above knee AMP for a bone tumour in the thigh demonstrates high step time = 0.801 s. Video demonstrates patient swings prosthesis to clear floor (above knee prosthesis). Patient arm swing affected. Pelvis hiked during foot clearance of right side.

7.4.3 Gait in tumour patients vs healthy controls

Patients vs healthy controls

Patients presented with a wide range of gait values compared to healthy controls (Table 7-6, Figures 7-6), and therefore besides step length and step velocity, other gait outcomes were not normally distributed (Appendix 23.0). There were no significant differences in age and BMI between patients and healthy controls and the gender distribution across groups was also identical.

Patients presented with a significantly higher step time, stance time, swing time, shorter step length and lower step velocity compared to healthy controls ($p<0.05$) (Table 7-6, Figures 7-6). A sub-group analysis by age revealed differences in gait outcomes between young and middle-aged+older patients (Appendix 24.0)

Higher temporal gait outcomes and lower step velocity in patients were seen because of cases from the 'BT above knee LSS', 'STS above knee LSS' groups and 'above knee AMP' groups (Figures 7-6 a, b, c, e). Whereas shorter step length was seen because of cases from the 'BT above knee LSS', 'STS above knee LSS' and STS below knee LSS' groups (Figure 7-6 d).

BT vs STS group

Although no significant differences in gait were noted between BT and STS groups ($p>0.05$), patients in the BT group presented with lower absolute values of stance time, stride time, swing time, higher step time, shorter step length and lower step velocity than those in the STS group. In addition, patients in the BT group took longer to complete the intermittent fast walk test (higher total time) than those in the STS group (Table 7-6).

LSS vs AMP surgery

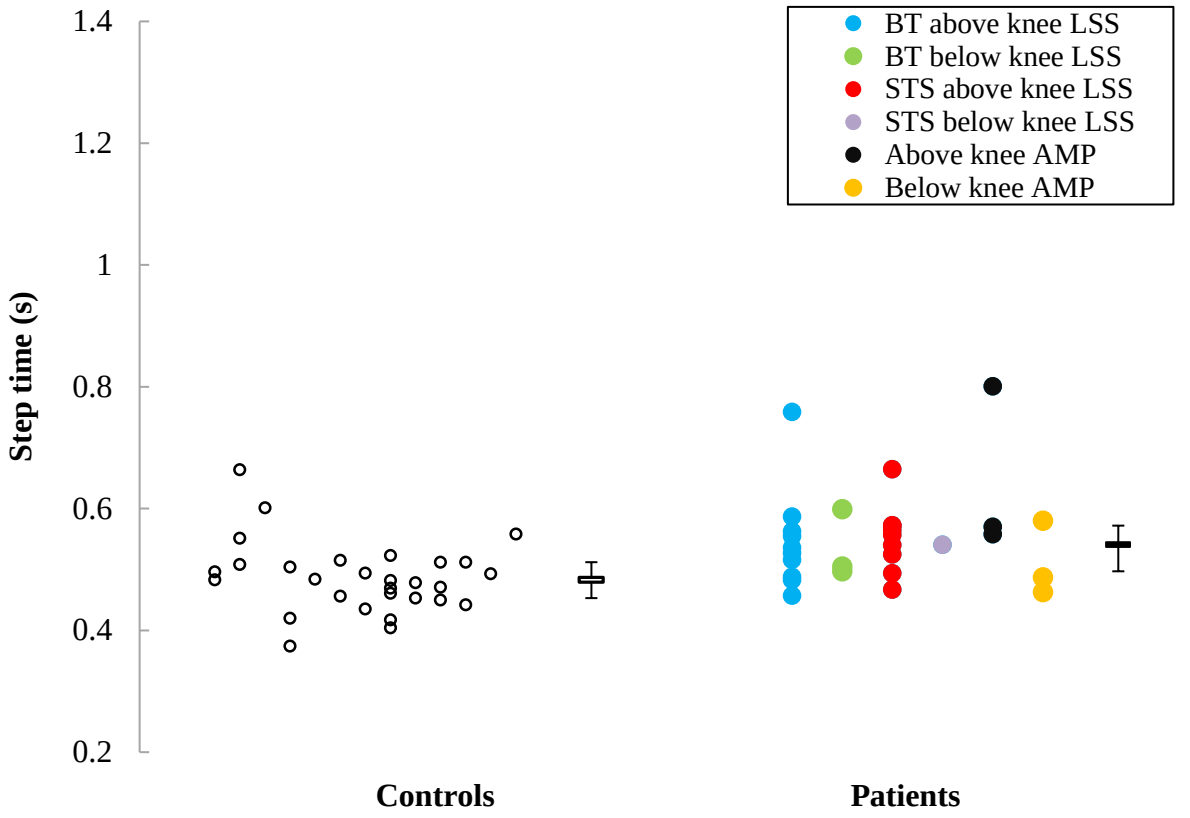
Although no significant differences in gait were noted between LSS and AMP groups ($p>0.05$), patients in the AMP group walked with higher absolute step time, stance time, stride time, swing time and total time compared to those in the LSS group. Patients in the AMP group also presented with higher values for step length and lower step velocity compared to those in the LSS group (Table 7-6).

Table 7-6: Gait in tumour patients versus healthy controls, BT vs STS, LSS vs AMP

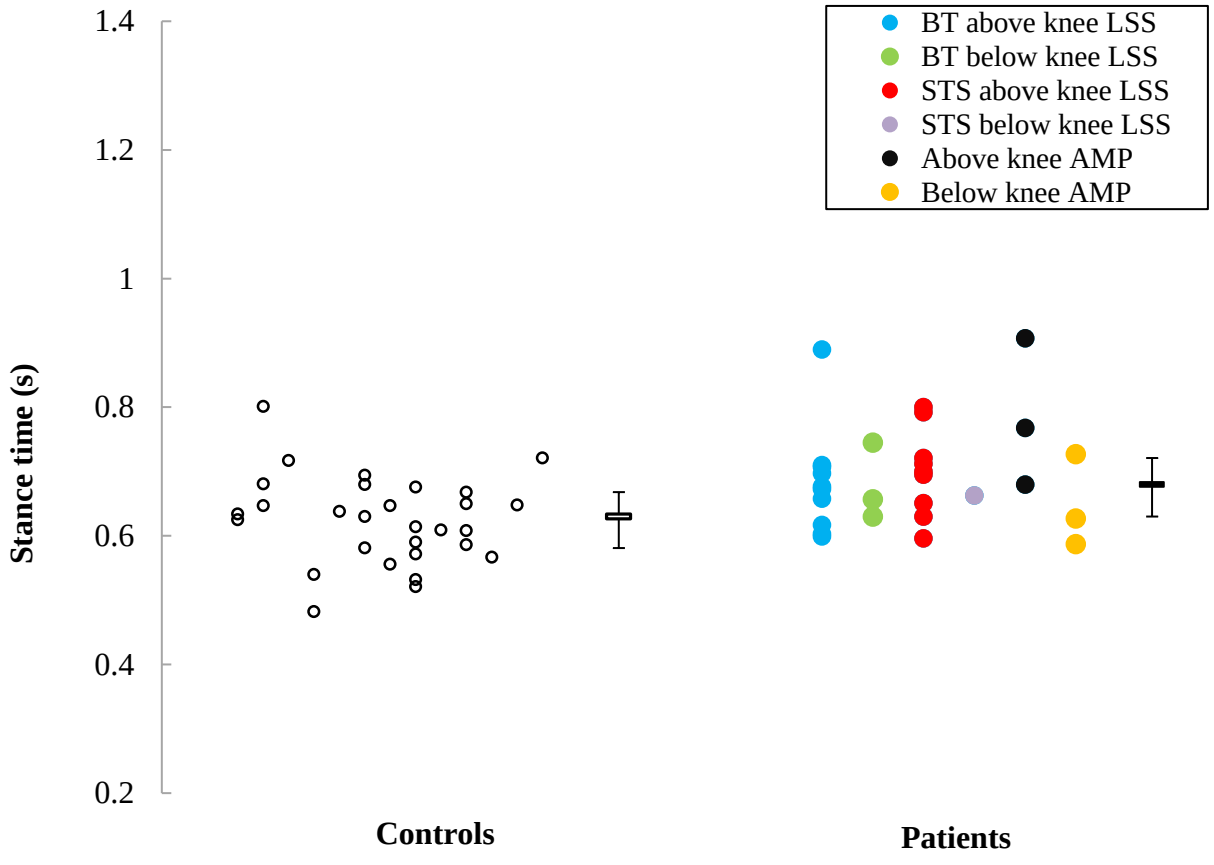
Gait measures	Healthy controls (n=29)	Tumour patients (n=29)	p-value for Patients vs controls	BT group (n=18)	STS group (n=11)	p-value for BT vs STS	LSS group (n=23)	AMP group (n=6)	p-value for LSS vs AMP
	Median/Mean Values (25^{th} – 75^{th} percentile, 1QR/Min -max)	Median/Mean Values (25^{th} – 75^{th} percentile, 1QR/Min -max)		Median/Mean Values (25^{th} – 75^{th} percentile, 1QR/Min -max)	Median/Mean Values (25^{th} – 75^{th} percentile, 1QR/Min -max)		Median/Mean Values (25^{th} – 75^{th} percentile, 1QR/Min -max)	Median/Mean Values (25^{th} – 75^{th} percentile, 1QR/Min -max)	
Step time (s)	0.483 (0.451- 0.512)	0.541 (0.496 - 0.573)	<0.001*	0.546 (0.495 - 0.582)	0.541 (0.494 - 0.572)	0.964	0.540 (0.497 - 0.572)	0.564 (0.481 - 0.635)	0.628
Stride time (s)	---	1.063 (0.986– 1.141)	---	1.062 (0.983 - 1.163)	1.073 (0.982 - 1.133)	0.928	1.060 (0.990 - 1.133)	1.109 (0.952 - 1.263)	0.686
Stance time(s)	0.630 (0.576-0.672)	0.680 (0.630 – 0.724)	0.001 *	0.679 (0.627 - 0.732)	0.695 (0.630 - 0.721)	0.946	0.677 (0.630 - 0.712)	0.704 (0.617 - 0.803)	0.628
Swing time (s)	0.328 (0.311 - 0.365)	0.383 (0.348 – 0.424)	<0.001*	0.375 (0.349 - 0.431)	0.390 (0.343 - 0.430)	0.857	0.383 (0.349 - 0.430)	0.381 (0.333 - 0.486)	0.979
Total time (s)	----	4.999 (3.999 – 5.920)	---	5.247 (4.225 - 6.126)	4.121 (3.677 - 5.275)	0.106	4.300 (3.677 - 5.949)	5.154 (4.646 - 5.952)	0.360
Step length (m)	0.695+/-0.106 (0.514 – 0.957)	0.641+/-0.092 (0.460 - 0.820)	0.044	0.638+/-0.084 (0.490 - 0.766)	0.645+/-0.109 (0.460 - 0.820)	0.837	0.630+/-0.097 (0.460 - 0.820)	0.681+/-0.067 (0.560 - 0.766)	0.252
Step velocity (m/s)	1.468 +/- 0.242 (1.078 – 2.169)	1.196+/0.189 (0.880 -1.539)	<0.001*	1.187+/-0.172 (0.913 - 1.448)	1.210+/-0.221 (0.880 - 1.539)	0.766	1.185+/-0.203 (0.880 - 1.539)	1.237+/-0.125 (1.019 - 1.380)	0.560

p-value – difference between groups (*=statistically significant)

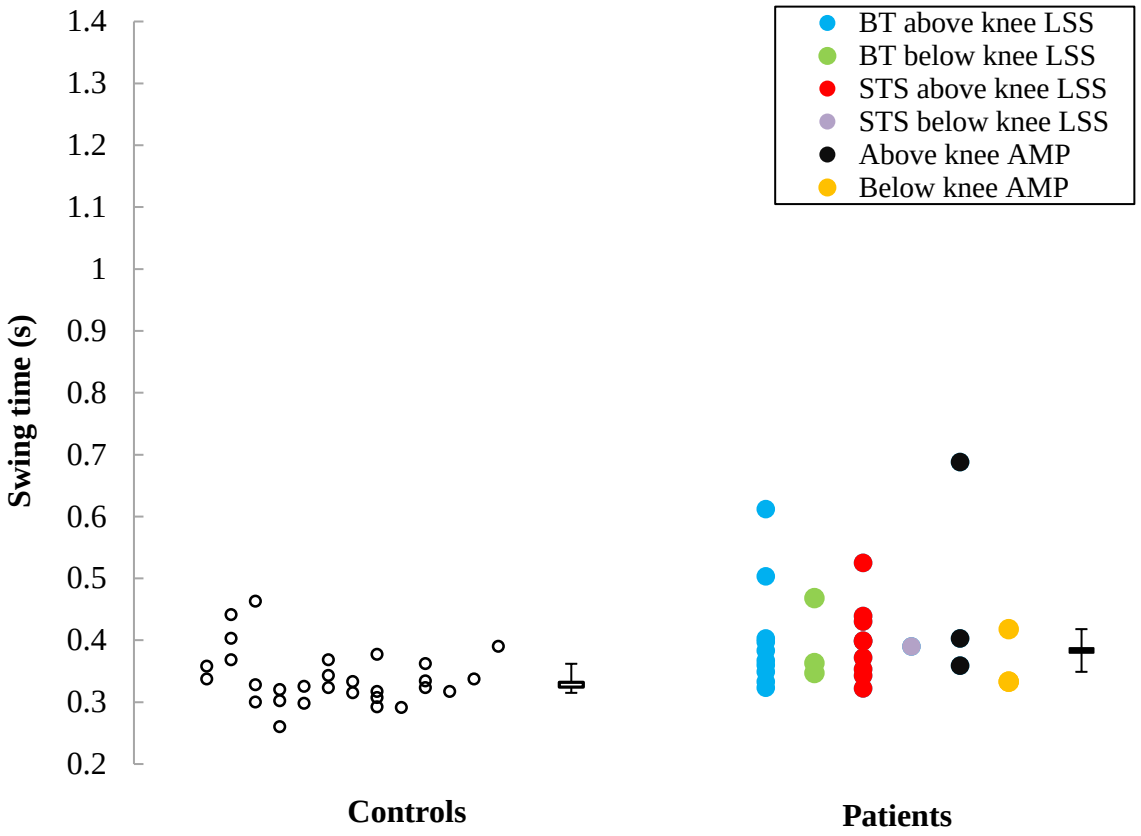
(a)


BT above knee LSS
BT below knee LSS
STS above knee LSS
STS below knee LSS
Above knee AMP
Below knee AMP
Step time (s)
1.4
1.2
1
0.8
0.6
0.4
0.2
Controls
Patients

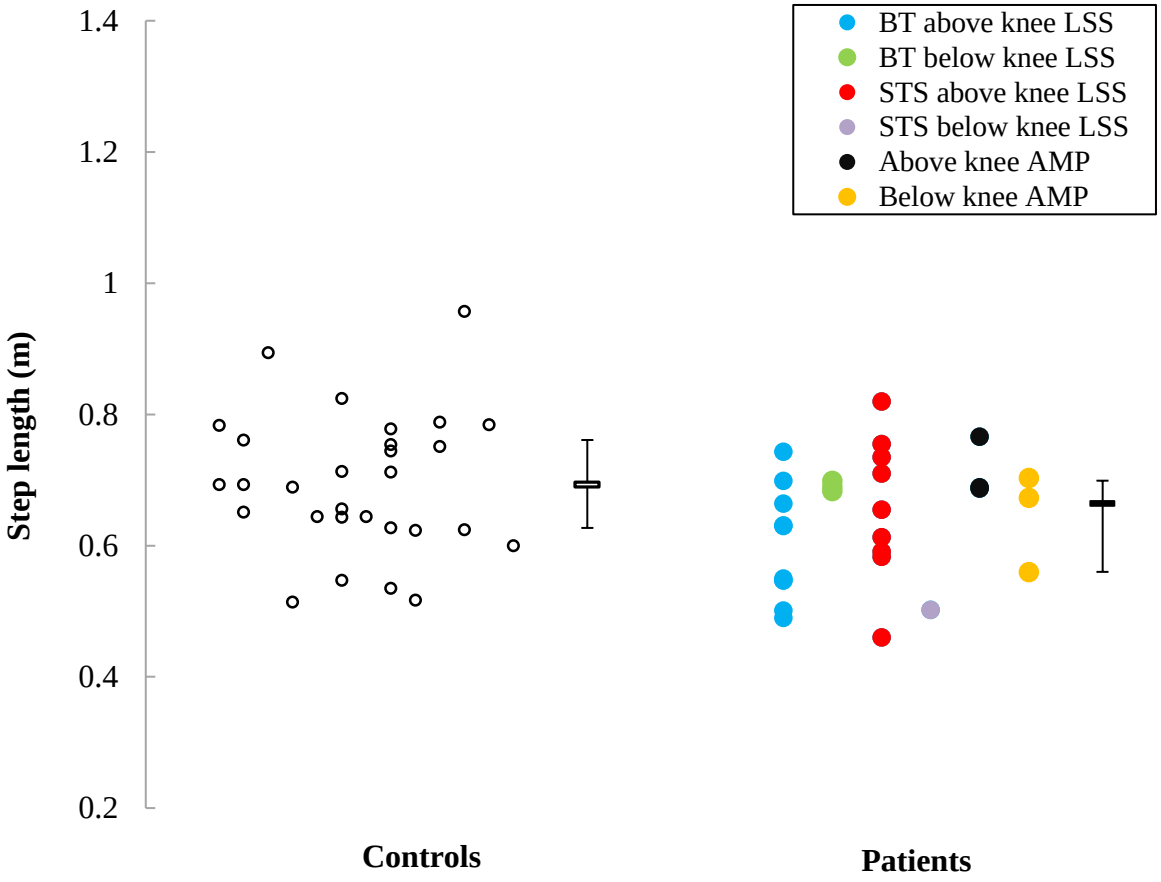
(b)


BT above knee LSS
BT below knee LSS
STS above knee LSS
STS below knee LSS
Above knee AMP
Below knee AMP
Stance time (s)
1.4
1.2
1
0.8
0.6
0.4
0.2
Controls
Patients

(c)


BT above knee LSS
BT below knee LSS
STS above knee LSS
STS below knee LSS
Above knee AMP
Below knee AMP
Swing time (s)
1.4
1.3
1.2
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
Controls
Patients

(d)


BT above knee LSS
BT below knee LSS
STS above knee LSS
STS below knee LSS
Above knee AMP
Below knee AMP
Step length (m)
1.4
1.2
1
0.8
0.6
0.4
0.2
Controls
Patients

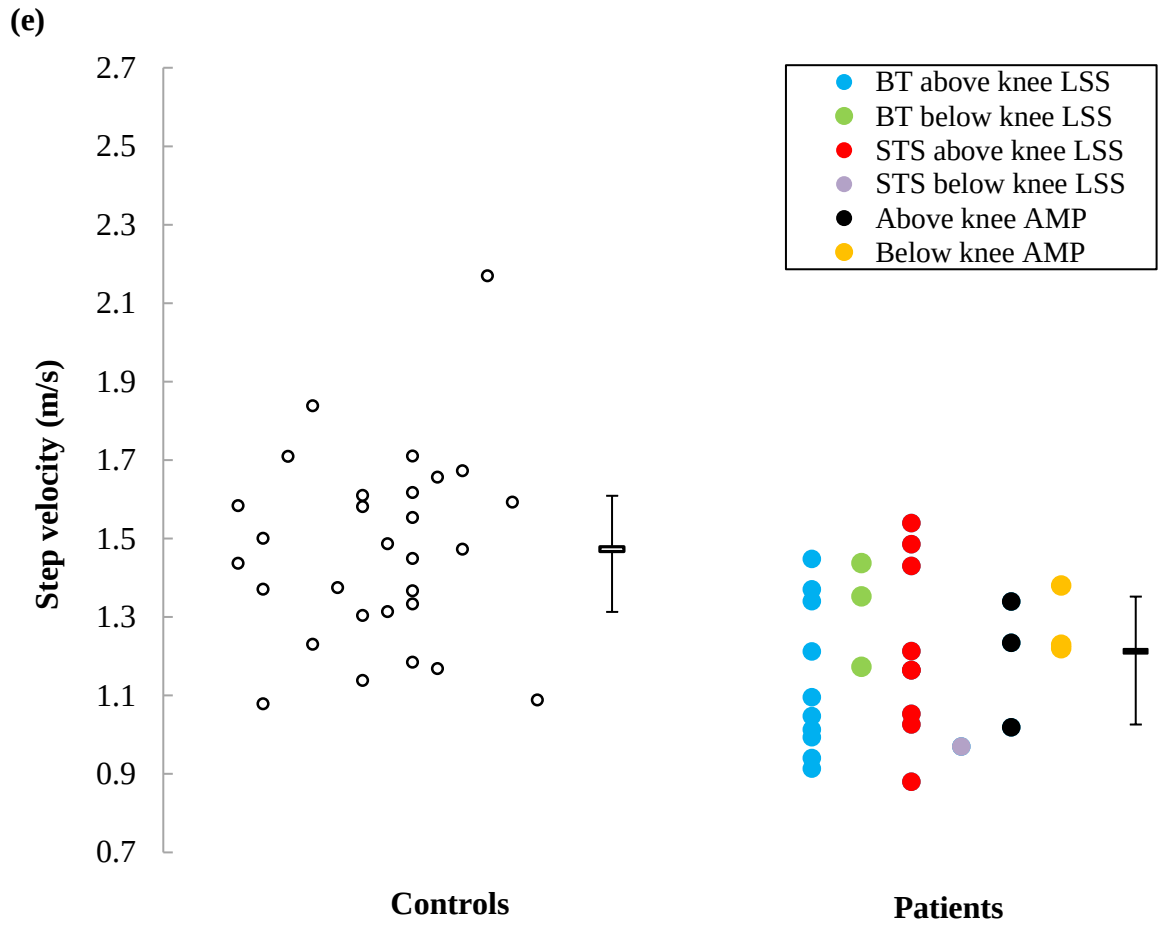


Figure 7-6: Jitter plots to show an altered gait in tumour patients compared to healthy controls ($p<0.05$). Higher step time (a), stance time (b), swing time (c) shorter step length (d) and lower step velocity (e) in patients compared to healthy controls ($p<0.05$)

7.4.4 Gait measures versus disease-specific clinical scales

Gait measures vs MSTS (impairment)

Moderate or strong negative correlations were found between MSTS and temporal gait measures of stance time, swing time and total time ($p<0.05$) (Table 7-7), indicating more impairment is associated with an increase in temporal gait outcomes (impaired gait).

A regression model showed that MSTS was a negative predictor of total time [Unstandardised co-efficient = -0.127, R square = 0.218, Standardised regression coefficients (Beta) = - 0.467, F-statistic = 0.011*, Significance of model p = 0.011* , n=29]. Another regression model revealed that MSTS was also a positive predictor of step velocity [Unstandardised co-efficient = 0.012, R square = 0.177, Standardised regression coefficients (Beta) = - 0.421, F-statistic = 0.023*, Significance of model p = 0.023*, n=29]. These findings highlight that more impairment predicts a longer time to complete the fast walk, and a lower step velocity in tumour patients.

Gait measures vs TESS (disability)

No significant correlations were found between gait measures and TESS (Table 7-7). However in regression models, adjusted for time since surgery, total time was a negative predictor of TESS ($p<0.05$) (Table 7-8). This suggests that a longer time to complete the fast walk test predicts high levels of disability.

Gait measures vs 3-metre TUG time (time taken to complete test)

Moderate or strong positive correlations were found between gait measures (swing time, total time) and 3-metre TUG time ($p<0.05$). Strong negative correlations were found between step velocity and 3-metre TUG time ($p<0.05$). This confirms that high temporal outcomes of gait and reduced step velocity predict a longer time to complete the 3-metre TUG test.

Gait measures vs QoL-CS (quality of life)

No significant correlations were found between gait and QoL-CS (Table 7-7). Regression models showed that total time was a negative predictor of QoL-CS, QoL physical and social sub-score (Table 7-8). This suggests a longer time taken to complete the fast walk test predicts a poorer QoL, especially the QoL physical and social domains.

In summary, MSTS total score was a positive predictor of step velocity and a negative predictor of total time. Furthermore, total time to complete fast walk was a positive predictor of disability (TESS) and QoL ($p<0.05$), in patients treated for lower extremity musculoskeletal tumours.

Table 7-7: Spearman's correlations between gait measures and disease-specific clinical scales

Clinical scales in sarcoma	Gait measures	All patients (n)	R value	p-value
MSTS total	*Pearson's Correlations for parametric data*			
(impairment)	Step velocity (m/s)	29	0.424	0.022*
	Spearman's Correlations for Non-parametric data			
	Total time(s)	29	-0.424	0.022*
MSTS ROM	Total time (s)	29	-0.392	0.039*
MSTS Pain	Stance time (s)	29	-0.423	0.022*
MSTS Joint Stability	Total time (s)	29	-0.522	0.004*
	Step velocity (m/s)	29	-0.587	0.001*
TESS (disability)	No significant correlations			
QoL-CS (QoL)	No significant correlations			

p-value – correlation between variables (*=statistically significant), n=sample number

Table 7-8: Regression Model: Gait measure (total time) predicting TESS and QoL (n=25)

Model number	Independent variables	Unstandardised coefficients	Standardised regression coefficients (Beta)	R square	F-statistic change	Significance of regression model (p-value)	Excluded variables
Model 1: TESS as dependent variable, model unadjusted for time since surgery							
1.	Constant	106.117		0.282	0.006*	0.006*	Age, BMI and location of tumour.
	Total time (s)	-5.360	-0.531				
Model 2: TESS as dependent variable, model adjusted for time since surgery							
2.	Constant	86.337		0.459	0.014*	0.001*	Age, BMI and location of tumour.
	Total time (s)	-3.935	-0.390				
	Time since surgery (in months)	0.140	0.444				
Model 3: QoL-CS total score as dependent variable							
3.	Constant	9.102		0.325	0.003*	0.003*	Age, time since surgery and level of tumour.
	Total time (s)	-0.477	-0.570				
Model 4: QoL-CS Physical sub-core as dependent variable							
4.	Constant	10.865		0.263	0.009*	0.009*	
	Total time (s)	-0.622	-0.513				
Model 5: QoL-CS Social sub-score as dependent variable							
5.	Constant	9.812		0.197	0.026*	0.026*	
	Total time (s)	-0.490	-0.444				

p-value and F-statistic (*=statistically significant)

7.4.5 Agreement of BWM measures with "gold standard" of video in clinic

26 cases were available for this analysis (n=26). The mean BWM step count was one step lower than the video step count. The ICC agreement showed excellent agreement between techniques (Table 7-9). Bland-Altman analysis indicated that absolute difference between BWM and video in most cases was scattered around the mean difference (Figure 7-7). However in five cases, the BWM under-estimated the step counts by 2 to 5 steps.

Table 7-9: ICC agreement for Video step count and BWM step count

Test (n=26)	Mean	SD	ICC Average measures	95% Confidence Interval		p-value
				Lower bound	Upper bound	
BWM step count	12.73 (13 steps)	2.72 (3 steps)	0.909	0.713	0.765	p<0.001*
Video step count	13.58 (14 steps)	2.50 (3 steps)				

Cronbach's Alpha = 0.932. Cronbach's Alpha Based on Standardized Items = 0.934, p-value –agreement between devices (*=statistically significant)
Two-way random effects model where both people effects and measures effects are random.
a. The estimator is the same, whether the interaction effect is present or not.
b. Type A Intraclass correlation coefficients using an absolute agreement definition.

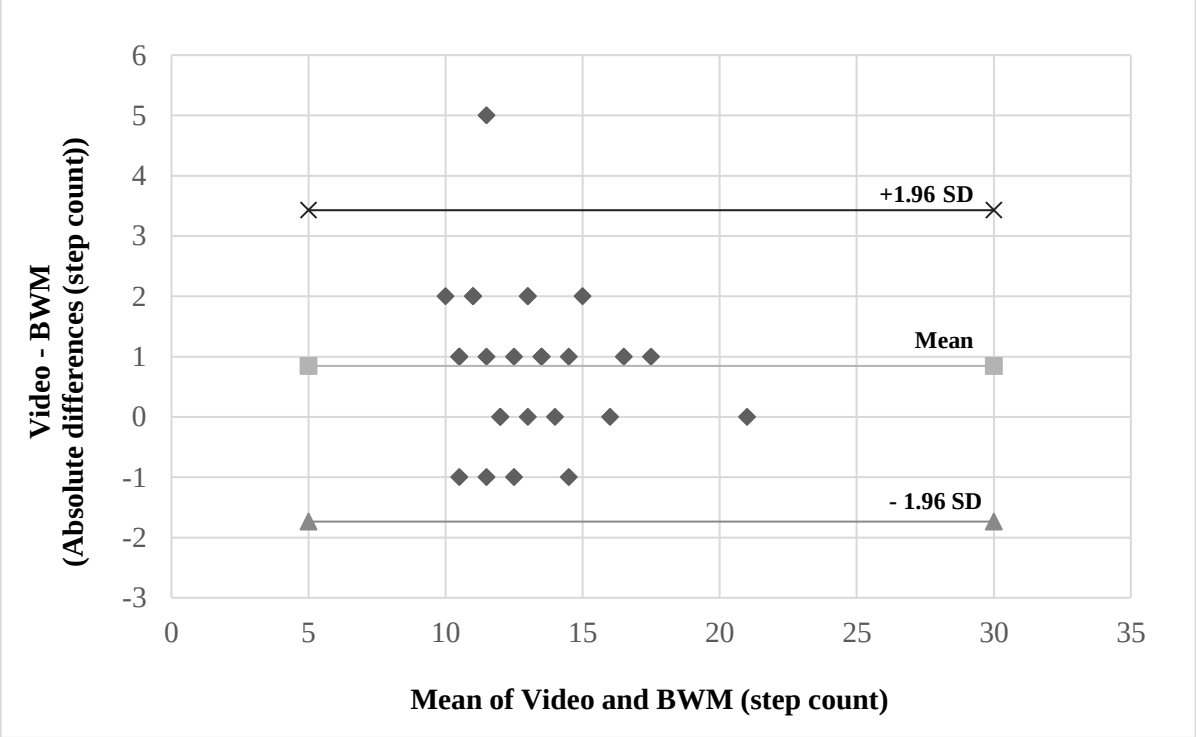


Figure 7-7: Bland-Altman Plot for Video step count vs BWM step count

7.4.6 Repeatability of BWM step count (Test 1 vs Test 2)

28 cases were available for this analysis. The mean and SD of BWM step count 1 (recorded during test 1) and BWM step count 2 (recorded during test 2) were the same, 13 steps and 3 steps respectively. The ICC agreement test showed an excellent agreement between BWM step count 1 and 2 (Table 7-10). Bland Altman indicated that absolute differences between most cases were scattered around the mean difference, which was '0', however in some cases a difference up to 3 steps was noted each ways (Figure 7-8).

Table 7-10: ICC agreement for BWM step count 1 vs BWM step count 2

Test (n=28)	Mean	SD	ICC single measures	95% Confidence Interval		p-value
				Lower bound	Upper bound	
BWM step count 1	12.75 (13 steps)	2.70 (3 steps)	0.900	0.796	0.953	p<0.001*
BWM step count 2	12.71 (13 steps)	2.59 (3 steps)				

Cronbach's Alpha = 0.946 Cronbach's Alpha Based on Standardized Items 0.946.
p-value – agreement between repetitions (*=statistically significant)
Two-way random effects model where both people effects and measures effects are random.
a. The estimator is the same, whether the interaction effect is present or not.
b. Type A Intraclass correlation coefficients using an absolute agreement definition.

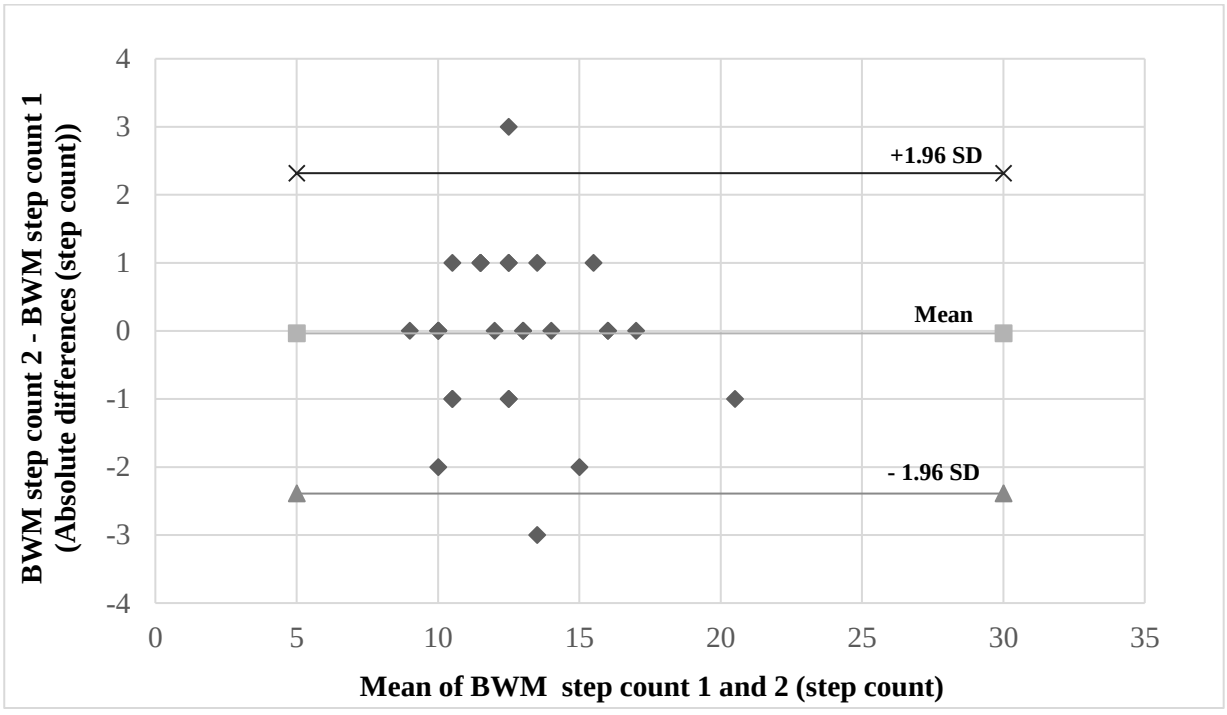


Figure 7-8: Bland-Altman Plot for BWM Step count 1 vs BWM Step count 2

7.5 iTUG time

7.5.1 Summary of iTUG measure

The iTUG measure described in Chapter 6 has been listed in Table 7-11.

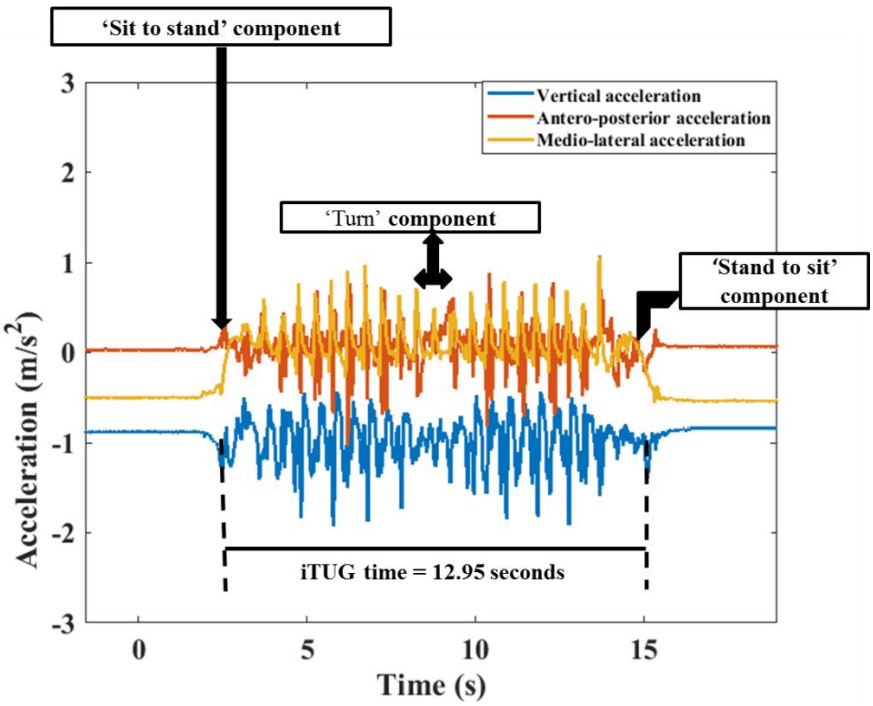
Table 7-11: Summary of iTUG measure

S.No	Type of iTUG measure	iTUG measure (unit of measurement)
1.	*Temporal*	iTUG time (s)

7.5.2 Example of normal versus impaired iTUG outcome

The interpretation of the iTUG time is similar to that of the standard TUG test, explained in Chapter 6, however the exact values are not comparable due to differences in the distance of each test. Patients with low iTUG times (i.e. patient completing the test quicker), have good function and may be classified as normal (Figure 7-9a), whereas those with high iTUG times (i.e. patients taking longer to complete the test) have poor function and can be classified as affected (Zampieri *et al.*, 2010) (Figure 7-9b).

(a)



(b)

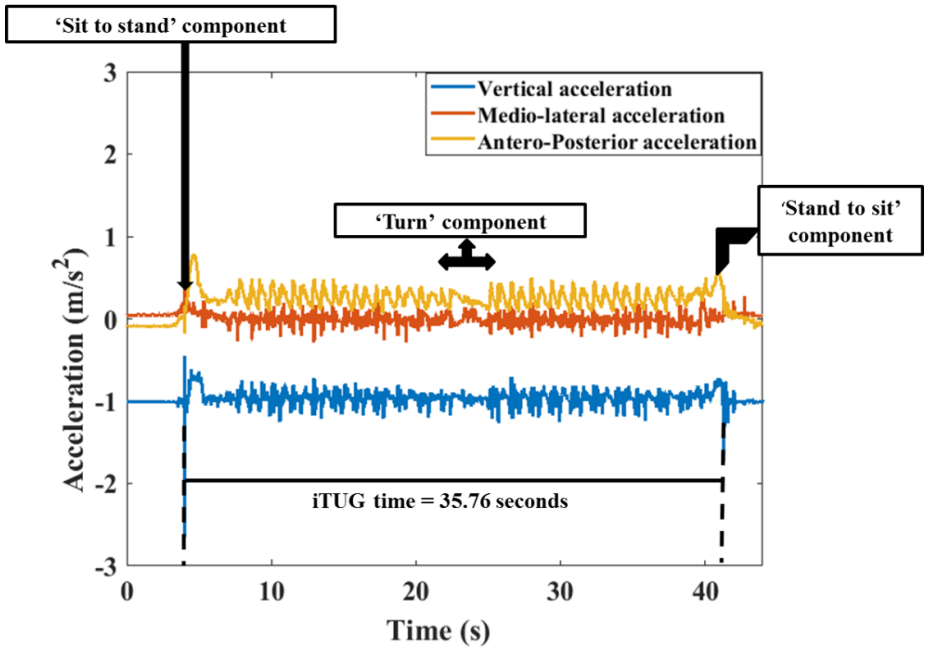


Figure 7-9: Example of normal iTUG outcome (low iTUG time) vs impaired iTUG outcome (high iTUG time) obtained in tumour patients
(a) Normal outcome: Low iTUG time in a LSS patient: 67 year old male patient treated with excision of a soft tissue tumour in the thigh demonstrates a low iTUG time = 12.95 s.
(b) Impaired outcome: High iTUG time in an elderly LSS patient: 71 year old female treated with an excision of a bone tumour in the pelvis and using an elbow crutch for ambulation demonstrates a high iTUG time = 35.76 s

7.5.3 iTUG time in tumour patients

BT vs STS group

Patients presented with a wide range of values 19.49 (16.61 – 24.28) and this data did not follow patterns of normal distribution (Appendix 25.0). Although no statistical significant differences were noted between BT and STS groups, patients in the BT group showed higher absolute values of iTUG time [19.817 (16.93 - 24.95)] than those in the STS group [17.97 (15.86 - 24.03)].

LSS vs AMP surgery

Although no statistical significant differences were noted between LSS and AMP groups, patients treated with LSS showed higher absolute values of iTUG time [19.48 (16.45 - 24.37) s] than AMP patients [19.34 (16.52 - 23.79)]. A sub-group analysis revealed that patients treated with an 'above knee AMP' took longer to complete the iTUG test [median of 22.04 s] than patients treated with a 'distal femoral endoprosthesis' [median of 16.45 s]

7.5.4 iTUG time vs disease-specific clinical scales

iTUG time vs MSTS

There was a strong negative correlation between MSTS and iTUG time ($p<0.05$) (Table 7-12). In a regression model, with iTUG time as a dependent variable, MSTS was a negative predictor of iTUG time ($p<0.05$) (Table 7-13). This suggests that more impairment is associated with and predicts longer time to complete the iTUG test, an indicator of poor physical capability.

iTUG time vs TESS

Moderate negative correlations were observed between iTUG time and TESS ($p<0.05$) (Table 7-12). In regression models, with TESS as dependent variables, iTUG was a negative predictor of TESS ($p<0.05$) (Table 7-13). This indicates that a longer time to complete the iTUG test (an indicator of poor physical capability) is associated with and predicts high levels of disability.

iTUG time vs QoL

Moderate negative correlations were observed between iTUG time and QoL-CS (Table 7-14). In regression models, with QoL-CS as dependent variables, iTUG was a negative predictor of QoL-CS total score, QoL physical and social sub-scores ($p<0.05$) (Table 7-13).

These findings confirm that a longer time to complete the iTUG test (an indicator of poor physical capability) is associated with and predicts a poor QoL, especially in physical and social domains.

Table 7-12: Spearman's rank correlations between iTUG time and TESS ($p<0.05$)

Clinical scales	iTUG	All patients (n)	R value	p value (sig *)	LSS group (n)	R value	p value (sig *)	AMP group (n)	R value	p value (sig *)
MSTS	iTUG time	33	-0.514	0.002*	27	-0.529	0.005*	6	-0.371	0.468
TESS	iTUG time	28	-0.438	0.020*	22	-0.435	0.043	6	-0.377	0.461
QoL-CS total score	iTUG time	28	-0.398	0.036*	22	-0.0446	0.038*	6	-0.232	0.658
QoL-CS Physical	iTUG time	28	-0.384	0.044*	22	-0.380	0.081	6	-0.406	0.425
QoL-CS Social	iTUG time	28	-0.494	0.008*	22	-0.412	0.057	6	-0.696	0.125

p-value – correlation between variables (*=statistically significant), n=sample number, --- = Not enough data available for test

Table 7-13: Regression model with iTUG time as dependent variable

Model number	Independent variables	Unstandardised coefficients	Standardised regression coefficients (Beta)	R square	F-statistic change	Significance of regression model (p-value)	Excluded variables
Model 1: iTUG time as dependent variable(n=33)							
1.	Constant	34.536		0.409	0.000062*	0.000062*	Age, BMI and location of tumour.
	MSTS	-0.535	-0.639				
Model 2: TESS as dependent variable(n=28)							
2.	Constant	119.800		0.407	0.000257*	0.000257*	Age, BMI and location of tumour.
	iTUG time	-1.940	-0.638				
Model 3: QoL-CS total score as dependent variable (n=28)							
3.	Constant	9.701		0.381	0.002*	0.002*	Age, time since surgery and level of tumour.
	iTUG time	-0.145	-0.590				
Model 4: QoL-CS physical sub-core as dependent variable(n=28)							
4.	Constant	12.306		0.373	0.001*	0.001*	Age and time since surgery.
	iTUG time	-0.220	-0.617				
Model 5: QoL-CS social sub-core as dependent variable(n=28)							
5.	Constant	11.218		0.334	0.002*	0.002*	Age, time since surgery and level of tumour.
	iTUG time	-0.186	-0.578				

p-value and F-statistic (*=statistically significant)

7.5.5 Agreement of BWM measures with manual standard technique "stopwatch" in clinic

Data from 33 patients were available for this analysis (n=33). The mean TUG time recorded by BWM (iTUG time) [21.18±6.23 s] was lower than the mean TUG time recorded by the stopwatch (stopwatch time) [22.88±6.93 s]. The ICC agreement showed excellent agreement between techniques (Table 7-14) and the Bland-Altman analysis confirmed that an absolute differences between BWM and stopwatch in most cases were scattered around the mean difference (Figure 7-10). Yet in few cases, the Bland-Altman showed that differences were either over-estimated or under-estimated by the BWM, and ranged from -8.52 to 11.71 s. These patients were termed as outliers. On video inspection of these outliers, it was observed that a majority were elderly patients who used their hands to support themselves from 'sit to stand' and 'stand to sit' during the iTUG test and were slow at performing the test.

Table 7-14: ICC Agreement for Stopwatch TUG time vs iTUG time

Test (n=33)	Mean	SD	ICC Average measures	95% Confidence Interval		p-value
				Lower bound	Upper bound	
iTUG time (s)	21.18	6.23	0.933	0.861	0.968	<0.001*
Stopwatch TUG time (s)	22.28	6.93				

Cronbach's Alpha = 0.939, Cronbach's Alpha Based on Standardized Items = 0.941, p-value – agreement between devices (*=statistically significant)
Two-way random effects model where both people effects and measures effects are random.
a. The estimator is the same, whether the interaction effect is present or not.
b. Type A Intraclass correlation coefficients using an absolute agreement definition.

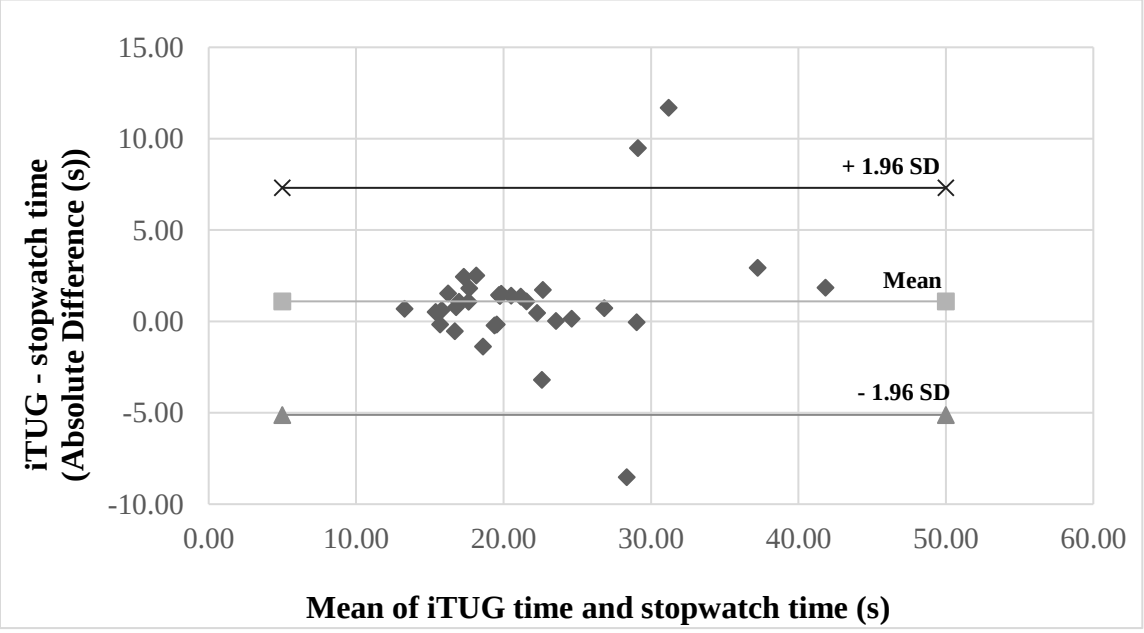


Figure 7-10: Bland-Altman Plot for Stopwatch TUG time vs iTUG time

7.5.6 Repeatability of iTUG time (Test 1 vs Test 2)

Data from 32 patients were available for this analysis (n=37). Patients completed the second iTUG test (iTUG time 2) [20.92±6.04 s] faster than the first iTUG test (iTUG time 1) [22.04±6.66 s] (Table 7-15, Figure 7-11). The mean absolute differences between iTUG time 1 and iTUG time 2 was 1.26±1.70 s (and a range of -4.59 to 3.73 s). The ICC agreement test showed an excellent agreement between iTUG time 1 and iTUG time 2 (Table 7-15). Bland-Altman analysis indicated that absolute differences between most cases were scattered around the mean difference, however in few cases large differences were seen (upto a difference of 6 s) (Figure 7-11).

Table 7-15: iTUG time 1 (Test 1) vs iTUG time 2 (Test 2)

Test (n=32)	Mean	SD	ICC Single measures	95% Confidence Interval		p-value
				Lower bound	Upper bound	
iTUG time 1 (s)	21.97	6.85				
iTUG time 2 (s)	20.85	6.13	0.945[a]	0.845	0.977	<0.001*

Cronbach's Alpha = 0.979, Cronbach's Alpha Based on Standardized Items = 0.982, p-value – agreement between repetitions (*=statistically significant)
Two-way random effects model where both people effects and measures effects are random.
a. The estimator is the same, whether the interaction effect is present or not.
b. Type A Intraclass correlation coefficients using an absolute agreement definition.

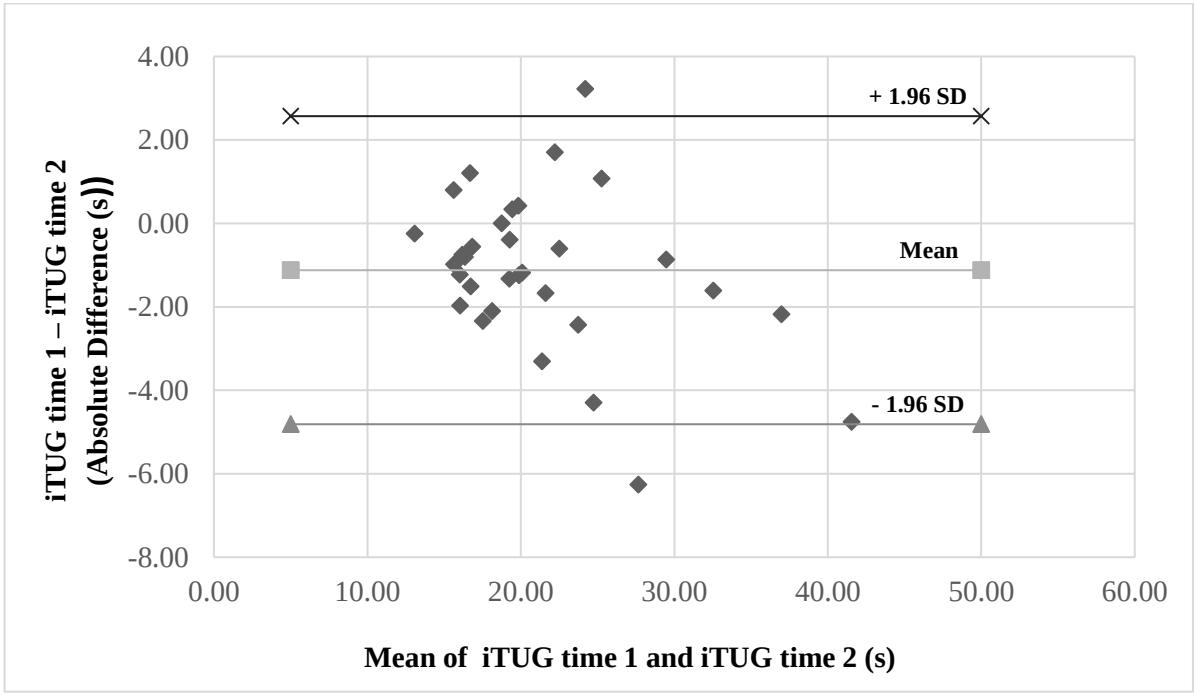


Figure 7-11: Bland-Altman Plot for iTUG time 1 (Test 1) vs iTUG time 2 (Test 2)

7.6 Discussion

This is the first study to investigate balance, fast walk and iTUG outcomes using an accelerometer-based BWM in patients treated for lower extremity musculoskeletal tumours. The study provides a valuable insight into the feasibility of quantifying balance, gait and iTUG outcomes using a BWM, acceptability of the BWM, and about different aspects of validity (comparison against healthy controls, relationships with established measures, agreement with manual techniques in clinic and repeatability). The clinical implications of this work have been discussed in individual sections.

7.6.1 Feasibility, data loss and acceptability of a BWM in the laboratory

We found that a BWM was feasible to use and quick to set up for assessment in patients treated for lower extremity musculoskeletal tumours. It was feasible to capture postural control measures characterized by four relatively independent characteristics: area, magnitude, frequency and jerk of sway; rhythm and pace domains of gait and iTUG time. The feasibility of obtaining outcomes in a short time scale, minimal data loss, acceptability, comfort in the clinic and user-friendliness of the device supports the clinical usefulness of the device and ease of rolling it out into clinical practice.

7.6.2 Balance, gait and iTUG outcomes in tumour patients vs healthy controls

In our study, tumour patients presented with a wide range of balance, gait and iTUG values, reflecting the heterogeneity of the clinical group. Altered balance and gait in patients compared to healthy individuals could be explained due to the impact of their tumour treatment including surgery.

Balance

The postural sway variables which were significantly higher in tumour patients compared to healthy controls were: ellipsis, jerk and RMS; therefore these were the most sensitive measures in detecting differences between patients and controls. In patients undergoing surgery for sarcoma in the lower extremity, losses in the sensory (Wickramasinghe *et al.*, 2014), motor (Davis, 1999) and proprioceptive (Fukumothi *et al.*, 2016) systems could explain alterations in standing balance, compared to controls. Poor sensory input from the peripheral muscles and nerves, may not be relayed to the central nervous systems (CNS) in a timely manner. Because of this, an appropriate response may not be formulated by the CNS, to activate postural muscle groups to align the head, eye, trunk, and position or movements of the limb to maintain balance and posture (Horak, 1987; Horak, 1997; Horak, 2006).

Our study findings however, contradicted a previous study which showed that patients completing a standing balance test on a force platform with eyes open were not significantly different from healthy controls for postural sway variables (de Visser *et al.*, 2001). Potential reasons might be that triaxial accelerometers are more sensitive than force platform measures (Mayagoitia *et al.*, 2002), and therefore our study could pick up subtle differences, which force platform measures did not.

In our study patients, lower absolute values of RMS_ML were noted compared to RMS_AP, and higher absolute jerk_ML compared to jerk_AP. As seen in previous balance models, balance control in ML (side-side) and AP (forward-backward) directions imply different balance control strategies (Winter, 1995). Whilst ML neuromuscular balance control links in with hip loading/unloading mechanisms, AP control links in with ankle control strategies (Winter, 1995). Higher values in certain directions, could highlight the balance control strategy affected, which could help designing of targeted exercises to improve the relevant system. The differences in AP and ML directions, although non-significant may indicate directional sensitivity (Paillard and Noe, 2015) which is not seen with other standard tests. This seems promising, however, will need further investigation in a larger study.

The investigation of balance outcomes across age groups (reported in Appendix 22.0) sheds light on balance control mechanisms in different age groups. For instance, young patients show a higher jerk, and a lower RMS and f95 of sway in comparison to young healthy controls. In contrast, middle-aged and elderly patients, demonstrate higher ellipsis and RMS, RMS_AP and RMS_ML of sway in comparison to middle-aged and elderly healthy controls. This is important information, and suggests that although young adults have the potential to control their sway with increased jerk, middle-aged and elderly patients might not be able to do so. This could be an indication that middle-aged and older adults could be at a higher risk of imbalance and falls (Fernie *et al.*, 1982) (Melzer *et al.*, 2004), compared to young adults and therefore need special attention.

Gait

Patients in our study presented with a higher step time, stance time, swing time, a shorter step length and lower step velocity compared to healthy controls, indicating these were sensitive measures for detecting differences between patients and healthy controls. An increased step time, swing time, and reduced step velocity in our study patients compared to controls, agrees with the literature (De Visser *et al.*, 2000; Beebe *et al.*, 2009), which is reassuring. However, findings of a higher stance phase and shorter step length in our patients compared to controls,

did not agree with previous studies (De Visser *et al.*, 2000; Rompen *et al.*, 2002). Differences in results of stance time could be attributed to the fact that, in the previous study, stance phase was quantified separately for the affected and unaffected limb, whilst in our study it was investigated as a combined value. Differences in step length could reflect that fact that our study included patients who had both a LSS and AMP for different tumour locations in the lower limb, whereas Rompen et al 2002, investigated gait in only LSS patients with a femoral endoprosthesis (Rompen *et al.*, 2002).

Like balance control, different mechanisms of gait control were seen in young and middle-aged+elderly patients. Young patients presented with a significantly higher step time, stance time, swing time, and lower step velocity compared to those in young controls (Appendix 26.0: Table 1). In comparison middle-aged and elderly tumour patients presented with a significantly shorter step length and lower step velocity compared to healthy controls (Appendix 24.0: Table 2). These findings re-iterate variation in functional deficits by age.

iTUG time

In our study iTUG time in patients [19.486 (16.610 – 24.280) s] was considerably longer than iTUG time in healthy controls [14.3 ± 0.5 s] from a previous study (Zampieri *et al.*, 2010), indicating iTUG time is sensitive to characterising this aspect of function. This also suggests that patients complete the iTUG test at a slower pace, confirming a reduced physical capability compared to controls.

Major clinical groups

Patients in the BT group showed poor balance, gait and iTUG outcomes compared to the STS group, which agrees broadly with previous research (Sugiura *et al.*, 2001). This can be explained by the deep location of BTs and extensive surgery including endoprosthesis or implants for a BT in the leg. In addition, AMP group showed poorer absolute balance and gait outcomes than the LSS group. These findings agree with a previous study that LSS preserves more function than AMP (Aksnes *et al.*, 2008). Poor function in amputees can be explained due to a major limb loss, and disrupted sensory and proprioceptive input in the residual limb (Ku *et al.*, 2014). Another reason could be asymmetry in body weight, mainly distributed in the non-amputated leg (Ku *et al.*, 2014).

Therefore alterations in balance, gait and iTUG outcomes were clearly seen in our study patients compared to healthy controls, even with a small sample size. This supports the use of the BWM for its ability to discriminate between patients and controls (an indicator of

discriminant validity).

7.6.3 Balance, gait and iTUG measures against disease-specific clinical scales

Balance

In our study, MSTS total score was a negative predictor of ellipsis, and MSTS joint stability sub-score of RMS. This is an indication that a lower MSTS (high impairment levels) predict poor balance outcomes in tumour patients. A higher RMS (poor balance) was associated with lower TESS scores (higher disability) and QoL scores (reduced QoL), which agrees with findings in other clinical conditions (Tyson *et al.*, 2007) (Schmid *et al.*, 2013).

Gait

MSTS total score was a negative predictor of total time of fast walk and a positive predictor of step velocity ($p<0.05$). In addition, total time of fast walk was a negative predictor of disability and QoL, mainly physical and social sub-scores ($p<0.05$). This indicates that high impairment levels predict increased gait deficits, which further predict a higher disability and reduced QoL.

iTUG time

MSTS was a negative predictor of iTUG time, implying that high impairment levels were significant predictors of poor iTUG outcomes. In addition, iTUG time was a negative predictor of disability and QoL, particularly physical and social sub-scores. This implies that functional impairments such as a higher iTUG time predicts higher levels of disability and reduced QoL (mainly physical and social components). Using one single performance test, the iTUG time' can give an indication of patients 'at risk' of higher disability and reduced QoL. When mapped to the ICF framework (Gilchrist *et al.*, 2009), relationships between BWM measures and disease-specific clinical scales were sensible, in terms of the relationship between impairment and disability, disability with QoL. This was clinically sensible as per the ICF framework (McDougall *et al.*, 2010) and is vital information for clinical management. These are also the most sensitive BWM measures to characterise function for their relationships with disease-specific clinical scales (indicators of convergent validity).

7.6.4 Agreement of BWM measures with manual standard techniques in clinic and repeatability of measurement

Step count

In our study, the mean BWM step count detected by the L5 monitor was 13 steps, which was one step less than the video step count. An excellent agreement was seen between BWM and video, and the Bland-Altman analysis indicated that absolute differences between BWM and video in most cases were scattered around the mean difference. Yet in seven cases, BWM under-estimated the step counts by 2 to 5 steps. Out of these seven cases, six cases showed a difference of 2 steps, and one case of 5 steps. Observational video analysis of the patient in whom the BWM underestimated the step count by 5 steps, revealed that the patient dragged their foot while walking, and therefore did not seem to have a defined heel strike. Out of five patients showing a difference of two steps, three patients showed obviously deviated gait on video. One LSS patient's (SC07) video showed, that the affected knee was constantly in extension, and the patient was not able to bear weight effectively on the affected lower limb, causing the patient to shift weight swiftly onto the unaffected lower limb. Another LSS patient presented with a mild obvious limp while weight bearing on the affected limb with the knee in slight flexion. Therefore clearly, some patients had some obvious gait deviations, which might be one of the potential causes of the algorithm not detecting all steps.

The remaining three patients (SC04, SC18 and SC36), however, did not show any obvious gait deviations. Inspection of these patients gait values showed that their step velocity was reduced (<1.4 m/s), compared to healthy individuals. Slower gait speeds are shown to impact step count, mainly causing an underestimation of steps (Sandroff *et al.*, 2014; Johnson, 2015). Therefore a reduced step velocity in these tumour patients, could be another reason for the underestimation of step count. Furthermore, in a controlled environment since participants usually stop and start to turn around during the intermittent fast walk test, a difference in actual and estimated step count may occur. A difference of one step might be clinically acceptable, however in other applications, there is a concern about accuracy, previously reported for waist-worn monitors (Feito *et al.*, 2012). When step count is interpreted, it is important to critically analyse the effect of bias between actual and measured steps, as this could also have an impact on estimation of spatio-temporal parameters of gait.

The ICC agreement test showed excellent agreement between BWM step count 1 and 2, and no difference was seen between means of BWM step count 1 and 2. Hence quantifying step count using a BWM is a reliable method of measuring step count, at two different repetitions.

iTUG time

Although excellent agreement was observed between iTUG time and stopwatch TUG time, the mean stopwatch time was 1.1 s higher than iTUG time. This was potentially because of differences in BWM and stopwatch methods or due to the inherent manual error from the stopwatch (Hetzler *et al.*, 2008). The BWM works differently from a stopwatch as it records an acceleration spike in signal when patient's low back (L5 monitor) moves upwards during 'sit to stand'. In contrast, the stopwatch starts and stops recording on the command "GO" and "STOP". Most of the outlier patients were slow in performing the 'sit to stand' or 'stand to sit' components of the test and also used assistance. In these patients, therefore, the stopwatch recording may start before the BWM acceleration threshold is reached when the low back starts moving. Therefore it may appear that the stopwatch has overestimated the time, but actually the stopwatch has captured the initial and final struggle of patients during the 'sit to stand' and 'stand to sit' components of the test. The BWM does not seem to pick up this struggle due to its inherent measurement method. Hence, during instrumentation of TUG test, a potential solution might be to synchronise the stopwatch and BWM to ensure the initial and final component of the tests are captured. The advantages of using a BWM rather than a stopwatch for quantifying a TUG test, are that a range of additional dynamic balance and gait measures such as arm swing during gait and postural transitions could be derived (Zampieri *et al.*, 2010).

iTUG time showed an excellent agreement between repetitions. The mean of iTUG time 2 was lower than iTUG time 1 by 1.12 s, demonstrating that patients performed the second repetition faster than the first. These results can be explained by the practice effect, causing the second repetition to be faster (Basso *et al.*, 1999). Therefore quantifying TUG test using a BWM is a reliable method of measuring activity timing, at two different repetitions.

7.6.5 Strengths

This was the first study of its kind to investigate balance, gait and iTUG outcomes in the clinic in patients with musculoskeletal tumours. This study has investigated the use of a BWM for balance, gait and iTUG assessment in a range of musculoskeletal tumour sub-types, confirming its applicability for these heterogeneous groups. The strength of a BWM assessment in our study, is that these are small, portable, clinically useful tools allowing simple cost-effective assessments compared to other motion analysis systems. A single BWM has an ability to capture multiple attributes of physical function, which is a major advantage

in busy clinics. As these BWMs are portable, functional evaluations could also be performed in the patient's homes, preventing unnecessary travel to specialist centres, for those living remotely. This will also ensure optimal cost-effective follow-ups, for patients who might seem 'at-risk' after a remote BWM assessment.

The strengths of the algorithms used in this study were that minimal data loss was encountered. In addition, these algorithms worked for both the younger and older age groups, who have different functional characteristics (Winter *et al.*, 1990; Ostrosky *et al.*, 1994). These algorithms also worked for different heterogeneous groups. Results looked promising as they satisfied the different aspects of validity (i.e convergent, discriminant and concurrent validity). The algorithms could be further tested for accuracy, by running multi-centre studies to improve consistency by minimising errors. In addition, multi-centre testing in a larger and more homogenous patient cohort might suggest the need for adaptive algorithms for particular types of patients (such as hemipelvectomies), as the range of disabilities may require more than one approach.

7.6.6 Limitations

One major limitation of this study is that as a pilot study with multiple comparisons and a small sample size the possibility of a type 1 and type 2 sampling error respectively, cannot be eliminated. Bonferroni corrections could potentially be used as a solution to correct type 1 sampling errors related to multiple comparisons (Armstrong, 2014), however may sometimes increase the chances of type 2 errors (Perneger, 1998). Therefore the sensitivity of measures to characterise outcomes needs to be assessed in a larger study with a higher power and seems more promising. The presence of a heterogeneous sample also makes it challenging to draw robust conclusions for distinct clinical sub-groups. The sample of healthy controls recruited in different studies introduces potential sources of investigator bias and selection bias. Although these sources of bias were minimised using appropriate techniques during data analysis, it was not possible to completely eliminate bias. As BWM clinic measures do not necessarily reflect the patient's behaviour in the real world environment, this needs to be captured separately (Addressed in chapter 8).

7.6.7 Recommendations for future work

Future work could involve adding challenges in standing, such as, adding perturbations or balance testing on varying surfaces. Furthermore, dynamic balance and stability need to be studied to learn about balance during transitions and activities. Currently BWM data

processing is not automated and requires segmentation, which takes time. This can pose a restriction to using a BWM in the clinical environment. Future work on automating data processing in BWM systems could be useful in promoting clinical translation. Distinct balance and gait characteristics across clinical sub-groups, warrant detailed investigation. Therefore future work could encompass deploying study protocols in a larger study with homogeneous sub-groups for example, LSS or AMP patients, pelvic or knee tumours. It is also important to test the validity of BWM measures within these sub-groups, the reliability of BWM measurement at 2 different clinic visits, and sensitivity to change over time for assessing complete robustness of BWM measures. Higher postural sway was a significant predictor of falls in older adults in the community (Johansson *et al.*, 2017), which might also be seen in our population and needs further exploration. Future work can be undertaken to investigate the relationships between BWM measures in the clinic and the community. For example: (a) to assess whether balance, gait and iTUG outcomes relate with or predict ambulatory PA (b) to assess whether balance relates with or predicts gait and iTUG outcomes.

7.7 Conclusion

This study supports the feasibility, acceptability and indicators of validity of an accelerometer-based BWM assessment of balance, gait and iTUG outcomes in patients treated for lower extremity musculoskeletal cancer. Certain measures were more sensitive than others for detecting differences between groups and for their relationships with existing clinical scales, and could be used to inform rehabilitation. BWM measures demonstrated excellent agreement between measurements, but some cases did not agree with standard techniques. Potential solutions could be to synchronise monitors and stopwatch to measure iTUG time accurately. For step count estimation: some cases did not agree with video, and a potential solution is to use a monitor at other recommended locations (example: thigh). In summary, a laboratory assessment using a BWM offers a cost-effective alternative to cumbersome systems for quantifying balance, gait and iTUG outcomes

Chapter 8: Free-living monitoring of ambulatory physical activity in the community using a body worn monitor after treatment for lower extremity musculoskeletal tumours

8.1 Introduction

One of the challenges in looking after patients treated for musculoskeletal tumours, who often live a long way from the specialist treatment centre, is understanding their physical functioning and delivering appropriate individualised rehabilitation to support them (Furtado *et al.,* 2016a). Free-living monitoring of a patient's PA in their homes and the community (also referred to as 'real world'or 'remote' monitoring) (Feito *et al.,* 2012; Del Din *et al.,* 2016d) might therefore be useful in screening patients remotely, identifying 'at-risk' patients and delivering targeted rehabilitation to those who need it. Free-living monitoring might also have a role to play in follow-up, detecting a deterioration in overall function or assessing the effects of cancer treatments (Lewis *et al.*, 2009). Historically, the assessment of gait after sarcoma was limited to the use of cumbersome laboratory systems, which provided information about patient's gait impairments in the clinic (Carty *et al.*, 2009a; Carty *et al.*, 2010a). The performance of patients in their own home environment, which is likely to be more relevant (Parsons and Davis, 2004) is not captured on a regular basis.

Wearable technologies such as small BWMs could provide an efficient and inexpensive solution for monitoring PA and aspects of gait in the community over prolonged periods of time (van Dam *et al.*, 2001; Rosenbaum *et al.*, 2008b). Traditional assessments in the laboratory by their nature provide limited information about short periods of activity in a controlled environment. Furthermore, laboratory gait assessments suffer from inherent limitations of a patient's heightened attention or the unintentional impact of undergoing physical testing on patient's behaviour known as the 'Hawthorne effect' (McCambridge *et al.,* 2014). Capturing ambulatory PA (also referred to as 'ambulatory behaviour' or 'macrogait') in the real uncontrolled environment (Horak *et al.,* 2009; Del Din *et al.*, 2016c; Del Din *et al.,* 2016d) can overcome these limitations and may give a true reflection of physical deficits. Capturing ambulatory activity may also indicate whether patients are taking enough steps or reaching recommended activity targets (Tudor-Locke and Bassett, 2004). Furthermore, additional information about the type and distribution of bouts of activity and bout length can give us detailed information about the quality of ambulatory behaviour (Godfrey *et al.*, 2014).

Previous studies have looked at the volume and intensity of PA in musculoskeletal tumour patients, with no information on bouts (Furtado *et al.*, 2016b). Quantifying ambulatory activity using information on bouts can inform the development of personalised exercise programs or activity interventions (Lara *et al.*, 2016), which can help to optimise outcomes. It can also inform the delivery of chemotherapy, radiotherapy and surgical decisions. Other potential advantages are a reduction of traditional follow-up clinics (Rutkowski and Ługowska, 2014) and a more manageable way of selecting patients for targeted rehabilitation interventions when they may live a long way from the specialist centre.

BWMs have been used at various locations for monitoring ambulatory PA, however thigh-worn activity monitors have shown to be valid and reliable in capturing physical behaviour in the home and community (Edwardson *et al.*, 2016; Godfrey *et al.*, 2016). Therefore a thigh-worn monitor was used in this study to quantify ambulatory PA outcomes and investigate their validity in patients treated for lower extremity musculoskeletal tumours.

8.2 Ambulatory behaviour

8.2.1 Summary of Ambulatory PA measures

A summary of ambulatory PA measures described in Chapter 6 have been listed in Table 8-1.

Table 8-1: Summary of extracted ambulatory PA measures

S.No	Ambulatory PA characteristics	Ambulatory PA measures
1.	Volume of ambulatory PA	Total steps/day Total ambulatory bouts/day Total ambulatory hours/day
2.	Pattern/Distributions of ambulatory bouts	Mean walk time/bout (seconds (s)) Alpha (α)
3.	Variability of ambulatory bouts	Variability (S_2)

8.2.2 Feasibility and acceptability of using a BWM in the community

Feasibility of using a BWM in the community

The thigh-worn BWM was feasible to use, straightforward and quick to set up. The data downloading and processing of raw acceleration signals was straightforward to perform and ambulatory PA outcomes were successfully derived. This was feasible to do and took up to 20 minutes for a beginner, 5 minutes for an expert, and up to 10 minutes if it required some troubleshooting, for example if signals were noisy.

Data loss encountered during community testing and data processing

Problems encountered in obtaining representative ambulatory PA outcomes from 6 patients are detailed in Table 8-2. Ambulatory PA outcomes for individual sarcoma patients, number of days obtained and data loss is also presented in Appendix 26.0. A final dataset of 28 adult cases were available for analysis (Table 8-2).

Table 8-2: Derivation of ambulatory behaviour outcomes and data loss

BWM outcomes	Ambulatory PA measures	Data used from patients	Data not used	Reason for data loss
Volume	Total steps/day	28/34	6/34	SC18 – Monitors not returned SC33 – Unable to extract data due to technical problems SC09 and SC10 – Ambulatory PA values do not match with clinical picture, investigated and removed from analysis SC28 and SC29 - Not representative, as recorded only 1 calendar day's data
	Total ambulatory bouts/day	28/34	6/34	
	Total ambulatory hours/day	28/34	6/34	
	Mean walk time/bout (s)	28/34	6/34	
Pattern	Alpha	28/34	6/34	
Variability	Variability (S_2)	28/34	6/34	

Acceptability of BWM in the community: feedback forms and activity diaries

The feedback forms and activity diary comments provided a valuable insight into acceptability and patient experience of the BWM. Patients, in general, reported the BWM use at home as easy, and did not find that the monitor hindered their activity or caused any problems. Of patients (n=20) who returned the feedback forms, 20/20 (100%) found the BWM acceptable, 17/20 (85%) user-friendly and 19/20 (95%) comfortable to wear at home.

Limitations reported by patients included: one patient felt the week wearing the monitor was not representative of their usual activity levels, as it was a less active week than usual. Patients also felt that the BWM was easy to lose when not being worn, and that the monitor when secured by adhesive tapes sometimes got detached. Patients reported difficulty with fixation (sticky mess by tape) of the BWM and another patient forgot to put on monitors till later on in the day. One patient found the method of application of the BWM confusing, with respect to its orientation and the direction of ports.

8.2.3 Ambulatory PA in tumour patients

In the free-living environment, patients presented with a wide range of ambulatory PA values (Table 8-3) and besides variability, all other variables did not follow patterns of normal distribution (Appendix 27.0).

BT vs STS group

The total steps/day accumulated by patients in the BT group were significantly lower than those in the STS group ($p<0.05$) (Table 8-3). Although no significant differences were noted for other variables, patients in the BT group presented with lower total ambulatory bouts/day, total ambulatory hours/day, mean walk time/bout, a higher alpha and high variability than those in the STS group ($p>0.05$).

LSS vs AMP surgery

Patients in the AMP group presented with a lower absolute volume of ambulatory PA (total steps/day, total ambulatory bouts/day and total ambulatory hours/day) compared to those in the LSS group ($p>0.05$) (Table 8-3). Whereas, absolute values of mean walk time/bout, alpha and variability were higher in patients in the AMP group compared to those in the LSS group (Table 8-3).

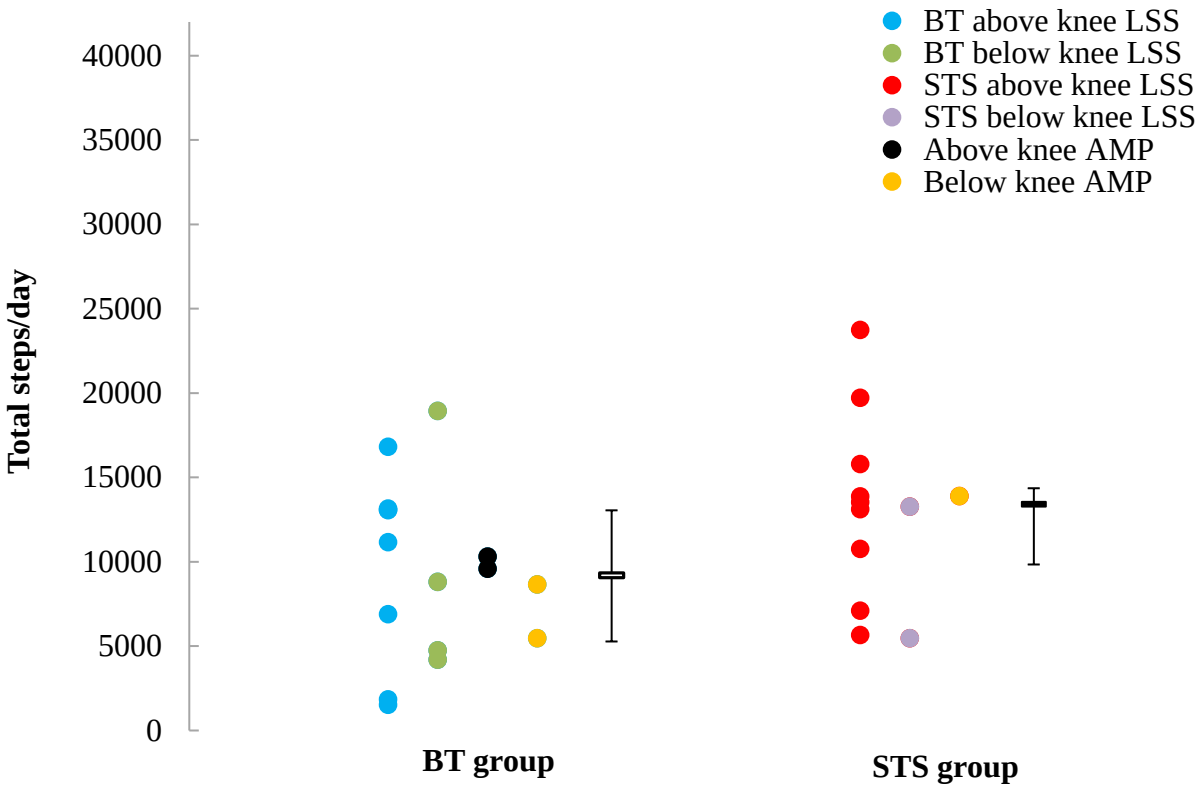
When plots were colour-coded, lowest volume of PA were due to patients from the 'BT above knee LSS' mainly, followed by cases from the 'BT with below knee LSS' and 'below knee AMP' (Figure 8-1 a, b and c). Low mean walk time/bout, high alpha and low variability values were noted in patients from the 'BT above knee LSS', 'BT below knee LSS' and 'Above knee AMP' groups (Figure 8-1 d, e, f).

Table 8-3: Ambulatory behaviour in tumour patients, BT vs STS, LSS vs AMP

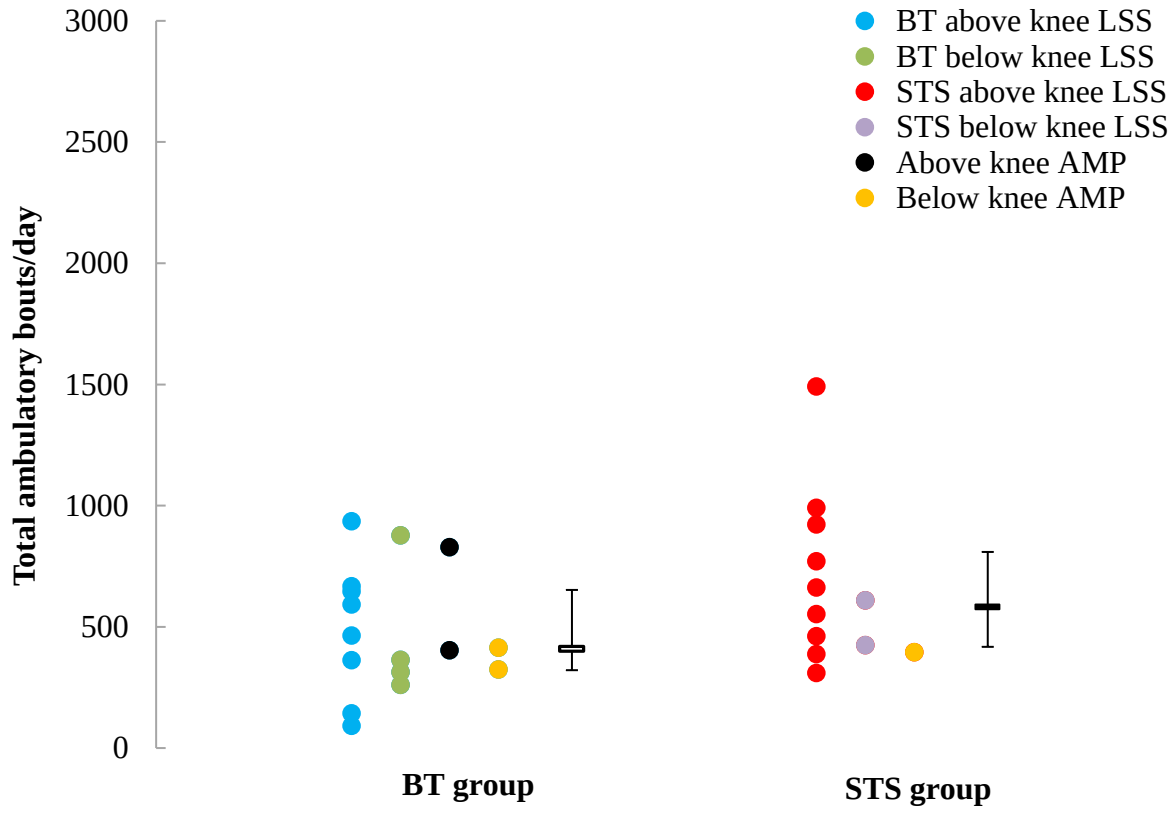
Ambulatory PA measures	Tumour patients (n=28)	BT group (n=16)	STS group (n=12)	p-value for BT vs STS groups	LSS group (n=23)	AMP group (n=5)	p-value for LSS vs AMP groups
	Median/Mean Values (25^{th} – 75^{th} percentile, 1QR/Min -max)	Median/Mean Values (25^{th} – 75^{th} percentile, 1QR/Min -max)	Median/Mean Values (25^{th} – 75^{th} percentile, 1QR/Min -max)		Median/Mean Values (25^{th} – 75^{th} percentile, 1QR/Min -max)	Median/Mean Values (25^{th} – 75^{th} percentile, 1QR/Min -max)	
Total Steps/day	10953	9189	13393	0.03*	13047	9577	0.569
	(5960 – 13790)	(4918 - 13059)	(8004 - 15308)		(5653 – 13877)	(7054 – 12089)	
Total ambulatory	463	409	581	0.13	552	403	0.569
bouts/day	(363 – 745)	(316 - 663)	(403 - 885)		(363 – 771)	(360 – 622)	
Total ambulatory	3.16	2.41	3.58	0.06	3.23	2.30	0.418
hours/day	(1.73 - 3.74)	(1.32 - 3.46)	(2.26 - 4.18)		(1.65 – 3.79)	(1.93 – 3.32)	
Mean walk time/bout	19.13	19.02	19.45	0.58	19.05	20.00	0.610
(s)	(16.57 - 21.47)	(16.75 - 20.32)	(16.41 - 22.02)		(16.53 – 21.73)	(15.56–26.25)	
Alpha (distribution)	1.59	1.59	1.57	0.10	1.58	1.60	0.529
	(1.57 – 1.61)	(1.58 - 1.64)	(1.56 - 1.61)		(1.57 - 1.62)	(1.56 – 1.63)	
Variability (S_2)	0.92	0.92	0.90	0.85	0.92	0.97	0.294
	(0.86 – 0.97)	(0.87 - 0.97)	(0.85 - 0.98)		(0.86 – 0.96)	(0.85 -1.04)	

p-value – difference between groups (*=statistically significant)

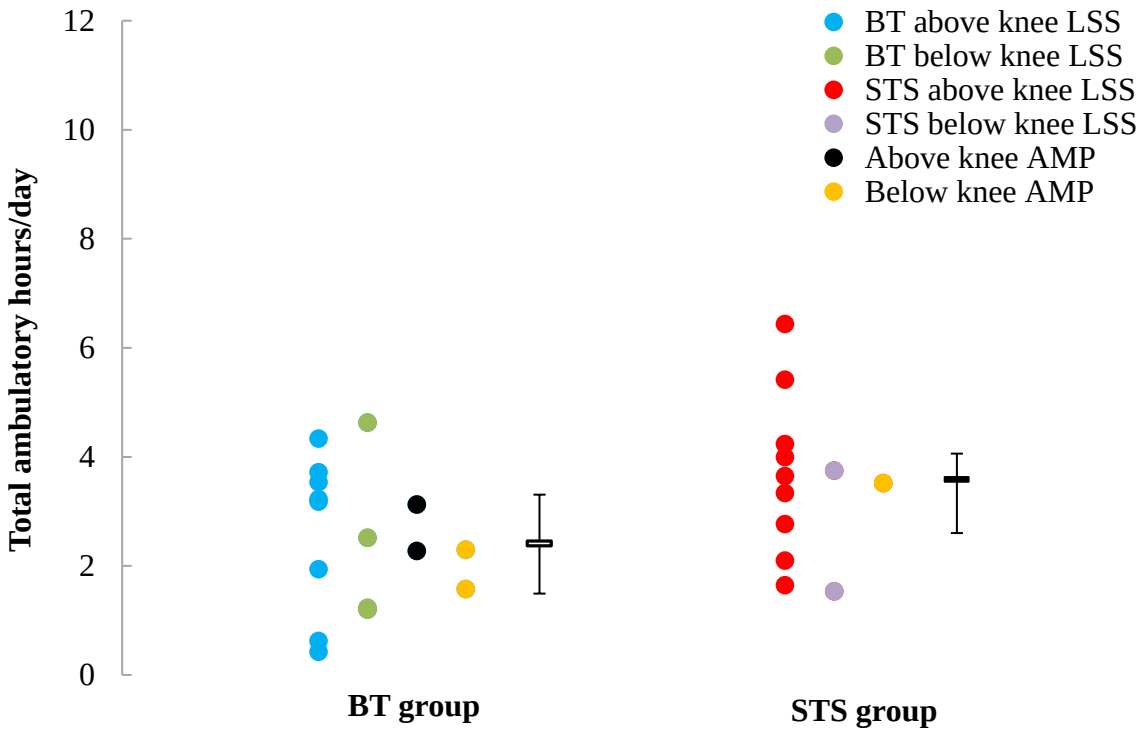
(a)


BT above knee LSS
BT below knee LSS
STS above knee LSS
STS below knee LSS
Above knee AMP
Below knee AMP
Total steps/day
40000
35000
30000
25000
20000
15000
10000
5000
0
BT group
STS group

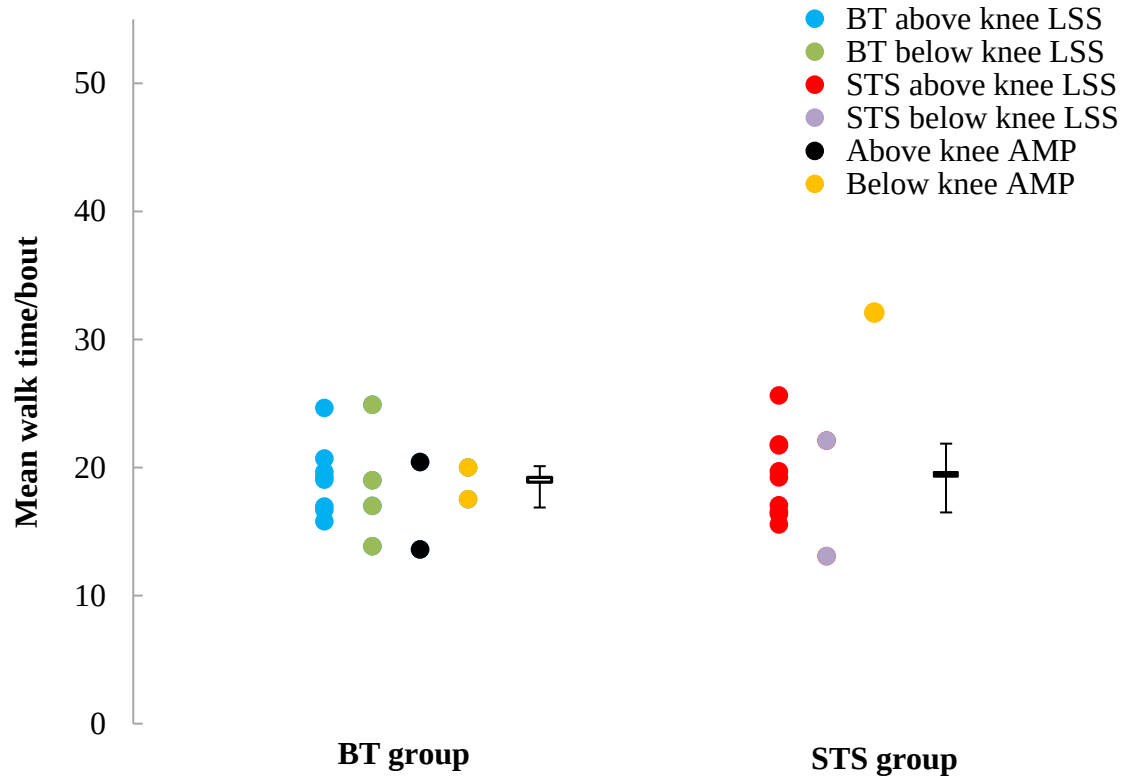
(b)


BT above knee LSS
BT below knee LSS
STS above knee LSS
STS below knee LSS
Above knee AMP
Below knee AMP
Total ambulatory bouts/day
3000
2500
2000
1500
1000
500
0
BT group
STS group

(c)


Total ambulatory hours/day
12
10
8
6
4
2
0
BT above knee LSS
BT below knee LSS
STS above knee LSS
STS below knee LSS
Above knee AMP
Below knee AMP
BT group
STS group

(d)


Mean walk time/bout
50
40
30
20
10
0
BT above knee LSS
BT below knee LSS
STS above knee LSS
STS below knee LSS
Above knee AMP
Below knee AMP
BT group
STS group

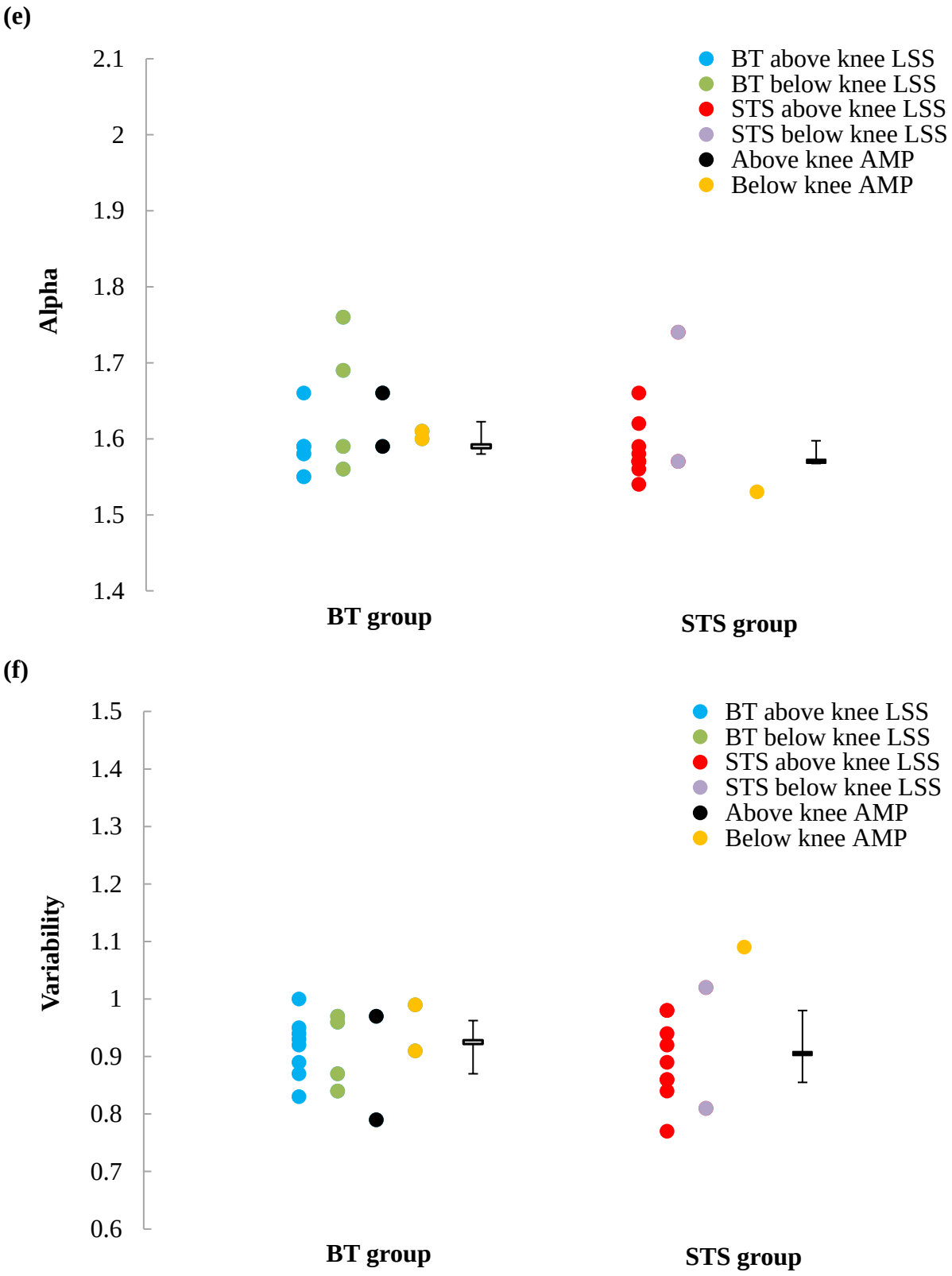


Figure 8-1: Jitter plots to show ambulatory behaviour in bone tumour (BT) group compared to soft tissue tumour (STS) group. (a) Significantly lower total steps/day in BT group compared to STS group ($p<0.05$) (b) Lower absolute total ambulatory bouts/day in BT compared to STS group (c) Lower absolute total ambulatory hours/day in BT compared to STS group (d) Lower absolute mean walk time/bout in BT compared to STS group (e) Higher absolute alpha in BT compared to STS group (f) Higher absolute variability in BT compared to STS

8.2.4 Ambulatory PA measures vs disease-specific clinical scales in sarcoma

Ambulatory PA vs MSTS (impairment)

No significant correlations were observed between MSTS and ambulatory PA outcomes ($p>0.05$) (Table 8-4). This indicates that impairment as measured by MSTS is not associated with ambulatory behaviour.

Ambulatory PA vs TESS (disability)

No significant correlations were observed between TESS total score and ambulatory PA ($p>0.05$) (Table 8-4). However, when associations between TESS sub-scores and ambulatory PA were investigated, strong or moderate positive associations were seen between TESS sitting, standing, kneeling, walking upstairs, walking ramp, social sub-scale and volume of PA ($p<0.05$) (Table 8-5). This indicates that poorer performance in activities such as standing, kneeling, walking upstairs, walking ramp and social activities are associated with a low volume of ambulatory behaviour. In addition, strong or moderate negative associations were observed between TESS standing, walking upstairs, walking on ramp, walking outside and alpha ($p<0.05$) (Table 8-5). This indicates that a worse performance in activities such as standing, walking upstairs, walking on ramp and walking outside are associated with accumulation of shorter bouts. A stepwise regression model with ambulatory PA as a dependent variable (adjusted for age, BMI and months post surgery) showed that TESS is a negative predictor of alpha ($p<0.05$), but not total steps/day and total ambulatory hours/day ($p>0.05$) (Table 8-6). This suggests that high levels of disability are associated with accumulation of shorter bouts.

Ambulatory PA vs 3-metre TUG time (time taken to complete test)

No significant correlations were observed between 3-metre TUG time and ambulatory PA ($p>0.05$) (Table 8-4). This indicates that a longer time taken to complete a 3-metre TUG test (poor physical capability), is not associated with poor outcomes of ambulatory behaviour.

Ambulatory PA vs QoL-CS (quality of life)

No significant correlations were observed between ambulatory PA and QoL-CS ($p>0.05$) (Table 8-4), suggesting a low ambulatory behaviour is not associated with a poor QoL.
In summary, besides certain TESS sub-scales, no other clinical scales showed significant associations with ambulatory PA. Furthermore TESS was the only significant predictor of alpha in these tumour patients (Table 8-6)

Table 8-4: Spearman's correlations between ambulatory PA and disease-specific clinical scales

Clinical scales in sarcoma	Ambulatory PA Measures	Sample number (n)	R value	p-value
MSTS (Impairment)	Total Steps/day	28	0.032	0.870
	Total ambulatory bouts/day	28	0.057	0.774
	Total ambulatory hours/day	28	-0.006	0.978
	Mean walk time/bout (s)	28	0.071	0.721
	Alpha	28	-0.107	0.587
	Variability (S_2)	28	-0.025	0.900
TESS (disability)	Total Steps/day	24	0.321	0.126
	Total ambulatory bouts/day	24	0.225	0.290
	Total ambulatory hours/day	24	0.277	0.190
	Mean walk time/bout (s)	24	0.214	0.315
	Alpha	24	-0.282	0.182
	Variability (S_2)	24	0.090	0.676
QoL-CS total score (QoL)	Total Steps/day	24	0.131	0.543
	Total ambulatory bouts/day	24	0.068	0.751
	Total ambulatory hours/day	24	0.097	0.653
	Mean walk time/bout (s)	24	0.254	0.231
	Alpha	24	-0.179	0.402
	Variability (S_2)	24	0.147	0.494

p-value – correlation between variables (*=statistically significant)

Table 8-5: Spearman's correlations between ambulatory PA and TESS sub-scales

TESS sub-scales in sarcoma		Ambulatory PA measures	Sample number (n)	R value	p-value
TESS activities and social sub-scales with significant relations	TESS Sitting	Total steps/day	24	0.541	0.006*
		Total ambulatory bouts/day	24	0.530	0.008*
		Total ambulatory hours/day	24	0.541	0.006*
	TESS Standing	Total steps/day	24	0.514	0.010*
		Total ambulatory bouts/day	24	0.439	0.032*
		Total ambulatory hours/day	24	0.597	0.002*
		Mean walk time/bout (s)	24	0.406	0.049*
		Alpha	24	-0.585	0.003*
	TESS Walking upstairs	Alpha	24	-0.405	0.050*
	TESS walking outside	Total steps/day	24	0.613	0.001*
		Total ambulatory bouts/day	24	0.474	0.019*
		Total ambulatory hours/day	24	0.566	0.004*
		Alpha	24	-0.418	0.042*
	TESS Walking ramp	Total steps/day	24	0.430	0.036*
		Mean walk time/bout (s)	24	0.414	0.044*
	TESS social	Total steps/day	24	0.464	0.022*
		Alpha	24	-0.512	0.010*

p-value – correlation between variables (*=statistically significant)

Table 8-6: Regression Models: TESS vs ambulatory PA (n=24)

Model number	Independent variables	Unstandardised coefficients	Standardised regression coefficients (Beta)	R square	F-statistic change	Significance of regression model (p-value)	Excluded variables
Model 1: Total steps/day as a dependent variable							
	Constant	3114.352		0.130	0.084	0.084	N/A
	TESS	99.701	0.360				
Model 2: Total ambulatory hours/day as a dependent variable							
2.	Constant	0.985		0.120	0.097	0.097	N/A
	TESS	0.026	0.347				
Model 3: Alpha as dependent variable, adjusted for age							
3.	Constant	1.666					Age, level of tumour and
	TESS	-0.001	-0.443	0.196	0.039*	0.039*	time since surgery
Model 4: Alpha as dependent variable with TESS and age as independent variables							
4.	Constant	1.725					
	TESS	-0.001	-.434				
	Age	-0.001	-0.596	0.551	0.001*	0.000492*	BMI, Months post surgery

p-value and F-statistic (*=statistically significant).

8.3 Discussion

This is the first study to investigate ambulatory behaviour in patients treated for lower extremity musculoskeletal tumours using a thigh-worn BWM with a focus on bouts, their mean length, patterns of activity and variability. The current study provides a valuable insight into the feasibility of quantifying ambulatory behaviour, acceptability of the BWM, and about different aspects of validity (comparison between major clinical groups and relationships with established measures). The clinical implications of this work have been discussed in individual sections.

8.3.1 Feasibility and acceptability of a BWM in the community

We found that the BWM was feasible to use and quick to set up for a community assessment in patients treated for lower extremity musculoskeletal tumours. The feasibility of obtaining ambulatory PA outcomes in a short time scale, acceptability, comfort and user-friendliness reported by patients supports the clinical usefulness of the device for community monitoring. Some problems with adhesion and skin irritation reported by patients, could be tackled by avoiding areas of dry or irritated skin and using hypoallergenic tapes. In addition, patients should be taught how to secure monitors firmly on the body part where it is to be applied (in this instance thigh), but also to ensure that it is not applied in a tight or constrictive manner. Labelling the monitors would be sensible to remind patients the correct direction of the ports. Providing patients with frequent reminders, and an information sheet; detailing the method of monitor application (with pictures) might be another solution (Matthews *et al.*, 2012). Since the patient might forget to put on monitors, this can cause a loss of valuable information on activity levels during the day. A potential solution showing success in previous research might be to add cues, so that individuals can increase the wearability time of monitors (Matthews *et al.*, 2012). Furthermore, since monitors are small and easy to lose, a two-step process might be an effective solution to secure monitors firmly. One step is to apply the adhesive tape and the next step is to use a band over the tapes. This could prove very useful for high-intensity functioning patients such as those who run or are involved in high-impact sports. Since patients found that monitors were easy to lose, a case for the monitor might help. One patient did not feel their week was representative of their usual activity levels. This limitation can be overcome by monitoring patients multiple times (or at least twice), for 7 days each, at an interval of few weeks. This might

provide a more robust method of 'free-living' monitoring and might also ensure representativeness and reliability, although one episode of 7 day monitoring was found to be valid and reliable in patients treated for lower extremity sarcomas (van Dam *et al.*, 2001).

8.3.2 Ambulatory PA in tumour patients – comparison to literature

In adults, ambulatory PA outcomes in patients showed broad clinical sense and some variables were comparable to ambulatory PA values in other studies (Sugiura *et al.*, 2001; Lara *et al.*, 2016), confirming face validity.

As this is the first study in this tumour group looking at information on bouts, comparisons of this information with previous studies in this tumour group was not possible. In our study, patients accumulated a total steps/day of 10953 (5960 – 13790), which was higher compared to that accumulated by patients [7119 ± 3563], and comparable to healthy controls [10,206 ± 1338] in another study (Sugiura *et al.*, 2001). Differences in results across studies could be attributed to the different devices used in each study. Sugiura et al, 2001, used a simple pedometer (Sugiura *et al.*, 2001), whereas our study used a triaxial accelerometer. Accelerometers are known to be highly sensitive and accurate devices in capturing short stepping episodes and are therefore superior to older devices (pedometers), which provide only basic information on step count (O'Neill *et al.*, 2017).

We compared our findings to a previous study (Lara *et al.*, 2016), which captured information on alpha and variability using the same device as in our study, the axivity (AX3), in retired older adults with a mean age of 62.0 ± 3.9 (60.60 to 63.40) years. However the device was applied on the fifth lumbar vertebra (L5) in this study. We conducted comparisons using the middle-aged+older patient group [age – 57.89±13.83 years] in our study, to eliminate the confounding effect of age. Patients in our study showed a lower alpha [(1.58 ±0.03)] compared to retired adults [2.49 (2.39 to 2.59)] (Lara *et al.*, 2016). Variability in our study patients [0.920 +/ 0.081] was higher than that of retired adults [0.61 (0.54 to 0.68)] and total ambulatory bouts/day in our study [503±252] was also higher than retired adults from this study [31 (17 to 45)] (Lara *et al.*, 2016). Therefore, our patients presented with a higher total ambulatory bouts/day, lower alpha (accumulation of longer bouts) and a higher variability compared to retired adults (Lara *et al.*, 2016). These findings could be explained on the basis that our study patients were relatively younger, and included patients

who worked and/or some who also pursued sports. The impact of different device locations on ambulatory PA outcomes cannot be ascertained in these studies.

8.3.3 Ambulatory PA in major clinical groups

Patients in the BT group accumulated significantly fewer total steps/day compared to patients in the STS group ($p<0.05$), showing this measure was sensitive to identifying differences in ambulatory behaviour between BT and STS groups, therefore confirming discriminant validity. Furthermore, patients in the BT group accumulated lower absolute total ambulatory hours/day, total ambulatory bouts/day, mean walk time/bout, a higher alpha and variability compared to patients in the STS group, however these findings were not significant ($p>0.05$). Significant differences in total steps/day between BT and STS groups, agree with previous studies showing that patients in the BT group present with reduced PA levels in comparison to those in the STS groups (Sugiura *et al.*, 2001). This is in keeping with the greater magnitude of surgical resection involving bone.

Although no significant differences were seen between LSS and AMP groups; amputees demonstrated lower absolute volume of ambulatory PA (total steps/day, total ambulatory bouts/day and total ambulatory hours/day) compared to those in the LSS group. This implies that amputees may have reduced activity levels compared to LSS patients. Furthermore, amputees presented with higher absolute alpha than LSS patients, indicating that amputees accumulated a greater distribution of shorter bouts. Although these findings are not significant, the clinical differences between groups generally agree with published literature that LSS preserves more function than AMP (Aksnes *et al.*, 2008). Reduced activity levels in amputees can be explained by the major limb loss, and disrupted sensory and proprioceptive inputs in the residual limb (Ku *et al.*, 2014), impacting their physical capability to move about during their ADLs. Patients with a reduced bout accumulation could be given cueing by physiotherapists to increase their number of bouts; and promote an increase in PA (Lara *et al.*, 2016).

8.3.4 Ambulatory PA measures vs disease-specific clinical scales

There were no significant relationships between MSTS and ambulatory PA ($p>0.05$), which is sensible as per the ICF model, and agrees with a published study in this tumour group (Rosenbaum *et al.*, 2008b). Furthermore, no significant relationships were observed between TESS and ambulatory PA ($p>0.05$), which agrees with previous research showing clinical scores

do not correlate with PA (Rosenbaum *et al.*, 2008b). An analysis of TESS sub-scales confirmed that

TESS sub-scales (sitting, standing, kneeling, walking upstairs, walking ramp, social) positively relate to the volume of ambulatory PA ($p<0.05$). This indicates that greater activity restrictions are associated with a lower volume of PA and vice-versa. In contrast, negative correlations were observed between TESS sub-scales (standing, walking upstairs, walking on ramp, walking outside) and alpha. This indicates that lesser activity restrictions are associated with the accumulation of longer bouts and vice-versa. A stepwise regression model, adjusted for age, showed that lower TESS score (greater activity restrictions) can predict a higher alpha (distribution of shorter bouts) and vice versa. These relationships are sensible as per the ICF model, confirming convergent validity. This is novel information and could be used in designing rehabilitation goals for patients. The most sensitive measures to characterise ambulatory behaviour for convergent validity are volume of PA and alpha, which is important to note for functional assessments.

8.3.5 Strengths

This was the first study of its kind to investigate community outcomes including both quantity and quality of ambulatory behaviour in patients with musculoskeletal tumours. This study has investigated the use of BWM in a range of musculoskeletal tumour sub-types, which confirms the applicability of the BWM across the heterogeneous sub-groups. The algorithms worked successfully in a wide range of patients, except for certain patient types (individuals using wheelchairs) which is important to consider for future studies. This suggests the algorithms need to be individually personalised and adapted to individual patient groups. Use of an open-source sensor (AX3) has advantages, such as one can develop, modify and personalise the systems openly. This is beneficial for heterogeneous groups and therefore applicable for this tumour group.

8.3.6 Limitations

Limitations of the study

The major limitation of this pilot and feasibility study in drawing firm conclusions is that the small sample size means the possibility of a Type 2 sampling error cannot be eliminated. Furthermore, the heterogeneous sample makes it challenging to draw robust conclusions for

distinct clinical sub-groups, each of which is small. The study might suffer from limitations such as investigator bias and selection bias, which cannot be eliminated. However appropriate measures were used during data analysis to keep these sources of bias minimised.

Limitations of the devices and algorithm

BWMs seem promising for objective, continuous, unobtrusive free-living monitoring of patients in their homes and community. Ambulatory behaviour is collected in the uncontrolled environment and therefore the context of the real life situations is unknown. This is important to take into account while interpreting this data. Whilst useful, quantifying ambulatory behaviour has its own challenges, as ambulatory behaviour can vary between different age groups (Tudor-Locke and Bassett, 2004; Tudor-Locke *et al.*, 2011a), weather conditions, time of the year, socio-economic background (Mansfield *et al.*, 2012), gender (Mansfield *et al.*, 2012) and geography (Bauman *et al.*, 1999). Hence blanket recommendations about the achievement of specific targets may not be ideal: it might be more useful to take a more personalised approach and stratify PA by age groups and other factors. There is also no consensus currently about which specific algorithm to use which might be a problem for consistent approaches across studies (Hickey *et al.*, 2017). Moreover as discussed in Chapter 5, studies including the real-world monitoring of ambulatory behaviour in tumour patients have used devices that are not validated (Furtado *et al.*, 2016b). BWMs have important applications in health care, but this requires the standardisation of valid devices algorithms. A single-thigh-worn monitor in this study provided useful information and satisfies aspects of convergent validity (relates to established measures) and discriminant validity (for patient sub-groups), which is promising. However some studies (Storm *et al.*, 2015) have suggested that the use of multiple monitors at different anatomical sites could give more useful information and might help overcome limitations.

8.3.7 Recommendations for future work

In order to rigorously test discriminant validity future research is warranted in larger samples. The volume of PA (total steps/day, total ambulatory bouts/day and total ambulatory hours/day) showed a wide range of values in patients. These results reflect the heterogeneity of outcomes after treatment for bone and soft tissue tumours, which in turn, might be attributed to the variation of our clinical sample with a range of tumour types, size, locations, and treatments. Therefore recommendations for future work must involve studies to deploy these study protocols

in homogenous sub-groups. Work is also needed to test the reliability of BWM measurement at 2 different clinic visits, and sensitivity to change over time to confirm these devices are fit for purpose in clinical practice.

8.4 Conclusion

This study confirms that a thigh-worn BWM is feasible to use to obtain ambulatory activity outcomes, acceptable to patients and their families and shows indicators of validity in patients treated for musculoskeletal tumours. BWMs provide important novel information on ambulatory activity (for example: alpha, variability), which can allow clinicians to identify the 'at risk' or 'physically inactive' patients early on, therefore stimulating a timely delivery of rehabilitation interventions. Ambulatory PA outcomes were comparable to the reference literature confirming face validity, and sensitive to differences between major clinical groups such as bone tumour or soft tissue tumours, confirming discriminant validity. Ambulatory PA outcomes also showed significant associations with disease-specific scales in this tumour group, confirming convergent validity. The total steps/day was the most sensitive measure to detect differences between BT and STS groups, whereas volume of PA and alpha were the most sensitive measures to for convergent validity. In summary, a thigh-worn monitor is a promising tool which forms a low-cost solution to remotely assess free-living ambulatory behaviour in patients treated for lower extremity musculoskeletal tumours.

Chapter 9: Discussion, recommendations for future work and conclusions

9.1 Summary

This chapter summarises key research findings of the thesis, recommends a general approach to improve health services for patients with bone and soft tissue tumours, gives a rationale for the introduction of objective measurements of physical functioning to support service improvements, describes how the ICF framework can guide this, recommends the direction of future work and finally discusses case studies showing the practical application of BWM measures in clinical practice.

9.2 Overview of key findings

The thesis contains several key findings about rehabilitation, physical functioning and its assessment in patients treated for lower extremity musculoskeletal tumours.
The main aims of the thesis set out in each phase, and results of each phase have been listed below:

9.2.1 Phase 1

Main aim: To investigate the current state of rehabilitation services and physical functioning in patients who had an AMP for lower extremity musculoskeletal tumours.
Main Results: Chapter 3 highlighted that patient experiences of rehabilitation services were variable and fell short of agreed national standards, particularly in the areas of information provision, access to limb fitting services, prosthetic provision, falls prevention and management, psychological counselling and allied health professional support (Furtado *et al.*, 2016a). Although there are five commissioned bone cancer surgery centres in UK, support for patients post-surgery was spread across a large number and range of limb fitting centres (Furtado *et al.*, 2016a). This could explain why patients did not receive timely support in the immediate post-operative period, as they usually lived remotely from specialist centres, and were dependent on someone to get them to rehabilitation clinics for treatment (Furtado *et al.*, 2016a). Chapter 3, therefore, provided support for free-living monitoring and delivery of care closer to homes of patients. Loss of a limb due to cancer has both physical and psychological consequences (Aksnes *et al.*, 2008), and

psychotherapeutic and physical rehabilitation interventions are needed (Srivastava and Chaudhury, 2014) to enhance recovery. Yet our national project showed that major service gaps exist in both psychological counselling and allied health professional support (Furtado *et al.*, 2016a). Chapter 3, therefore, confirmed the lack of standardisation of health services for this group of sarcoma patients, and their variable experience of rehabilitation after AMP (Furtado *et al.*, 2016a). A need for improving and streamlining rehabilitation services was identified in this phase.

Chapter 4, showed that in England, patients treated with AMP for a lower limb tumour present with low self-reported functional and QoL scores compared to international comparators (Furtado *et al.*, 2015). A high percentage of these patients (70.4%) depend on walking aids, especially those with proximal AMP (Furtado *et al.*, 2015), confirming a high level of disability. 'Impossible' or 'most difficult' activities for these patients were kneeling, gardening and yard work, participating in sports, walking upstairs, walking outdoors, and participating in leisure activities; highlighting the struggle patients face in daily life (Furtado *et al.*, 2015). In addition, significant predictors of poor physical function were high pain levels, older age groups and more proximal levels of surgery, and pain was significant in patients using walking aids (Furtado *et al.*, 2015). This chapter therefore confirms high levels of disability and activity restrictions, as well as factors affecting physical function and dependence on walking aids for this tumour group. Further research to investigate underlying mechanisms and causes of poor physical functioning and the need to provide targeted rehabilitation was identified in this chapter.

9.2.2 Phase 2

Main aim: To investigate the current state of objective clinical measurement of balance, gait and PA after treatments for lower extremity musculoskeletal tumours

Main results: In Phase 2 (Chapter 5) of this thesis, a systematic review of the literature revealed a deficit of research quantifying the key components of physical functioning (balance, gait and PA), using clinically useful tools, in patients treated for lower extremity musculoskeletal tumours (Furtado *et al.*, 2016b). Studies identified in this review did not use consistent and valid tools developed specifically for patients with sarcoma (Furtado *et al.*, 2016b). Therefore, a need to develop cost-effective, portable and valid tools to assess balance, gait and PA was identified in this phase.

9.2.3 Phase 3

Main aim: To pilot the use of small BWMs to develop novel objective measures of physical functioning in the clinic and community; in patients treated for lower extremity musculoskeletal tumours.

Main results: Phase 3 (Chapter 6, 7 and 8) of the PhD, confirms that small accelerometer-based BWMs were feasible to use in this patient group, for the rapid assessment of balance, gait, iTUG in the clinic and ambulatory behaviour outcomes in the community. Patients also find this device acceptable, comfortable and user-friendly; supporting its use in routine practice. This phase also showed that balance and gait measures could discriminate between patients and controls (confirming discriminant validity) and ambulatory PA measures could discriminate between bone and soft tissue tumour patient groups (an indicator of discriminant validity). BWM outcomes, both in the clinic and community, were significantly associated with established measures such as, TESS, MSTS and QoL-CS (confirming convergent validity). BWM outcomes also demonstrated excellent agreement with manual techniques such as stopwatch and video, with certain case exceptions. This is promising, showing that the BWM generates sensible results, but more work is needed on algorithms for this group to improve these findings. Certain measures of balance, gait, iTUG and ambulatory PA were found to be more sensitive than others in characterising physical functioning. For example:

For postural control: The most sensitive measures for discriminating between patients and healthy controls were ellipsis, root mean square (RMS) and jerk. Whereas most sensitive measures for their relationships with established measures were, RMS and RMS_AP for their associations with TESS and QoL; and ellipsis, RMS and jerk with MSTS; and RMS_AP for being a significant predictor of TESS and QoL.

For gait: The most sensitive measures for discriminating between patients and healthy controls were step time, stance time, swing time, step length and step velocity. Whereas, most sensitive measures for their relationships with established measures were, total time and step velocity for correlations with MSTS, and total time for being a significant predictor of TESS and QoL.

For iTUG (instrumented timed up and go) time: iTUG time was a sensitive measure, as showed significant relationships with established measures (MSTS, TESS and QoL-CS).

For Ambulatory behaviour: The most sensitive measure for discriminating between major clinical groups (BT and STS group) were total steps/day. Whereas, most sensitive measures for their relationships with established measures were, volume of ambulatory PA and alpha for their associations with TESS walking and social sub-scales, and alpha for being predicted by TESS.

This is important clinical information which can be used to improve the assessment of outcomes and guide clinical management. Examples of how this information can be implemented in clinical practice is discussed further in Section 9.3 – sub-section 9.3.2. In summary, the results of this phase support the development of BWMs as outcome measurement tools, after overcoming limitations of algorithms/devices.

9.3 General Discussion

9.3.1 General approach to improving services

As seen in Phase 1 of this thesis, service standards do not meet recommended standards and could be the cause of variable patient experience (Furtado *et al.*, 2016a). When health care systems do not meet recommended standards, serious concerns may also arise about the impact of service shortfalls on outcomes (Cowing *et al.*, 2009). As an initiative to optimise health care, a comprehensive system of health care delivery is recommended to improve patient experience and quality of care (Cowing *et al.*, 2009). This includes a focus on management of patient expectations, accessibility to services, patient satisfaction, patient support, communication, use of valid and reliable performance measures, availability of resources, staff training, staff-patient ratio and embedding of good clinical guidelines (Cowing *et al.*, 2009). As complete service redesign is often challenging, targeting and developing existing services may be a more straightforward and practical way of improving services. Delivery of high quality services must involve patient empowerment (Klein, 2004) and the use of evidence based outcome measures to monitor and guide clinical management. This positively embeds a patient-centred approach, involvement of patients in decisions about their care, delivery of accurate information about patient outcomes, and can increase the patient's active participation in optimising their outcomes. This is a critical step in achieving clinical effectiveness, in accordance with pillars of clinical governance (Klein, 2004). This PhD thesis, therefore, proposes the following recommendations for service transformation.

9.3.2 Development of BWM assessment of balance, gait and iTUG outcomes in the clinics for patients with musculoskeletal tumours

As seen in Chapter 2, self-reported measures suffer from inherent limitations (Troiano and Dodd, 2008) and introducing objective measurements of health into clinical practice could significantly improve information available to clinicians (Kwong *et al.*, 2014). Using simple portable tools such as accelerometers in the clinic, could give clinicians better data about multiple aspects of physical functioning, including information about balance, gait and iTUG outcomes (as shown in Phase 3). Similarly BWMs may give insights about aspects of physical capability (Godfrey *et al.*, 2015) and activities which patients find difficult to perform over and above that given in TESS sub-scales. This could include information about the causes or predictors of activity restrictions, for which the methods of data collection and analysis in the thesis could be used as a model. For instance, clinicians could measure 'peak acceleration', 'peak velocity' and 'RMS of sway' during 'staircase ascent or descent' using a BWM, alongside existing disease-specific scales. This may indicate the underlying causes of difficulty in staircase ascent, which might include for example: impaired balance or gait, joint motion restrictions or reduced muscle strength. BWMs could then be further used for interventional feedback to improve activity performance and the management of these underlying impairments.

Since certain BWM measures were found to be more sensitive than others to characterise 'aspects of function', such as 'differentiate patients from controls' and 'relate with established measures', this information could be used to inform clinical practice. Sensitive BWM measures are useful mainly because they satisfy indicators of validity and health care professionals can confidently trust their accuracy. Examples of these are given below:

1) In a patient with a history of falls, balance can be assessed using BWM measures which this thesis shows have the ability to discriminate between patients and controls (ellipsis, RMS, jerk). These BWM measures would not only give clinicians objective values for balance outcomes but also could guide the delivery of rehabilitation. These measures could also be useful in then reassessing improvements in balance during and after completion of rehabilitation, and evaluating if improvements have reached the level of healthy individuals.

2) A clinician is in the process of designing a tailor-made rehabilitation programme for a patient with poor balance (high postural sway), mobility and QoL; who mainly wishes to improve their QoL. Phase 3 of the thesis, highlights that, impaired balance is a significant predictor of poor

QoL, and in this case poor balance is reported. Therefore in theory, alongside other multi-modality treatments to improve QoL, balance impairments must also be assessed and managed. Since this patients shows a high postural sway, assessment of balance could be best performed using valid indicators, such as balance measures sensitive for their relationships with QoL. RMS_AP was found to be a sensitive measure in the thesis, as is a negative predictor of QoL ($p<0.05$). The clinician could therefore select this RMS_AP measure, to evaluate balance impairments and guide balance rehabilitation (with the goal to reduce RMS_AP), as this might further predict a better QoL.

9.3.3 Development of BWM assessment of ambulatory behaviour outcomes in the free-living environment for patients treated for musculoskeletal tumours

Solutions for the free-living monitoring of health have been promoted in health services across the world to follow-up patients more effectively (Patel *et al.*, 2012). Since sarcoma is a rare cancer and patients may live a long way from a treatment centre, the ability to remotely monitor sounds appealing. As seen in the thesis, BWMs provide an opportunity to monitor ambulatory behaviour in the patient's own home and community. This has proved helpful in other health conditions (Del Din *et al.*, 2016d) as 'inactive' or 'at risk' patients are easily identified, without patients having to attend specialist centres. For instance, BWMs have been used in cohorts of older patients and those with Parkinson's disease to monitor outcomes remotely and inform clinical management (Bachlin *et al.*, 2010; Del Din *et al.*, 2016c; Del Din *et al.*, 2016d).

Recently BWMs have also been promoted for continuously monitoring PA outcomes and patient safety and guiding rehabilitation (Din *et al.*, 2016): BWMs are also used to facilitate health promotion, using telehealth, mobile applications, activity trackers which support an increased exercise adherence in individuals 'at risk'. Examples are: obese and cardio-vascular risk patients (Warburton *et al.*, 2006; Benedetti *et al.*, 2009), therefore supporting these individuals to achieve healthy and active lifestyles. BWMs can promote self-management and empower patients. For example, BWMs can also be used to monitor patients in their homes and identify at-risk patients not performing well after discharge from hospital or during rehabilitation. Feedback to improve PA could be delivered to these patients, in the form of cueing directly from the device, telephone calls from the monitoring team, or referrals to local physiotherapists or exercise groups. However although challenges around compliance with treatment might remain, these could at least be monitored. The delivery of targeted, specialised rehabilitation to address the multiple level of

impairments seen in a patient treated for sarcoma may be difficult, but links with local rehabilitation staff in the area could help tackle this problem.

Other recommendations are: physical rehabilitation programmes and self-management strategies can be embedded in hospitals and community to improve QoL of cancer survivors (van Weert *et al.*, 2008) (Parsons and Davis, 2004). Such programmes can also influence other domains of survivorship including psychosocial distress, lower educational attainment, and employment, also strongly linked to QoL in childhood cancer survivors (CS) (Ishida *et al.*, 2011) (Zeltzer *et al.*, 2008). Wider use of sensors to improve health services include 'smart home' technology, which is essentially incorporating sensors in the environment (Stefanov *et al.*, 2004; Benini *et al.*, 2006), usually patient's homes. 'Smart homes' can then be augmented with BWM monitoring to provide more detailed information about patient's function.

9.3.4 ICF approach to introduce BWMs into rehabilitation services:

As seen earlier, the ICF is an evidence based model which encourages a structured approach to rehabilitation assessment and promotes targeted intervention (Steiner *et al.*, 2002). The thesis gives us important information regarding relationships between functional, pain and QoL outcomes within the ICF, for this tumour group. For instance, phase 3 supports, that when outcomes were mapped to the ICF framework, body related impairments such as MSTS was found to be a significant predictor of balance and gait. Therefore, rehabilitation exercises leading to improvements in MSTS sub-domains of ROM, joint stability and proprioception might predict better balance and gait outcomes. In addition, balance and gait were found to be significant predictors of TESS and QoL. TESS, on the other hand, was a significant predictor of alpha and TESS sub-scales showed significant relationships with ambulatory PA. Balance and gait rehabilitation to improve balance and gait outcomes, might therefore predict higher TESS and QoL scores. Whereas, higher TESS scores might further predict a higher volume of ambulatory PA and a lower alpha (higher distribution of longer bouts).

In addition, pain intensity and interference in ADLs drives lower TESS and QoL scores, therefore pain management strategies could reduce pain and drive better TESS and QoL scores. When mapped to the ICF framework, this means that, if physicians rate a patient with a low MSTS, there are high chances that the patient might be at a high risk of impaired balance and gait. In addition, patients with impaired balance and gait might present with higher disability, and

eventually with a reduced QoL. Physiotherapy services could use this information obtained from BWMs to guide rehabilitation strategies and promote shared decision making, based on information and education.

9.3.5 Recommendation for health care services

Survivorship continuum

The survivorship continuum starts from diagnosis and continues until long term rehabilitation in patients treated for musculoskeletal cancer (Richards *et al.*, 2011; Kwong *et al.*, 2014; Tobias and Gillis, 2015) (Figure 9-1). Therefore provision of support and rehabilitation from the point of diagnosis until long-term is important.

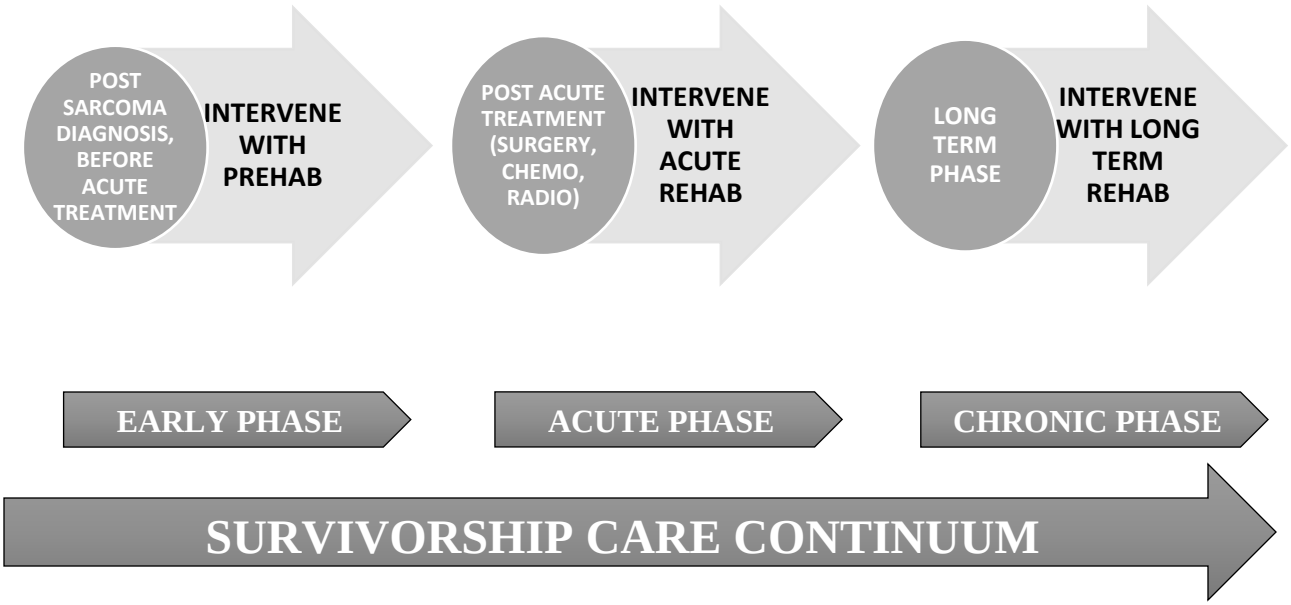


Figure 9-1: Survivorship Care Continuum in Musculoskeletal tumour disease.
[PREHAB refers to prehabilitation and REHAB refers to rehabilitation]

BWMs in Prehabilitation: From diagnosis to the start of acute treatment

BWMs can be used in different phases of rehabilitation to guide assessment and management. There is increasing evidence supporting the delivery of rehabilitation interventions early in the survivorship care continuum, in the interval between diagnosis and first treatment, also known as 'prehabilitation' (PREHAB) (Silver, 2015). Early assessment using BWMs can provide an important opportunity to discuss expected outcomes, understand the individual needs of patients, provide personalised support and promote physical health (Silver and Baima, 2013). In this

thesis, we demonstrated that a significant proportion of patients who undergo AMP for sarcoma do not have access to pre-AMP counselling and information (Furtado *et al.*, 2016a). Therefore as well as missing the opportunity for PREHAB, patients may be unaware about what to expect after major limb loss, increasing the risk of poor survivorship and QoL outcomes (Furtado *et al.*, 2015). PREHAB has been shown to improve health outcomes, reduce complications of treatment and lower health-care costs in adult cancer patients (Silver and Baima, 2013; Silver, 2015), and improve QoL outcomes after orthopaedic surgery (Brown *et al.*, 2012). In the treatment of other cancers, patients who were more active before surgery demonstrated faster post-operative recovery (Nilsson *et al.*, 2016), which is likely to promote faster to normal RNL.

The nature of PREHAB interventions can be wide-ranging (Figure 9-2) and may include early assessment of home environments, employment and other roles (Tobias and Gillis, 2015) as well as early interventions to improve PA, general and psychological health (Brown *et al.*, 2012). Present rehabilitation services are less than ideal, as rehabilitation service standards do not meet recommended national standards of service provision (Furtado *et al.*, 2016a). Early rehabilitation assessment and discussions before treatment about expected outcomes, the support/interventions available, and anticipated impact on daily life may help improve this. There may be a particularly strong case for the development of exercise interventions using BWMs for this tumour group, given the physical disabilities following treatment, but they have not become routine (Silver, 2015).

The holistic assessment of patients requiring PREHAB could follow the comprehensive conceptual framework, ICF, to promote health, disability and QoL. This framework can be used to promote a structured approach for the holistic assessment and management of individual health domains (Steiner *et al.*, 2002) in the PREHAB phase (Escorpizo *et al.*, 2010).

PREHABILITATION (PREHAB) INTERVENTIONS TO INCORPORATE IN A PERSONALISED PREHAB PRESCRIPTION

Following assessment, an individualised PREHAB recommendation could be based on selections from a range of interventions, mapping to the domains of the ICF

Interventions to improve overall physical activity levels:
Patient education/awareness about increasing physical activity.
Reminders to increase physical activity (e.g.: text messaging, use of mobile phone apps, BWMs etc.).
Self-management/home exercises using BWMs
Interventions to improve specific identified impairments/physical problems anticipated
Referral to exercise classes/community fitness groups for any specific impairments or physical limitations identified.
Specific instructions

Other forms of support:
In addition to above physical rehabilitation strategies to improve QoL, directing patients to appropriate clinical facilities/professionals, where feasible and possible, to target other aspects of QoL
Remote support (e.g. telephone calls) for close monitoring and an ongoing support and referral to appropriate therapy/treatments
Referral to seek advice from Sarcoma Nurse Specialist, and directing for support from Cancer charities.

Appropriate therapy/training could involve the following:
Referral for cognitive behavioural therapy (CBT).
Referral to Psychologist for anxiety and depression.
Referral to appropriate support officers for support to return to work.
Referral to cancer support groups, patient support/awareness conferences
Awareness of Sports support centres for cancer survivors.

Figure 9-2: PREHAB interventions to incorporate in a personalised PREHAB Prescription

BWMs in rehabilitation: From the acute (start of treatment) to the chronic (long-term) phase – Using the Rehabilitation Problem-Solving Form (RPS-Form)

This thesis clearly shows that after treatment for extremity sarcoma, patients typically have impairments such as abnormal balance and gait, dependence on walking aids, disability, poorer QoL and falls. The overall impact of treatment varies widely depending on factors including the anatomical location of the tumour, the extent of surgery and radiotherapy, age and complications of treatment (Davis *et al.*, 2000). The ICF system can be used in clinical practice to streamline physical assessments and delivery of rehabilitation interventions by using a Rehabilitation Problem-Solving Form (RPS-form) (Rauch *et al.*, 2008) (Steiner *et al.*, 2002).

The RPS-form is based on the ICF framework and supports a patient-centred and systematic approach to the integration of novel outcome assessments, PROM and clinical record data in developing rehabilitation interventions. It also facilitates the eliciting of patient and family priorities for treatment. We have adapted the RPS-form to use it for sarcoma rehabilitation (Figure 9-3). A major advantage of this approach is that the model can incorporate a range of measures of physical functioning, for instance in our clinical population, it can collate information from TESS, MSTS, and BWM outcomes of balance, gait, iTUG and ambulatory PA. Outcomes from these devices can therefore be incorporated in the RPS-form and be used to guide delivery of rehabilitation and care. The potential to monitor PA remotely in the community and deliver individualised interventions in patient's homes may be of particular benefit to older adults – who form a high percentage of our population of interest (Shepherd and While, 2012).

Using the RPS-form brings the opportunity to incorporate these measures in clinical practice as part of a holistic assessment and by doing so further understand their potential to guide delivery of rehabilitation interventions (Figure 9-4) (Escorpizo *et al.*, 2010). This approach could significantly benefit this heterogenous group, as involves personalised assessments and clinical problem-solving approaches (Steiner *et al.*, 2002), which can guide delivery of evidence-based personalised rehabilitation prescription plans (Steiner *et al.*, 2002; Escorpizo *et al.*, 2010). The potential for a holistic and evidence-based rehabilitation intervention to improve QoL is significant, given the strong links between physical functioning and QoL after sarcoma treatment (Furtado *et al.*, 2015). Higher physical performance supported by evidence based rehabilitation strategies may therefore considerably impact the physical, psychological and social domains and well-being of patients.

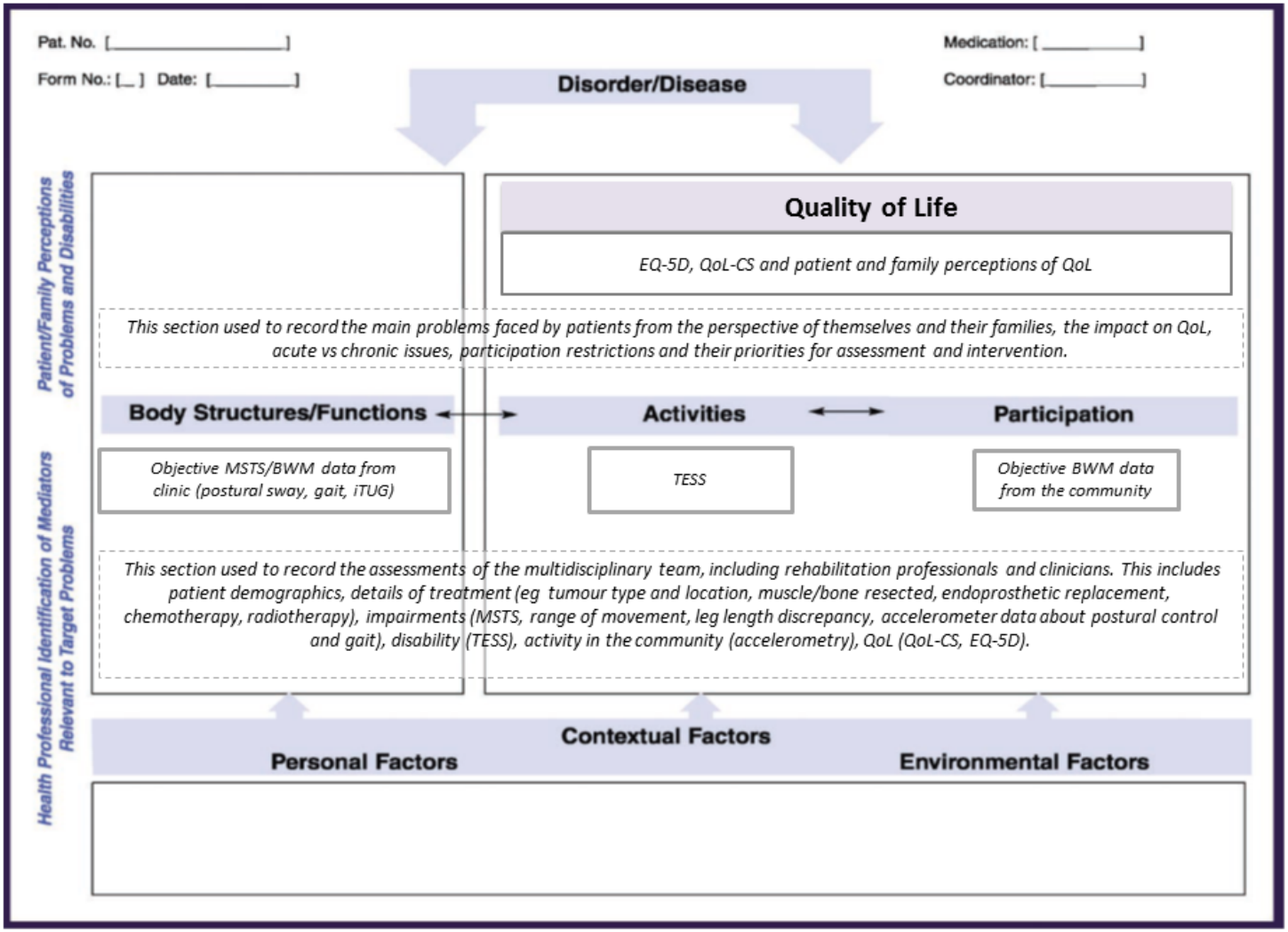


Figure 9-3: Example of the Rehabilitation Problem-Solving Form (RPS-Form) in the framework for musculoskeletal tumours. This figure was taken from (Steiner et al., 2002) and is adapted to fit the framework for musculoskeletal tumours.

REHABILITATION INTERVENTIONS TO INCORPORATE IN A PERSONALISED REHABILITATION PRESCRIPTION

Management of impairments:

- Local physiotherapist or self-management – based on complexity and compliance.
- Targeting structural impairments:
- Patient education about their structural impairments.
- Self-management stretching and active ROM exercises.
- Joint mobilization.
- Capsular stretches.
- Muscle strengthening exercises.
- Resistance training (using weights, theraband or gym equipment based on time since surgery, impairment level etc.)
- Joint stability exercises.
- Proprioceptive exercises.
- Targeting functional impairments:
- Altered postural control:
- Patient awareness about postural imbalance and prevention of falls.
- Postural control exercises with challenging surfaces
- Balance board/ball exercises.
- Core stability exercises.
- Reach outs stabilising/maintaining postural sway exercises.
- Attention demanding balance training
- Altered gait impairments:
- Patient education about Gait retraining and exercises.
- Gait retraining on treadmill.
- Mirror feedback exercises for improving gait deviations.
- Tactile feedback.
- Activity pace training.
- Management of pain leading to altered gait.
- Management of fatigue leading to altered gait.

Disability management:

- Instruction and support to improve particular activities (e.g. stair climbing)
- Activity training.

Interventions to improve overall physical activity levels:

- Patient education/awareness about increasing physical activity.
- Reminders to increase physical activity (e.g. text messaging, use of mobile phone apps etc.).
- Self-management/home exercises.
- Referral to exercise classes/community fitness groups.

Other forms of support:

- In addition to above physical rehabilitation strategies to improve QoL, our team will also aim to direct patients to appropriate clinical facilities/professionals, where feasible and possible to target other aspects of QoL
- Remote support (e.g. telephone calls) for close monitoring and an ongoing support and referral to appropriate therapy/treatments
- Referral to seek advice from Sarcoma Nurse Specialist, and directing for support from Cancer charities.
- Appropriate therapy/training could involve following:
- Referral for cognitive behavioural therapy (CBT).
- Referral to Psychologist for anxiety and depression.
- Referral to dietician for appropriate diet – for reducing BMI.
- Referral to appropriate support officers for support to return to work.
- Referral to cancer support groups, patient support/awareness conferences
- Awareness of Sports support centres for cancer survivors.

Figure 9-4: Rehabilitation Interventions to incorporate in a Rehabilitation Prescription Plan

BWMs in falls and rehabilitation

Phase 1 of this thesis, highlights that a high incidence of falls is reported, especially in patients belonging to distal level AMP groups, perhaps because more active patients might be falling more often. Cancer survivors are known to be at a higher risk of falls, due to the disease, management and inactivity as a result of chemotherapy/radiotherapy/surgery (Brown *et al.*, 2012). The common known modifiable risk factors for falls are impaired balance and gait (Nevitt *et al.*, 1989; Rubenstein and Josephson, 2006). In Phase 4 (Chapter 5 and 7), we have seen that balance and gait were significantly affected in patients compared to healthy individuals. Furthermore, reduced PA and depression are recognised as factors contributing to falls in cancer patients (Brown *et al.*, 2012). A reduced performance in all individual factors mentioned above, further increases the risk of falling. Therefore a holistic model for assessment, prevention and management of falls could be of great value in this population (Rubenstein *et al.*, 2001; Rubenstein and Josephson, 2002).

Personalised rehabilitation programmes may reduce the risk of falls by improving muscle strength, balance, gait, PA and mental health (Rubenstein and Josephson, 2006). Structured exercise programs have also shown to reduce risk of falls in older community dwelling adults (Arnold *et al.*, 2008). Therefore exercises could also be useful in reducing the risk of falls in patients treated for musculoskeletal cancer. Exercise modalities such as endurance training can improve maximal oxygen consumption (V02 max) (Hepple et al., 1997), whereas resistance and weight training can improve strengthening of muscles and performance of ADLs (Beltran Valls et al., 2014) Similarly balance outcomes are positively affected by flexibility training, resistance training and balance training exercise programs (Bird et al., 2009). Mental health was also improved by a wide range of exercises (Anderson and Shivakumar, 2013). Small BWMs have a major role as in balance and gait rehabilitation (Horak *et al.*, 2015a), which can ultimately reduce falls. Therefore there is an opportunity to further investigate and develop an intervention to reduce the risk of falls in this population.

9.3.6 Case studies: Examples of how a structured assessment of physical functioning using the RPS-form in a clinical context can guide rehabilitation

Case studies of two patients are presented below to demonstrate the clinical applications of BWM measures. As specific classifications for current clinical scales (except 3-metre TUG test) are lacking, for the purpose of the case studies below, patients who did not score full scores, were classified as low scores. Whereas for BWM measures, a patient's functional status was classified as 'affected' or 'not affected' based on comparisons to normative data of healthy individuals, major clinical groups obtained in Chapter 7 or the literature (Tudor-Locke and Bassett, 2004; Tudor-Locke *et al.*, 2011a; Tudor-Locke *et al.*, 2011b) .

Case study 1: Impaired balance and gait in a physically active patient: 77 year old man treated with LSS for a metastatic bone cancer

A 77 year old male was treated with a proximal femoral resection with insertion of a modular Stanmore bipolar hemi-arthroplasty implant for a bone metastasis in the proximal femur, 84 months before assessment. The patient weighed 86.5 kilograms and was 1.66 m in height, and had a BMI – 31.4 (mild obesity).

This patient presented with the following scores on established scales and BWM measures:

i. Musculoskeletal tumour disease-specific assessment

MSTS scores*: *low

- MSTS total score: 21/35
- MSTS sub-score of joint ROM: 1/5
- MSTS sub-scores of pain, joint stability, muscle strength, functional and emotional domains: 3/5 in each

TESS scores: low

- TESS total score: 60.7/100

3-metre TUG time: high

- 3-metre TUG time: 17.7seconds. This indicates good mobility, can go out alone, mobile without a walking aid, and has a high risk of falls (refer to Appendix 14.0).

QoL-CS scores: low

- QoL-CS total score was low: 6.0/10
  QoL-CS sub-scores were low: physical sub-score: 5.3/10, psychological: 6.8/10, social: 6.0/10 and spiritual: 4.7/10.

ii. BWM laboratory data – balance and gait

Balance: Patient demonstrated high values of postural sway compared to healthy controls (Table 9-1), suggesting impaired balance (affected).

Gait: Patient presented with high values of temporal outcomes of gait, and a shorter step length and low step velocity (Table 9-1), compared to healthy controls from our study, suggesting an impaired gait (affected).

iTUG time: The patient completed the iTUG test in 26.48 seconds, longer than other patient groups in our study, and suggesting reduced physical capability (affected).

Table 9-1: Balance and gait outcomes in Case study 1

Balance		**Gait**	
Ellipsis	0.3857 m^2/s^4	Step time	0.563 s
f95_ML	2.4800 Hz	Stance time	0.677 s
f95_AP	1.3600 Hz	Swing time	0.383 s
Jerk	0.7227 m^2/s^5	Stride time	1.060 s
Jerk_AP	0.2947 m^2/s^5	Total time	6.137 s
Jerk_ML	0.4281 m^2/s^5	Step length	0.490 m
RMS	0.0048 m/s^2	Step velocity	0.913 m/s
RMS_AP	0.0036 m/s^2		
RMS_ML	0.0031 m/s^2,		

iii. BWM community monitoring data - ambulatory PA

- Total steps/day - 13047 - This patients ambulatory PA outcomes met the public health recommendations for healthy older adults mention that normative data average 2,000-9,000 steps/day (Tudor-Locke *et al.*, 2011a) (not affected).
- Total ambulatory bout/day - 647
- Total ambulatory hours/day - 3.72
- Alpha – 1.55
- Mean walk time/bout – 20.69
- Variability – 0.95

This ambulatory PA data indicates that the patient achieves the recommended steps/day in older adults. In addition, alpha is low compared to controls, indicating a greater distribution of longer bouts. The patient's ambulatory bouts were also found to be more variable and seemed

to accumulate a higher proportion of longer bouts. This was confirmed as the mean walk time/bout was 20.69 s, higher than controls.

iv. Holistic assessment – RPS-form assessment:

In summary, this patient is a physically active patient, with impairments (reduced ROM, muscle strength and joint stability) and moderate disability. This patient also presents with impaired balance and gait and is at a high risk of falls. This patient shows lower QoL scores than patients in other groups in our study. Adding these components into the RPS-form (based on the ICF framework) gives a holistic functional picture of this patient. Other aspects to note on the RPS-form are the environmental and contextual factors affecting patient outcomes, patient choices and preferences about goals they wish to achieve, and family preferences and input. For patients presenting with comorbidities, the potential influence of these comorbidities on physical function will also be listed. This can be used in conjunction with the outcome data to develop the personalised rehabilitation plan.

v. Comprehensive personalised rehabilitation plan

Using the RPS-form structured assessment, a personalised rehabilitation plan is developed for this patient. As impairments are linked with disability, and balance and gait with disability and QoL, targeting impairments is likely to reduce disability and improve QoL in this patient. The main impairments to be targeted in this case study and related to the direct impact of surgery are joint ROM, stability, and muscle strength. These could be targeted using rehabilitation interventions from Figure 9-4, such as stretching exercises, capsular stretches, joint mobilisation after ruling out contra-indications, muscle strengthening, resistance training and proprioceptive and joint stabilisation exercises (static and dynamic). In addition, balance impairments could be managed by prescribing supervised balance exercises, postural control exercises with challenging surfaces but taking into consideration the age of the patient, balance board/ball exercises, core stability exercise, reach outs stabilising/maintaining postural sway exercises, attention demanding balance training. Gait impairments could be managed by prescribing gait exercises such as gait retraining and exercises, gait retraining on treadmill, mirror feedback exercises for reducing gait deviations, tactile feedback, cueing using BWMs, activity pace training. Managing pain and fatigue leading to altered gait could be another targeted intervention. In addition, it would be useful to increase the patient's awareness about their postural imbalance and thus prevent falls. Disability management could also be delivered by giving this patient instructions, support and training to improve particular

activities which they find difficult as per the TESS questionnaire. Furthermore increasing supervised activity training for this patient would be an effective treatment. In addition to the above physical rehabilitation strategies to improve QoL, rehabilitation staff must also aim to direct patients to appropriate clinical facilities to target other aspects of QoL such as psychological and social components. Remote support (e.g. telephone calls) for close monitoring and an ongoing support and referral to appropriate therapy/treatments.

Case study 2: Impaired balance and gait in a patient with low physical activity: 21 year old man treated with a below AMP for an osteosarcoma in the tibia

A 21 year old male was treated with a below knee AMP for an osteosarcoma (BT) in the right tibia, 68 months post surgery. The patient weighed 80.8 kilograms and was 1.81m in height, and had a BMI – 24.6 (not obese).

This patient presented with the following scores on established scales and BWM measures:

i. Established clinical scales

MSTS scores: low

- MSTS total score: 25/35
- MSTS sub-scores in pain and function domains: 1/5
- MSTS sub-score in muscle strength domain: 3/5
- MSTS sub-scores in joint ROM, joint stability, deformity and emotional domains: 5/5

TESS scores: low

- TESS total score: 68.3/100

3-metre TUG time: normal

- 3-metre TUG time: Patient had a time of 8.5 seconds, which indicates patient has normal mobility and is not at a high risk of falls (refer to Appendix 14.0).

QoL-CS scores: low

- QoL total score: 7.8/10
- QoL sub-scores: physical sub-score: 8.1/10, psychological: 8.6/10, social: 6.6/10 and spiritual: 6.6/10.

ii. BWM laboratory data – balance, gait and iTUG

Balance: Patient demonstrated high values of postural sway (Table 9-2) compared to healthy controls, indicating impaired balance (affected).

Gait: Patient presented with high values of temporal outcomes of gait, longer step length and a lower step velocity (Table 9-2) compared to healthy controls from our study, indicating an impaired gait (affected).

iTUG time: The patient completed the iTUG test in 19.63 seconds (affected), which was longer than other patient groups in our study.

Table 9-2: Balance and gait values in Case study 2

Balance		**Gait**	
Ellipsis	0.0497 m^2/s^4	Step time	0.580 s
f9_ML	2.7000 Hz	Stance time	0.727 s
f95_AP	2.1400 Hz	Swing time	0.418 s
Jerk	0.1049 m^2/s^5	Stride time	1.150 s
Jerk_AP	0.0570 m^2/s^5	Total time	5.162 s
Jerk_ML	0.0479 m^2/s^5	Step length	0.703 m
RMS	0.0016 m/s^2	Step velocity	1.229 m/s
RMS_AP	0.0013 m/s^2		
RMS_ML	0.0009 m/s^2		

iii. BWM community monitoring data - ambulatory PA

- Total steps/day - 8653 - This patients ambulatory PA outcomes does not meet the public health recommendations for healthy adults (Tudor-Locke and Bassett, 2004)
- Total ambulatory bout/day – 414
- Total ambulatory hours/day – 2.30
- Alpha – 1.61
- Mean walk time/bout – 20 s
- Variability – 0.99

This ambulatory PA data indicates that the patient does not achieve the recommended steps/day (<10000 steps which is classed as active) (affected). In addition, alpha is higher than other clinical groups in the study, indicating a greater distribution of shorter bouts (affected). The patient's ambulatory bouts were also found to be less variable and seemed to accumulate a higher proportion of shorter bouts (affected).

iv. Holistic assessment – RPS-form assessment

In summary, this patient is a young physically 'some what' active amputee, not meeting public PA recommendations (Tudor-Locke and Bassett, 2004) and presenting with impairments (pain, muscle strength and function). This patient also presents with impaired balance, gait and iTUG outcomes. This patient shows lower QoL scores than many other patient groups in our study. This patient is low on scores in most components of the RPS-form (based on the ICF framework) giving clinicians a holistic functional picture of this patient. The environmental and contextual factors, patient choices and family preferences can also be noted in the RPS-form, which can inform the development of the personalised rehabilitation plan.

v. Comprehensive personalised rehabilitation plan

Using the RPS-form structured assessment, a personalised rehabilitation plan has been developed for this patient. As impairments are linked with disability, and balance and gait with disability and QoL, targeting impairments might reduce disability and improve QoL in this patient. The main impairments to be targeted in this case study are pain, muscle strength, function, balance and gait impairments which can be managed in a similar manner as detailed in Case study 1. In addition, managing structural, and balance and gait impairments, could improve confidence of the patient to take more number of steps and accumulate a higher number of longer bouts. Furthermore, ambulatory PA outcome also needs to be directly targeted by: promoting patient education/awareness about increasing physical activity, and reminders or cueing to increase physical activity (e.g. text messaging, use of mobile phone apps etc.), self-management/home exercises or referral to exercise classes/community fitness groups. As alpha was high indicating a greater distribution of shorter bouts, cues to increase the length of bouts would be encouraged. As this is a young gentleman, supervision through regular free-living monitoring might be an effective solution.

9.4 Conclusion

In summary, in patients treated for AMP for a bone or soft tissue tumour in the lower extremity, rehabilitation services fall short against national standards and patient reported outcomes are poor. This raises significant concerns and points towards the transformation of health systems to optimise care. Main factors driving poor function have been identified and need to be managed and individualised to each patient guided by the ICF framework. Significant links between function and QoL, necessitates the introduction of a structured delivery of rehabilitation programs. Balance, gait and PA are affected after treatments for lower extremity musculoskeletal tumours, yet do not form a part of routine monitoring and management. Evidence on balance, gait and PA physical assessments is lacking and most tools used in the available studies do not satisfy indicators of validity and reliability. This raises concerns about accuracy and warrants the development of valid and reliable measures of function. Small BWMs could be potential low-cost solutions to rapidly assess these aspects of function, as they are feasible to use, acceptable, comfortable and provide valid information on outcomes. Certain measures of BWM outcomes are more sensitive than others, in characterising postural control, gait or ambulatory PA outcomes for different components of validity and can be used to guide rehabilitation practice.

Chapter 10: Appendices

1. Appendix 1.0: Participation invitation letter and information sent out to patients for the multi-centre Survey

Orthopaedic Research Department.
Date:

«title» «forename» «surname»
«address1»
«address2»
«address3»
«postcode»

OUTCOMES AFTER SARCOMA TREATMENT

Dear «title» «surname»,

Treatment for sarcoma often leads to physical impairments or difficulty with particular tasks. We are surveying patients across the country to find out more about this so that we can make recommendations about how to improve services and treatments.

We ask that you complete the questionnaire in this envelope. There are questions about how well you manage everyday tasks, pain, and your general wellbeing. Some questionnaires also ask about limb-fitting services. This is information that we can only get from patients like you.

All information collected will be kept strictly confidential and you will not be personally identified in any reports. Participation is voluntary and if you decide **not** to take part it will not affect your future care in any way.

If you are happy to take part, please complete the enclosed questionnaire **and return it in the pre-paid envelope.** Please try to answer every question and take a few minutes to check that you have not missed any pages. The questionnaire should take no more than half an hour to complete.

If you have any questions please contact a member of the Orthopaedic Research Team at the Freeman Hospital, Newcastle Upon Tyne on **0191-223-1514**, where you can speak to someone or leave a message.

If you do not wish to participate in this survey, please tick the box below and return this letter in the pre-paid envelope.

☐ I do not wish to participate in this survey.

With many thanks,
Yours sincerely,
Sherron Furtado
Sarcoma Research Physiotherapist
Musculoskeletal Services.
Newcastle NHS Foundation Trust,
Room 22a, Level 1, Freeman Hospital.
Freeman Road, High Heaton, Newcastle Upon Tyne, Tyne and Wear, NE7 7DN
01912231514

2. Appendix 2.0: Questionnaire to assess patient experience of rehabilitation (limb fitting) services after an amputation for sarcoma

Amputation for Bone or

Soft tissue Sarcoma

Questionnaire: Part Two

The Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne.

Oxford University Hospitals NHS Trust, Oxford.

The Robert Jones and Agnes Hunt Orthopaedic Hospital NHS Foundation Trust, Oswestry.

The Royal National Orthopaedic Hospital NHS Foundation Trust, Stanmore.

The Royal Orthopaedic Hospital NHS Foundation Trust, Birmingham.

Dear Patient

We would like to know more about the experience of patients who have had an amputation for sarcoma, because we are interested in whether or not the services that patients receive meet their needs. This questionnaire asks you about your experience of amputation and the limb fitting services you have received. Thank you for taking the time to complete it.

Thank you for completing this questionnaire.

Section 1: Before limb fitting

Please tick the most appropriate response:

1. Were you offered a preamputation consultation?

- ☐ Yes
- ☐ No
- ☐ Can't remember

If you answered **yes**, how well did it prepare you for amputation?

- ☐ Very well
- ☐ Well
- ☐ Neither well nor poorly
- ☐ Poorly
- ☐ Very poorly

If you answered **no,** do you think it would have been helpful?

- ☐ Yes
- ☐ No

2. Were you given the opportunity to meet someone who had already undergone a similar amputation before the amputation surgery?

- ☐ Yes
- ☐ No

If **yes**, was this helpful?

- ☐ Yes
- ☐ No

Section 2: Information

3. What aspects of limb fitting were you given information about? (Tick all answers that apply)

- ☐ Use of liners, socks, pads, sockets.
- ☐ Care of wound and artificial limb.
- ☐ Health promotion.
- ☐ Prevention and management of complications.
- ☐ Falls prevention and management techniques.
- ☐ Phantom limb sensation/pain.
- ☐ Limb volume changes.
- ☐ Increased effort during walking after amputation.
- ☐ Self management of artificial limb in different environments.
- ☐ Sporting & leisure activities.
- ☐ Availability of specialised local driving assessments
- ☐ Employment/Training.
- ☐ Local, national support groups and organisations.
- ☐ Support from Charities.
- ☐ Who to contact if you have a problem with your limb
- ☐ Something else (please specify) _____
- ☐ Can't remember

4. Was there any other information you would have found helpful?

- ☐ Yes
- ☐ No

If you answered yes, please expand,

_____

Section 3. Your experience of limb fitting

5. Which limb fitting centre do you go to?

_____

6. How do you usually get there?

- ☐ I drive
- ☐ I get driven by someone else in a private car
- ☐ Ambulance or ambulance car
- ☐ Public transport
- ☐ Taxi
- ☐ Something else

How long (approximately) does it take you to get there

_____ minutes

7. How soon after surgery did you visit the limb fitting centre?

- ☐ Within the first week
- ☐ Between 1 week and 1 month
- ☐ Between 3 and 6 months.
- ☐ Between 6 and 12 months.
- ☐ More than a year after surgery.
- ☐ I don't remember.

8. Did you use an early walking aid like a femurette or Pneumatic Post-Amputation Mobility aid (PPAM) during physiotherapy?

- ☐ Yes.
- ☐ No.
- ☐ Not Applicable.

If you answered yes: How soon after the surgery did you use it?

- ☐ Within the first week
- ☐ Between 1 week and 1 month
- ☐ Between 3 and 6 months.
- ☐ Between 6 and 12 months.
- ☐ More than a year after surgery.
- ☐ I don't remember.

9. How soon after surgery were you given a limb to use at home?

- ☐ Within the first week
- ☐ Between 1 week and 1 month
- ☐ Between 3 and 6 months.
- ☐ Between 6 and 12 months.
- ☐ More than a year after surgery.
- ☐ I don't remember.
- ☐ I haven't been given a limb.

10. How often do you use your artificial limb?

- ☐ Almost all the time
- ☐ At least daily
- ☐ At least once a week
- ☐ At least once a month
- ☐ Rarely
- ☐ Never

11. How many artificial limbs do you presently own?

_____

12. Do you agree with the statement “When I have a problem with my prosthesis, the repair and maintenance of prosthesis is handled in an appropriate time?”

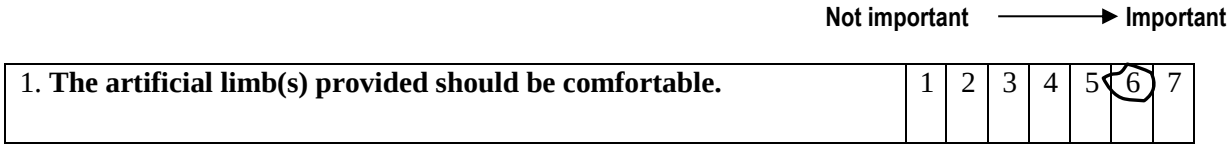
- ☐ Strongly agree
- ☐ Agree
- ☐ Neither agree nor disagree
- ☐ Disagree
- ☐ Strongly disagree

This section has pairs of questions.

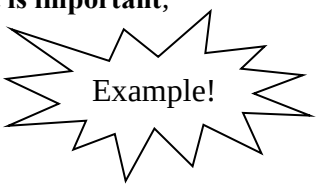
Please circle the most appropriate response:

The **first question** of each pair asks about what you think a good limb fitting service *should* be like, not about the service where you were treated.

Let's look at an example.

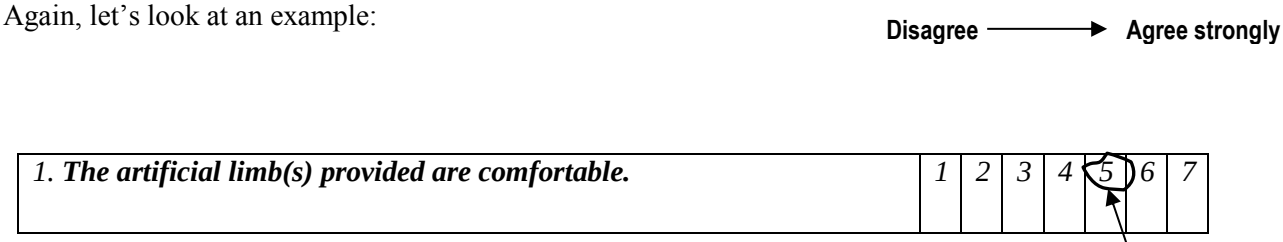


Question 1 looks at the importance of the comfort of the artificial limb. If it is ***very important*** to you that the limb is comfortable, you should circle the number **6 or 7**. If you **don't think it is important**, you should circle the **1 or 2**. If you have less strong opinions, you can circle 3, 4 or 5.

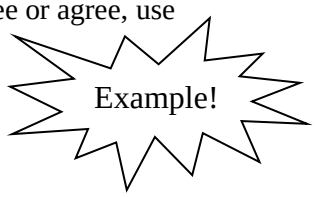


The **second question** of each pair looks at what you think of the limb fitting service where you were treated

Again, let's look at an example:



Here, if you strongly agree that your limb(s) are generally comfortable, you would put a 6 or 7. If you strongly disagree, you would put a 1 or 2. If you are not sure, or do not strongly disagree or agree, use 3, 4 or 5.



1. The artificial limb(s) provided should be comfortable.

Not important ⟶ Important

1	**2**	**3**	**4**	**5**	**6**	**7**

1.The artificial limb(s) provided is (are) comfortable.

Disagree ⟶ Agree strongly

1	**2**	**3**	**4**	**5**	**6**	**7**

2. The cosmetic appearance of artificial limbs should be satisfactory to the patient.

Not important ⟶ Important

1	**2**	**3**	**4**	**5**	**6**	**7**

2. The cosmetic appearance of my artificial limb(s) is satisfactory to me

Disagree ⟶ Agree strongly

1	**2**	**3**	**4**	**5**	**6**	**7**

3.The materials and components used to make the prosthesis should be of a high quality.

Not important ⟶ Important

1	*2*	*3*	*4*	*5*	*6*	*7*

3.Materials and components used to make my prosthesis are of a high quality.

Disagree → Agree strongly

1	*2*	*3*	*4*	*5*	*6*	*7*

4.Clinical staff should listen to my views on my care.

Not important → Important

1	*2*	*3*	*4*	*5*	*6*	*7*

4.Clinical staff do listen to my views on my care.

Disagree → Agree strongly

1	*2*	*3*	*4*	*5*	*6*	*7*

5.Limb fitting services should be flexible and convenient for patients

Not important → Important

1	*2*	*3*	*4*	*5*	*6*	*7*

5.My Limb Fitting Service is flexible and convenient for me

Disagree → Agree strongly

1	*2*	*3*	*4*	*5*	*6*	*7*

6.Prosthetists (limb fitters) should understand the specific needs of their patients.

Not important → Important

1	*2*	*3*	*4*	*5*	*6*	*7*

6.My prosthetist (limb fitter) understands my specific needs

Disagree → Agree strongly

1	*2*	*3*	*4*	*5*	*6*	*7*

7.Patients should have sufficient one-to-one time with their prosthetist (limb fitter).

Not important → Important

1	*2*	*3*	*4*	*5*	*6*	*7*

7.I have sufficient one-to-one time with my prosthetist (limb fitter).

Disagree → Agree strongly

1	*2*	*3*	*4*	*5*	*6*	*7*

8.Patients should be provided with adequate privacy during limb fittings

Not important → Important

1	2	3	4	5	6	7

8.I am provided with adequate privacy during my limb fittings

Disagree → Agree strongly

1	2	3	4	5	6	7

9.New artificial limbs and repairs should be completed in a timescale that suits the patient

Not important → Important

1	2	3	4	5	6	7

9.My new artificial limbs and repairs are completed in a timescale that suits me

Disagree ⟶ Agree strongly

1	2	3	4	5	6	7

10.Patients should have easy access to expert medical/nursing care related to their amputation/condition.

Not important ⟶ Important

1	2	3	4	5	6	7

10.I have easy access to expert medical /nursing care related to my amputation/condition.

Disagree ⟶ Agree strongly

1	**2**	**3**	**4**	**5**	**6**	**7**

Section 4.

Please tick the most appropriate response:

23 Where did you go for physiotherapy after surgery?

- ☐ The limb fitting centre
- ☐ Someone visited me at home

Somewhere else (please say where) _____

24. Do you agree with the statement "My physiotherapist set clear rehabilitation goals"

- ☐ Strongly agree.
- ☐ Agree.
- ☐ Neither agree nor disagree.
- ☐ Disagree
- ☐ Strongly disagree

If not, why not? _____

25. "Did you have a fall during your rehabilitation?"

- ☐ Yes
- ☐ No

If you had a fall, was it dealt with adequately?

- ☐ Yes
- ☐ No

If it was not, could you tell us why not?

---

26. How satisfied were you with the support provided by the occupational therapist for the following:

Training for return to paid or unpaid work and maintenance of the work role.

- ☐ Very satisfied.
- ☐ Somewhat satisfied.
- ☐ Neither.
- ☐ Somewhat dissatisfied
- ☐ Very dissatisfied
- ☐ Not Applicable

Training for recreational activities.

- ☐ Very satisfied.
- ☐ Somewhat satisfied.
- ☐ Neither.
- ☐ Somewhat dissatisfied
- ☐ Very dissatisfied

27. Did you have access to psychological support and counselling during limb fitting?

- ☐ Yes
- ☐ No

28. If you had complaints or feedback were these handled appropriately by the limb fitting team?

- ☐ Yes
- ☐ No

If no, please provide more information

Section 5. Amputation in the media

Please tell us what you think about people with amputation you see on the television or in the media.

29. Do you agree with the statement "Athletes and military personnel perform better because they have access to better prostheses than I do"

- ☐ Strongly agree
- ☐ Agree
- ☐ Neither agree nor disagree
- ☐ Disagree
- ☐ Strongly disagree

Section 6. Please answer the following questions about yourself:

Date of Birth: _____/_____/_____ or Age: _____

Day/ Month/ Year

Gender:

- ☐ Male
- ☐ Female

Height in feet/inches: ____ Weight in pounds/stones: ____

Walking aid used:

- ☐ Yes
- ☐ No

Date Questionnaire Completed: _____/_____/_____

Day/Month/Year

Please add any additional comments.

Please take a couple of minutes to check that you have answered every question. Thank you for participating in this survey

3. Appendix 3.0: Toronto Extremity Salvage Scale (TESS) - Patient–reported disease-specific clinical scales to assess function in adults

(See full TESS scale in Appendix 11.0)

Bone and Soft Tissue Sarcoma Audit

Please complete Part 1 and Part 2 of the questionnaire and return it in the prepaid envelope enclosed. If you have any questions about this survey please contact the Orthopaedic Research Team on 0191-223-1514. Participation is voluntary and you can refuse to take part, without giving a reason, and this will not affect your future care or relationship with staff. Data collected will be anonymous, held securely and at the end of the audit, destroyed as per Trust Policy.

For office use only – Hospital Staff to complete:

Adult Questionnaire

Diagnosis : _____

Anatomical Site of tumour :_____

Surgery Date: _____/_____/_____

Type of Lower Limb Loss or Deficiency :

☐ Through Hip ☐ Above Knee ☐ Symes

☐ Through knee ☐ Below Knee

Number of months post surgery:_____

Side of Surgery : 1. Right 2.Left

Type : 1. Bone Sarcoma 2. Soft tissue Sarcoma

Present Status : ☐ Sign of Active Disease

☐ No Sign of Active Disease

Participant Code : _____

Date Issued : _____

Questionnaire: Part 1

TORONTO EXTREMITY SALVAGE SCALE (TESS)

The following questions are about activities commonly performed in daily life. Each question asks that you mark each item (as in the examples below) opposite the description that best describes your ability to perform each task during the **past week.** Some activities will be extremely easy for you to do; others will be extremely difficult or impossible.

EXAMPLE

Riding a bicycle is:

1_____impossible to do.

2_____extremely difficult.

3_____moderately difficult.

4_____a little bit difficult.

5_____not at all difficult.

888____This task is not applicable for me.

You should choose the response "impossible to do...." if the activity is **something that you normally do** in your daily activities but are **now unable to do** because of physical limitations such as weakness, stiffness or pain.

If you do not perform an activity as part of your normal lifestyle you would choose the response "888" to indicate that the item is not applicable.

Mark all items ensuring that you choose the description that most accurately describes your abilities in the **past week.**

The following questions ask about your ability to perform activities that are common to every day life. Considering the amount of difficulty you have performing the activity due to the current problem you are having with your leg, please answer the questions by choosing the answer that best describes your ability to do the activity **over the past week.**

4. Appendix 4.0: Brief Pain Inventory – Short Form (BPI-SF) - Patient-reported pain scale.

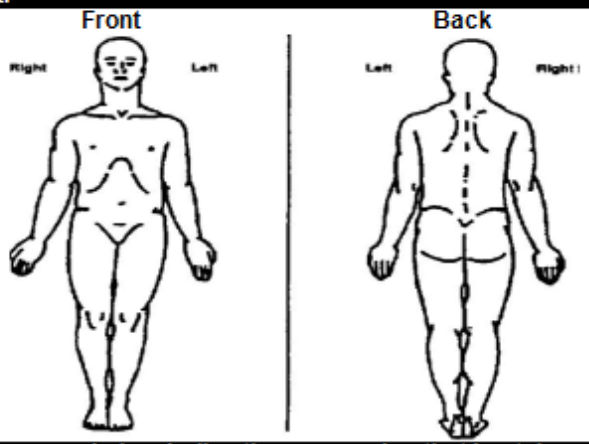
QUESTIONS ON PAIN

The following questions concern the amount of pain you have experienced in your lower limb (hip, thighs, knees, leg, ankle or foot) following your surgery. For each question please mark the appropriate answer related to the pain experienced in your lower limb.

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every- day kinds of pain today?

1. Yes 2. No

2 On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

7. What treatments or medications are you receiving for your pain?

---

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely interferes.

B. Mood.

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely interferes.

C. Walking Ability.

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely interferes.

D. Normal Work(Includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely interferes.

E. Relations with other people.

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely interferes.

F. Sleep.

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely interferes.

G. Enjoyment of Life.

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely interferes.

5. Appendix 5.0: Quality of Life – Cancer Survivors (QoL-CS) - Patient-reported disease-specific clinical scale to assess QoL in adults

(See full QoL-CS scale in Appendix 12.0)

QUALITY OF LIFE SCALE

Directions: We are interested in knowing how your experience of having cancer affects your Quality of Life. Please answer all of the following questions based on your life **at this time**.
Please circle the number from 0 - 10 that best describe your experiences:

Physical Well Being: To what extent are the following a problem for you:

1. **Fatigue**

no problem	0	1	2	3	4	5	6	7	8	9	10	severe problem

2. **Appetite changes**

no problem	0	1	2	3	4	5	6	7	8	9	10	severe problem

3. **Aches or pain**

no problem	0	1	2	3	4	5	6	7	8	9	10	severe problem

4. **Sleep changes**

no problem	0	1	2	3	4	5	6	7	8	9	10	severe problem

5. **Constipation**

no problem	0	1	2	3	4	5	6	7	8	9	10	severe problem

6. **Nausea**

no problem	0	1	2	3	4	5	6	7	8	9	10	severe problem

7. **Menstrual changes or fertility**

no problem	0	1	2	3	4	5	6	7	8	9	10	severe problem

6. Appendix 6.0: Search Strategy A and B for systematic review

Search Strategy A - Ovid MEDLINE

exp Bone Neoplasms/
exp chondrosarcoma/ or desmoplastic small round cell tumor/ or exp fibrosarcoma/ or hemangiosarcoma/ or histiocytoma, malignant fibrous/ or leiomyosarcoma/ or exp liposarcoma/ or exp lymphangiosarcoma/ or exp mixed tumor, mesodermal/ or myxosarcoma/ or exp osteosarcoma/ or exp sarcoma, alveolar soft part/ or exp sarcoma, small cell/ or exp sarcoma, synovial/
exp sarcoma/
((bone or soft tissue) adj6 (cancer or tumo*r or sarcoma or neoplasm)).mp
Sarcoma, Ewing/
"Giant Cell Tumor of Bone"/
Chondroblastoma/
exp Chondroma/
exp Soft Tissue Neoplasms/
exp neoplasms, adipose tissue/
neoplasms, nerve tissue/ or neurofibroma/ or neurofibrosarcoma/ or neuroma/ or neurothekeoma/ or exp neoplasms, vascular tissue/
"Neoplasms, Connective and Soft Tissue"/ or myofibroma/ or exp myxoma/ or sarcoma, clear cell/ or sarcoma, small cell/ or leiomyoma/ or myoma/
1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
Physical Fitness/
Motor Activity/
"Activities of Daily Living"/
Disabled Persons/
“functional disability”.mp
“outcome assessment”.mp
(function$ adj20 (ability or limitation or disability or outcome or global or physical)).mp
(physical adj20 (activity or performance or fitness or disability or outcome)).mp
“activity restriction”.mp
health status/
14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23
exp Extremities/
evaluat$.mp
assess$.mp
measur$.mp
26 or 27 or 28
13 and 24 and 25 and 29

Search Strategy B - Ovid MEDLINE

exp Bone Neoplasms/
exp chondrosarcoma/ or desmoplastic small round cell tumor/ or exp fibrosarcoma/ or hemangiosarcoma/ or histiocytoma, malignant fibrous/ or leiomyosarcoma/ or exp liposarcoma/ or exp lymphangiosarcoma/ or exp mixed tumor, mesodermal/ or myxosarcoma/ or exp osteosarcoma/ or exp sarcoma, alveolar soft part/ or exp sarcoma, small cell/ or exp sarcoma, synovial/ (61305)
exp sarcoma/ (122861)
((bone or soft tissue) adj6 (cancer or tumo*r or sarcoma or neoplasm)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (37324)
Sarcoma, Ewing/ (6065)
"Giant Cell Tumor of Bone"/ (1478)
Chondroblastoma/ (1017)
exp Chondroma/ (3687)
exp Soft Tissue Neoplasms/ (21367)
exp neoplasms, adipose tissue/ (17163)
neoplasms, nerve tissue/ or neurofibroma/ or neurofibrosarcoma/ or neuroma/ or neurothekeoma/ or exp

neoplasms, vascular tissue/ (74535)
"Neoplasms, Connective and Soft Tissue"/ or myofibroma/ or exp myxoma/ or sarcoma, clear cell/ or sarcoma, small cell/ or leiomyoma/ or myoma/ (25308)
1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (313014)
exp Extremities/ (291793)
evaluat$.mp. (2562060)
assess$.mp. (2083898)
measur$.mp. (2447881)
15 or 16 or 17 (5519992)
Postural Balance/ (16685)
"postural sway".mp. (1440)
"postural control".mp. (3334)
"postural equilibrium".mp. (129)
Gait/ (20199)
exp Walking/ (23323)
walk*.mp. (79029)
ambulation.mp. (9250)
exp Motor Activity/ (218267)
"physical activity".mp. (59062)
"activity restriction*".mp. (571)
"Activities of Daily Living"/ (53354)
"daily life activity".mp. (115)
"daily activity".mp. (2442)
"activity limitation*".mp. (1927)
"ambulatory activity".mp. (594)
"sedentary activity".mp. (311)
"gait cycle*".mp. (1385)
"movement intensit*".mp. (44)
19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 (369086)
13 and 14 and 18 and 38 (91)

7. Appendix 7.0: Participation Information Sheet (PIS)

The Newcastle upon Tyne Hospitals NHS NHS Foundation Trust | Newcastle University

Participant Information Sheet

Evaluation of Physical Functioning after treatment for Lower Extremity Bone and Soft tissue Tumours – A Feasibility Study of New Technologies

You are invited to participate in a research study, which will look into the potential for using new technologies to assess walking and other physical activities in patients who have been treated for bone or soft tissue tumours. Before you decide to participate we would like you to understand why the research is being done and what it would involve. Please take the time to read this information sheet and discuss it with your family and friends and/or GP before deciding about taking part.

One of the members of our team will go through the information sheet with you and answer any questions you have.

What is the purpose of this study?
Understanding how well patients can perform physical activities after treatment for bone or soft tissue tumours is important as treatment can have a major effect. We need better information about outcomes after treatment if we are to improve the treatments we offer. To date we have relied on questionnaires and observation to measure this.

New devices are now available which may give us better information about physical functioning. Some of these devices have been used successfully in other areas, but we don't know how useful they might be when used for patients who have had treatment for bone or soft tissue sarcoma. The aim of this study is to test these new devices with patients who have had treatment for bone or soft tissue sarcoma, to see if they can provide useful information, to find out how acceptable they are to patients and to compare the results with older assessment methods.

What are these technologies

The Xsens System is a series of sensors that provides information about the position of the joints during movement and has been used for motion tracking in the movie industry. It consists of five small sensors (38 x 53 x 21mm) which are connected to each other by a short wire. The sensors will be positioned at the pelvis, thighs and lower leg using Velcro straps.

The Open Source Movement Sensor (activity monitor) is a physical activity monitor that contains a very small chip called an accelerometer. This measures changes in movement, and stores information about movement that can be used to analyse activity patterns. The monitors are very small (36x39x13 mm) and lightweight and are made from skin safe hypo-allergenic materials. The monitors will be positioned using Velcro straps or adhesive tape.

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The Kinect System is a motion sensor used for video gaming and which can track the movements of someone standing in front of it.

Why have I been invited?

You have been invited to take part in the study because you have been treated for a bone or soft tissue tumour in the leg and are under the care of Newcastle Upon Tyne Hospitals NHS Foundation Trust

Do I have to take part?

It is up to you to decide to take part in the study. We will discuss the study, go through the information sheet, and give you the opportunity to look at the devices. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive. Participation in this study is purely voluntary and if you decide not to participate it will not affect your further care in the hospital.

What happens if I take part?

If you agree to take part in this study you will continue to receive the same standard of care as before. The study involves a one off assessment in the hospital which will take about an hour and a questionnaire to complete. The assessment involves carrying out a series of physical activities such as walking, standing up from sitting in a chair, and walking up and down stairs whilst wearing the Xsens and activity monitors and in front of the Kinect device.

You will then be asked to wear activity monitors for 7 days in your normal environment, for example at home or at work. These are worn on the wrist and the thigh and can be removed when bathing or sleeping. The devices collect information about how active you are, but do not collect data about where you are. We would also like you to complete an activity diary whilst the devices are being used. We ask that you send the monitors and the diary back to us in a stamped addressed envelope which we will provide.
You will not be held liable for any loss or damage to the monitors.

What are the potential disadvantages and risks of taking part?
There will be no X- rays or medical care involved in this study. The devices carry no known risks and we have not experienced any cases to date where wearing a device has been an issue. However, if you have any concerns or doubts you should stop wearing it and contact us directly.
There are no specific advantages to you for taking part in the study. However we hope the information we get from the study will help to improve the care of people diagnosed with bone or soft tissue tumours.

When will the study end?
The study involves a one off assessment and will end after you return the monitors.

Will my taking part in the research be confidential?
All information collected about you during the course of the research will be kept strictly confidential. Access to the data collected will be limited to those directly involved in the running of this study and you will be assigned a study code to protect your personal details. The data generated from this study may be used for presentation or publication but you will not be identified as an individual at any time. We will ask your permission to notify your GP of your participation in the study.

Where will the information be stored?
Data from this study will be stored by the Orthopaedic Research Staff in a secure office and will be kept on paper and computer for 5 years after the study finishes in accordance with the data protection legislation. Recordings will be anonymised and used only to ensure the reliability of the assessments.

What if there is a problem?
If you have a concern about any aspect of this study, you should ask to speak to the researcher who will do their best to answer your questions. If you remain unhappy, you can contact the Research Department on 01912231514 or 0191 21 39199.

Who is organising and funding the research?
The study is being led by Mr Craig Gerrand, Consultant Orthopaedic Surgeon and will be undertaken by the research staff working in the Department of Orthopaedic Surgery at the Freeman Hospital, Newcastle upon Tyne in collaboration with Newcastle University.

The Research Physiotherapist Sherron Furtado is responsible for day to day running of the study.
A Research Physiotherapist from the Orthopaedic Research Department will consent you for this study and carry out all of the evaluations with you. The funding for this study is covered by two charities "Children with Cancer, UK" and "Sarcoma UK".

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given a favourable opinion by Newcastle Research Ethics Committee.

Thank you for taking the time to read this Patient Information Sheet. If you have any questions about this study please contact the Chief Investigator, Mr Craig Gerrand via Miss Sherron Furtado on 0191 21 39199 or alternatively email her on sherron.furtado@nuth.nhs.uk.

If you would like to discuss any issues in confidence please contact the Patients Advisory Liaison Service (PALs). Part of the Newcastle Hospitals NHS Foundation Trust, Newcastle upon Tyne. PALs Office: North of Tyne PALS. Contact: Catherine Lee Telephone: 8000320202 Email:northoftynepals@nhct.nhs.uk

The Newcastle upon Tyne Hospitals NHS NHS Foundation Trust
Newcastle University

These pictures show you what the devices look like:

The XSens system

Activity monitor on the wrist

Kinect camera.

8. Appendix 8.0: Consent form

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Newcastle University

CONSENT FORM

Evaluation of Physical Functioning after treatment for Lower Extremity Bone and Soft tissue Tumours – A Feasibility Study of New Technologies

Name of Lead Researcher: Mr Craig Gerrand

Patient Identification Number for this trial: _____

Please initial the box corresponding to each statement.

1. I confirm that I have read and understood the Participant Information Sheet dated 26th August 2013 (version 1.0) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. I agree that if I withdraw for any reason data already collected with consent can be retained and used in the study. ☐

3. I understand that relevant sections of my medical notes and data collected during the study can be stored for up to 5 years, and may be looked at by individuals from the Orthopaedic Research Department, Newcastle University, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to the assessment being recorded. I understand that the recording will be anonymised and will be seen only by the direct research team. ☐

5. I agree to my GP being informed of my participation in the study. ☐

6. I agree to take part in the above study. ☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of person obtaining consent.	Date	Signature

When completed: 1 copy for participant, 1 copy for researcher site file, 1 (original) to be kept in medical notes.

Bone and Soft tissue Tumour Study Consent form Adult Version 1.0, 26th August 2013

9. Appendix 9.0: Review of clinical records for LSS and AMP groups

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Review of clinical records and measurement of baseline data

To be completed by Research Staff - Fill appropriate section.

Section 1: Clinical record of patients who have undergone limb sparing surgery.

Study Code : _____

1) Diagnosis: _____

2) Anatomical Site of tumour:

☐ Hip/Pelvis ☐ Above Knee ☐ Below Knee ☐ Ankle/Foot

3) Type of Limb Sparing Surgery :

☐ Resection ☐ Endoprosthesis ☐ Allograft

☐ Autograft ☐ Free flap ☐ Pedicled flap

☐ Other. Please specify _____

4) Multiple surgery/revision surgery : 1) Yes 2) No

If Yes : details

_____

_____

_____

5) Surgery Date: ____/____/____

Number of months post surgery:_____

6) Side of Surgery : 1. Right 2.Left

7) Type : 1. Bone Sarcoma 2. Soft tissue Sarcoma

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8) Radiotherapy : ☐ Yes ☐ No

If Yes : details

_____

_____

9) Details of Chemotherapy received :

_____

_____

10)Complications following surgery : ☐ Yes ☐ No

If Yes : details

_____

_____

_____

11)Present Status : ☐ Sign of Active Disease

☐ No Sign of Active Disease

12)Height in feet/inches: ____ Weight in pounds/stones: ____

Body mass index: ____

Please add any additional details:

_____

_____

_____

_____

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Section 2: Clinical Records of patients who have undergone amputation

Study Code : _____

1) Diagnosis : _____

2) Anatomical Site of tumour :

☐ Hip/Pelvis ☐ Above Knee ☐ Below Knee ☐ Ankle/Foot

3) Surgery Date: ____/____/____

4) Amputation: 1. Primary 2. Secondary

5) Type of Lower Limb Loss or Deficiency :

☐ Through Hip ☐ Above Knee ☐ Symes

☐ Through knee ☐ Below Knee

6) Number of months post surgery:_____

7) Side of Surgery : 1. Right 2.Left

8) Type : 1. Bone Sarcoma 2. Soft tissue Sarcoma

9) Radiotherapy : ☐ Yes ☐ No

If Yes : details

_____

_____

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10)Details of Chemotherapy received :

_____

_____

11)Complications following surgery : ☐ Yes ☐ No

If Yes : details

_____

_____

12)Uses Prosthetic Leg 1. Yes 2. No

If Yes: Give details:

_____

_____

_____

13)Present Status ☐ Sign of Active Disease

☐ No Sign of Active Disease

14)Height in feet/inches: ____ Weight in pounds/stones: ____

Body mass index: ____

13)Please add any additional details:

_____

_____

_____

_____

10. Appendix 10.0: GP letters

Orthopaedic Research Department
Department of Orthopaedic Surgery
Date:

«title» «forename» «surname» *[Details of GP]*
«address1»
«address2»
«address3»
«postcode»

«title» «forename» «surname» *[Details of Patient]*
«Date of Birth», «NHS Number»
«address1»«address2»«address3»«postcode»

Dear Dr «title» «surname»,

This letter is to make you aware that the above patient has been recruited into the Study "Evaluation of Physical Functioning in Lower Extremity Bone and Soft tissue Tumours – A Feasibility Study of New Technologies." This patient was invited to take part in the study because they have undergone treatment for a bone or soft tissue tumour affecting the lower extremity.

This feasibility work aims to explore the potential for new technologies such as Activity Monitors, the Xsens motion tracking system and Kinect to be effective as objective measures of activity and gait

Participation in the study involves a one off assessment in the hospital followed by a 7 day period of activity monitoring in the patient's normal environment. The assessment in the hospital should take no longer than 1 hour and will consist of completing health related questionnaires, clinic based measures and carrying out a series of activities whilst wearing the Activity Monitors and in front of the Kinect System.

This study is being supported by 2 charitable grant giving bodies: "Children with Cancer" and "Sarcoma UK". All information collected from the study is strictly confidential and securely stored. Participants will be assigned a study code and all personal identifiers will be removed from the data for the purposes of dissemination.

Yours sincerely

Sherron Furtado.
Sarcoma Research Physiotherapist.
Orthopaedic Research Department.
Level 1, Room 22.
Freeman Hospital.
Tel: 0191 21 39199.

11. Appendix 11.0: Toronto Extremity Salvage Scale (TESS) - Patient–reported disease-specific clinical scales to assess function in adults

Bone and Soft tissue Tumour Study

Please complete the following questionnaire and return it in the prepaid envelope enclosed. If you have any questions about this questionnaire please contact the Orthopaedic Research Team on 0191-448-917. Participation is voluntary and you can refuse to take part, without giving a reason, and this will not affect your future care or relationship with staff. Data collected will be anonymous, held securely and at the end of the audit, destroyed as per Trust Policy.

Please complete the following:

Date of Birth: _____/_____/_____

Day/ Month/ Year

Date questionnaire completed: : _____/_____/_____

Day/ Month/ Year

Please tick the appropriate box:

Gender:

☐ Male
☐ Female

Walking aid used:

☐ **Yes**
☐ **No**

Please turn to the next page.

For office use only – Hospital Staff to complete

Study Code : _____

Date Issued : _____/_____/_____

Day/ Month/ Year

TORONTO EXTREMITY SALVAGE SCALE (TESS)

The following questions are about activities commonly performed in daily life. Each question asks that you mark each item (as in the examples below) opposite the description that best describes your ability to perform each task during the **past week.** Some activities will be extremely easy for you to do, others will be extremely difficult or impossible.

EXAMPLE

Riding a bicycle is:

1____impossible to do.

2____extremely difficult.

3____moderately difficult.

4____a little bit difficult.

5____not at all difficult.

888____This task is not applicable for me.

You should choose the response "impossible to do...." if the activity is **something that you normally do** in your daily activities but are **now unable to do** because of physical limitations such as weakness, stiffness or pain.

If you do not perform an activity as part of your normal lifestyle you would choose the response "888" to indicate that the item is not applicable.

Mark all items ensuring that you choose the description that most accurately describes your abilities in the **past week.**

The following questions ask about your ability to perform activities that are common to every day life. Considering the amount of difficulty you have performing the activity due to the current problem you are having with your leg, please answer the questions by choosing the answer that best describes your ability to do the activity **over the past week.**

1) Putting on a pair of trousers is:

1____impossible to do.

2____extremely difficult.

3____moderately difficult.

4____a little bit difficult.

5____not at all difficult.

888____This task is not applicable for me.

2) Putting on shoes is:

1____impossible to do.

2____extremely difficult.

3____moderately difficult.

4____a little bit difficult.

5____not at all difficult.

888____This task is not applicable for me.

3) Putting on socks or stockings is:

1____impossible to do.

2____extremely difficult.

3____moderately difficult.

4____a little bit difficult.

5____not at all difficult.

888____This task is not applicable for me.

4) Showering is:

1____impossible to do.

2____extremely difficult.

3____moderately difficult.

4____a little bit difficult.

5____not at all difficult.

888____This task is not applicable for me.

5) Light household chores such as tidying and dusting are:

1____impossible to do.

2____extremely difficult.

3____moderately difficult.

4____a little bit difficult.

5____not at all difficult.

888____This task is not applicable for me.

6) Gardening and yard work are:

1____impossible to do.

2____extremely difficult.

3____moderately difficult.

4____a little bit difficult.

5____not at all difficult.

888____This task is not applicable for me.

7) Preparing and serving meals is:

1____impossible to do.

2____extremely difficult.

3____moderately difficult.

4____a little bit difficult.

5____not at all difficult.

888____This task is not applicable for me.

8) Going shopping is:

1____impossible to do.

2____extremely difficult.

3____moderately difficult.

4____a little bit difficult.

5____not at all difficult.

888____This task is not applicable for me.

9) Heavy household chores such as vacuuming and moving furniture is:

1____impossible to do.

2____extremely difficult.

3____moderately difficult.

4____a little bit difficult.

5____not at all difficult.

888____This task is not applicable for me.

10) Getting in and out of the bath tub is:

1____impossible to do.

2____extremely difficult.

3____moderately difficult.

4____a little bit difficult.

5____not at all difficult.

888____This task is not applicable for me.

11) Getting out of bed is:

1____impossible to do.

2____extremely difficult.

3____moderately difficult.

4____a little bit difficult.

5____not at all difficult.

888____This task is not applicable for me

12) Rising from a chair is:

1____impossible to do.

2____extremely difficult.

3____moderately difficult.

4____a little bit difficult.

5____not at all difficult.

888____This task is not applicable for me.

13) Kneeling is:

1____impossible to do.

2____extremely difficult.

3____moderately difficult.

4____a little bit difficult.

5____not at all difficult.

888____This task is not applicable for me.

14) Bending to pick something up off the floor is:

1____impossible to do.

2____extremely difficult.

3____moderately difficult.

4____a little bit difficult.

5____not at all difficult.

888____This task is not applicable for me.

15) Walking upstairs is:

1____impossible to do.

2____extremely difficult.

3____moderately difficult.

4____a little bit difficult.

5____not at all difficult.

888____This task is not applicable for me.

16) Walking downstairs is:

1____impossible to do.

2____extremely difficult.

3____moderately difficult.

4____a little bit difficult.

5____not at all difficult.

888____This task is not applicable for me.

17) Driving is:

1____impossible to do.

2____extremely difficult.

3____moderately difficult.

4____a little bit difficult.

5____not at all difficult.

888____This task is not applicable for me.

18) Walking within the house is:

1____impossible to do.

2____extremely difficult.

3____moderately difficult.

4____a little bit difficult.

5____not at all difficult.

888____This task is not applicable for me.

19) Walking outdoors is:

1____impossible to do.

2____extremely difficult.

3____moderately difficult.

4____a little bit difficult.

5____not at all difficult.

888____This task is not applicable for me.

20) Sitting is:

1____impossible to do.

2____extremely difficult.

3____moderately difficult.

4____a little bit difficult.

5____not at all difficult.

888____This task is not applicable for me.

21) Walking up or down hills or a ramp is:

1____impossible to do.

2____extremely difficult.

3____moderately difficult.

4____a little bit difficult.

5____not at all difficult.

888____This task is not applicable for me.

22) Standing upright is:

1____impossible to do.

2____extremely difficult.

3____moderately difficult.

4____a little bit difficult.

5____not at all difficult.

888____This task is not applicable for me.

23) Getting up from kneeling is:

1____impossible to do.

2____extremely difficult.

3____moderately difficult.

4____a little bit difficult.

5____not at all difficult.

888____This task is not applicable for me.

24) Getting in and out of a car is:

1____impossible to do.

2____extremely difficult.

3____moderately difficult.

4____a little bit difficult.

5____not at all difficult.

888____This task is not applicable for me.

25) Participating in sexual activities is:

1____impossible to do.

2____extremely difficult.

3____moderately difficult.

4____a little bit difficult.

5____not at all difficult.

888____This task is not applicable for me.

26) Completing my usual duties at work is: (Work includes both a job outside the home and as a homemaker.)

1____impossible to do.

2____extremely difficult.

3____moderately difficult.

4____a little bit difficult.

5____not at all difficult.

888____This task is not applicable for me.

27) Working my usual number of hours is: (Working includes both a job outside the home and as a homemaker.)

1____impossible to do.

2____extremely difficult.

3____moderately difficult.

4____a little bit difficult.

5____not at all difficult.

888____This task is not applicable for me.

28) Participating in my usual leisure activities is:

1____impossible to do.

2____extremely difficult.

3____moderately difficult.

4____a little bit difficult.

5____not at all difficult.

888____This task is not applicable for me.

29) Socializing with friends and family is:

1____impossible to do.

2____extremely difficult.

3____moderately difficult.

4____a little bit difficult.

5____not at all difficult.

888____This task is not applicable for me.

30) Participating in my usual sporting activities is:

1____impossible to do.

2____extremely difficult.

3____moderately difficult.

4____a little bit difficult.

5____not at all difficult.

888____This task is not applicable for me.

1) **Considering all the activities in which I participate in daily life, I would rate the ability to perform these activities during the past week as:**

1____impossible to do.

2____extremely difficult.

3____moderately difficult.

4____a little bit difficult.

5____not at all difficult

2) **I would rate myself as being:**

1____completely disabled.

2____ severely disabled.

3____ moderately disabled.

4____ mildly disabled.

5____ not at all disabled.

Please comment below on any activities you find difficult to perform or on any other difficulties you experience due to the problem you currently have in your leg that you feel are important and have not been asked about in this questionnaire.

_____

_____

_____

_____

Please check to make sure that you have answered all the questions.

Thank you for taking the time to answer these questions.

12. Appendix 12.0: Quality of Life – Cancer Survivors (QoL-CS) - Patient-reported disease-specific clinical scale to assess QoL in adults

QUALITY OF LIFE SCALE

Directions: We are interested in knowing how your experience of having cancer affects your Quality of Life. Please answer all of the following questions based on your life **at this time**.
Please circle the number from 0 - 10 that best describe your experiences:

Physical Well Being: To what extent are the following a problem for you:

1. Fatigue

no problem	0	1	2	3	4	5	6	7	8	9	10	severe problem

2. Appetite changes

no problem	0	1	2	3	4	5	6	7	8	9	10	severe problem

3. Aches or pain

no problem	0	1	2	3	4	5	6	7	8	9	10	severe problem

4. Sleep changes

no problem	0	1	2	3	4	5	6	7	8	9	10	severe problem

5. Constipation

no problem	0	1	2	3	4	5	6	7	8	9	10	severe problem

6. Nausea

no problem	0	1	2	3	4	5	6	7	8	9	10	severe problem

7. Menstrual changes or fertility

no problem	0	1	2	3	4	5	6	7	8	9	10	severe problem

8. Rate your overall physical health

Extremely poor	0	1	2	3	4	5	6	7	8	9	10	excellent

<u>Psychological Well Being Items:</u>

9. How difficult is it for you to cope today as a result of your disease and treatment?

not at all difficult	0	1	2	3	4	5	6	7	8	9	10	very difficult

10. How good is your quality of life?

extremely poor	0	1	2	3	4	5	6	7	8	9	10	excellent

11. How much happiness do you feel?

none at all	0	1	2	3	4	5	6	7	8	9	10	a great deal

12. Do you feel like you are in control of things in your life?

not at all	0	1	2	3	4	5	6	7	8	9	10	completely

13. How satisfying is your life?

not at all	0	1	2	3	4	5	6	7	8	9	10	completely

14. How is your present ability to concentrate or to remember things?

extremely poor	0	1	2	3	4	5	6	7	8	9	10	excellent

15. How useful do you feel?

not at all	0	1	2	3	4	5	6	7	8	9	10	extremely

16. Has your illness or treatment caused changes in your appearance?

not at all	0	1	2	3	4	5	6	7	8	9	10	extremely

17. Has your illness or treatment caused changes in your self concept (the way you see yourself)?

not at all	0	1	2	3	4	5	6	7	8	9	10	extremely

How distressing were the following aspects of your illness and treatment?

18. Initial diagnosis

not at all distressing	0	1	2	3	4	5	6	7	8	9	10	very distressing

19. Cancer treatments (i.e. chemotherapy, radiation, or surgery)

not at all distressing	0	1	2	3	4	5	6	7	8	9	10	very distressing

20. Time since my treatment was completed

not at all distressing	0	1	2	3	4	5	6	7	8	9	10	very distressing

21. How much anxiety do you have?

none at all	0	1	2	3	4	5	6	7	8	9	10	a great deal

22. How much depression do you have?

none at all	0	1	2	3	4	5	6	7	8	9	10	a great deal

To what extent are you <u>fearful</u> of:

23. Future diagnostic tests

no fear	0	1	2	3	4	5	6	7	8	9	10	extreme fear

24. A second cancer

no fear	0	1	2	3	4	5	6	7	8	9	10	extreme fear

25. Recurrence of your cancer

no fear	0	1	2	3	4	5	6	7	8	9	10	extreme fear

26. Spreading (metastasis) of your cancer

no fear	0	1	2	3	4	5	6	7	8	9	10	extreme fear

<u>Social Concerns</u>

27. How distressing has illness been for your family?

not at all	0	1	2	3	4	5	6	7	8	9	10	a great deal

28. Is the amount of support you receive from others sufficient to meet your needs?

not at all	0	1	2	3	4	5	6	7	8	9	10	a great deal

29. Is your continuing health care interfering with your personal relationships?

not at all	0	1	2	3	4	5	6	7	8	9	10	a great deal

30. Is your sexuality impacted by your illness?

not at all	0	1	2	3	4	5	6	7	8	9	10	a great deal

31. To what degree has your illness and treatment interfered with your employment?

no problem	0	1	2	3	4	5	6	7	8	9	10	severe problem

32. To what degree has your illness and treatment interfered with your activities at home?

no problem	0	1	2	3	4	5	6	7	8	9	10	severe problem

33. How much isolation do you feel is caused by your illness or treatment?

none	0	1	2	3	4	5	6	7	8	9	10	a great deal

34. How much financial burden have you incurred as a result of your illness and treatment?

none	0	1	2	3	4	5	6	7	8	9	10	a great deal

Spiritual Well Being

35. How important to you is your participation in religious activities such as praying, going to church?

not at all important	0	1	2	3	4	5	6	7	8	9	10	very important

36. How important to you are other spiritual activities such as meditation?

not at all important	0	1	2	3	4	5	6	7	8	9	10	very important

37. How much has your spiritual life changed as a result of cancer diagnosis?

less important	0	1	2	3	4	5	6	7	8	9	10	more important

38. How much uncertainty do you feel about your future?

not at all uncertain	0	1	2	3	4	5	6	7	8	9	10	very uncertain

39. To what extent has your illness made positive changes in your life?

none at all	0	1	2	3	4	5	6	7	8	9	10	a great deal

40. Do you sense a purpose/mission for your life or a reason for being alive?

none at all	0	1	2	3	4	5	6	7	8	9	10	a great deal

41. How hopeful do you feel?

not at all hopeful	0	1	2	3	4	5	6	7	8	9	10	very hopeful

Thank you for completing the questionnaire.

13. Appendix 13.0: Musculoskeletal Tumour Society Scoring system (MSTS) - Clinician reported disease-specific clinical scale to assess function in adults

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CLINIC BASED ASSESSMENT

Bone and Soft tissue Tumour Study

Evaluation of Physical Functioning after treatment of Lower Extremity Bone and Soft tissue Tumours – A Feasibility Study of New technologies

MUSCULOSKELETAL RATING SYSTEM (MSTS)

Motion:

All measures are based on active motion. The accompanying diagrams may be of assistance. Record the actual degrees for each motion. Sum the degrees of motion for all movements and circle the appropriate range of degrees under the motion heading.

Pain

Pain is rated on the same basis for each anatomic region and is evaluated on the basis of severity, constancy and use of mediation. Circle the appropriate medication or list it under other if it is not among those listed. Circle the appropriate rating based on the following criteria:

Excellent (5): No pain, no use of medication

Good (3): Modest or intermittent pain that is not disabling; intermittent use of anti inflammatory or non narcotic

Fair (1): Moderate pain that is not continuous but is disabling when present; occasional or intermittent use of narcotic (or equivalent) medication

Poor (0): Severe, continuous, disabling pain, continuous use of narcotic (or equivalent) medication

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Stability

Circle the supports used with a listing under other if the support has not been identified. Circle the appropriate rating based on the described criteria.

Deformity

Deformity in abduction, internal or external rotation refers to the arm being fixed in position. For example, a 20 degree internal rotation contracture means that the arm is fixed in 20 degrees of internal rotation such that it unable to rotate to neutral (zero degrees of rotation) and into external rotation. Shortening is measured in centimeters and refers to unequal arm lengths. Absence refers to subjects who have undergone amputation and will not be used in this study as all patients have undergone limb sparing surgery. The only exception is if the patient underwent amputation for a subsequent complication.

Strength

Strength is graded for each range of motion according to the International Rating or Medical Research Council criteria as follows:

0 – There is no palpable muscle contraction

1 – There is a palpable muscle contraction but the joint cannot be moved through a range of motion even with gravity eliminated

2 – The joint can be moved through a range of motion only with gravity eliminated

3 – The joint can be moved through a range of motion against gravity but no added resistance can be overcome

4 – Able to overcome some resistance applied manually through the range of motion against gravity. However, the resistance is less than the unaffected limb can overcome

5 – The same amount of resistance as the unaffected limb can be overcome through the range of motion

Record the strength for each range of motion and then circle the appropriate rating according to the criteria.

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Functional Activity

Circle the restricted activities listed under other any additional restrictions

Circle the rating according to the following criteria:

Recreational restrictions are those that do not seriously affect the patient's life-style or occupation

Partial disability includes restrictions that significantly affect the patient's life-style or produce partial occupational disability

Total disability signifies restrictions that cause major alterations in life-style or prevent the patient from resuming his occupation

Emotional Acceptance

Circle the appropriate rating based on the subject's choice of the following statements:

1. I am enthusiastic about the results of my procedure and if confronted with the same situation again, I would select the same treatment
2. I am satisfied with the result and if confronted with the same situation I would, after considerable thought, select the same treatment
3. I accept the result of my treatment although I do not like it; however, if another operation were available to improve the result, I would not have it
4. I hate the result of my treatment and if another operation were available to improve the result, I would have it

If the respondent chooses option 4, ask for the causes of dissatisfaction and circle the appropriate response. Use other and list any further reasons

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Musculoskeletal Tumour Rating Scale (MSTS): Foot/Ankle/Distal Leg

Study ID number_____; Score_____;

Score	1.Motion (Flexion - extension, foot vs. leg)	2. Pain	3. Stability	4.Deformity	5. Strength (In Dorsiflexion of ankle)	6. Functional Activity	7. Emotional Acceptance
5	>90 degrees	None	0-5 degrees varus/valgus;	0-5 degrees varus/valgus or equinus; no shortening	Normal Resistance (5)	No restrictions	Enthusiastic
3	60-90 degrees	Modest	5-10 degrees varus/valgus	5-10 degrees varus/valgus or equinus <1cm shortening	Less than normal resistance (4)	Recreational restrictions only	Satisfied
1	30-60 degrees	Moderate	10-20 degrees varus/valgus	10-20 degree varus/valgus or equinus 1-2cm shortening	Can only overcome gravity (3)	Partial disability	Accepts
0	0-30 degrees	Severe	>20 degrees varus/valgus cannot bear weight	>20 degree varus/valgus or equinus >2cm shortening; amputation	Cannot overcome gravity (0,1,2)	Total disability	Dislikes

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Musculoskeletal Tumour Rating Scale (MSTS): Proximal leg/knee/distal thigh

Study ID number_____; Score _____;

Score	1. Motion (Flexion-extension, leg vs thigh)	2. Pain	3. Stability	4. Deformity	5. Strength (in extension of knee)	6. Functional Activity	7. Emotional Acceptance
5	>90 degrees	None	0-5 degree varus/valgus; no giving way	0-5 degrees varus/valgus; 0-5 degree Flexion Contracture, no shortening	Normal resistance(5)	No restrictions	Enthusiastic
3	60-90 degrees	Modest	5-10 degree varus/valgus; no giving way	5-10 degree varus/valgus; 0-5degree Flexion Contracture; <1cm shortening	Less than normal resistance(4)	Recreational activities	Satisfied
1	30-60 degrees	Moderate	10-20 degree varus/valgus; occasional giving way	10-20 degree varus/valgus; 10-20 degree Flexion Contracture; 1-3cm shortening	Can only overcome gravity(3)	Partial disability	Accepts
0	0-30 degrees	Severe	>20 degrees varus/valgus; cannot bear weight or knee gives way	10-20 degree varus/valgus; 10-20 degree Flexion contracture; >3cm shortening; amputation	Cannot overcome gravity(0,1,2)	Total disability	Dislikes

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Musculoskeletal Tumour Rating Scale (MSTS): Proximal thigh/hip/pelvis

Study ID number_____; Score _____;

Score	1.Motion (Combined active flexion, abduction, and rotation of lower extremity on trunk)	2. Pain	3. Stability	4.Deformity	5. Strength (In abduction of hip)	6. Functional Activity	7. Emotional Acceptance
5	>180 degrees	None	Negative trendelenburg	0-5 degree adduction or flexion contracture; <1cm shortening	Normal (5)	No restrictions	Enthusiastic
3	120-180 degrees	Modest	Compensated trendelenburg without cane	5-10 degree adduction or flexion contracture; 1-2cm shortening	Less than normal resistance (4)	Recreational restrictions only	Satisfied
1	60-120 degrees	Moderate	Compensated trendelenburg with cane	10-20 degree adduction or flexion contracture; 2-4cm shortening	Can only overcome gravity (3)	Partial disability	Accepts
0	0-60 degrees	Severe	Compensated trendelenburg cannot bear weight	>20 degree adduction or flexion contracture; >4cm shortening; amputation	Cannot overcome gravity (0,1,2)	Total disability	Dislikes

14. Appendix 14.0: 3-metre Timed Up and Go (TUG) test

The Newcastle upon Tyne Hospitals NHS NHS Foundation Trust Newcastle University

Timed Up and Go (TUG) Test: Traditional Stop-watch TUG test

1. Equipment: arm chair, tape measure, tape, stop watch.
2. Begin the test with the subject sitting correctly in a chair with arms, the subject's back should resting on the back of the chair. The chair should be stable and positioned such that it will not move when the subject moves from sitting to standing.
3. Place a piece of tape or other marker on the floor 3 meters away from the chair so that it is easily seen by the subject.
4. Instructions: "On the word GO you will stand up, walk to the line on the floor, turn around and walk back to the chair and sit down. Walk at your regular pace.
5. Start timing on the word "GO" and stop timing when the subject is seated again correctly in the chair with their back resting on the back of the chair.
6. The subject wears their regular footwear, may use any gait aid that they normally use during ambulation, but may not be assisted by another person. There is no time limit. They may stop and rest (but not sit down) if they need to.
7. Normal healthy elderly usually complete the task in ten seconds or less. Very frail or weak elderly with poor mobility may take 2 minutes or more.
8. The subject should be given a practice trial that is not timed before testing.
9. Results correlate with gait speed, balance, functional level the ability to go out, and can follow change over time.
10. Interpretation < 10 seconds = normal
    < 20 seconds = good mobility, can go out alone, mobile without a gait aid.
    < 30 seconds = problems, cannot go outside alone, requires a gait aid.

A score of more than or equal to fourteen seconds has been shown to indicate high risk of falls.

15. Appendix 15.0: Patient activity diaries

Day 7 _____ Date ____/____/____

1 am _____
2 am _____
3 am _____
4 am _____
5 am _____
6 am _____
7 am _____
8 am _____
9 am _____
10 am _____
11 am _____
12 noon _____
1 pm _____
2 pm _____
3 pm _____
4 pm _____
5 pm _____
6 pm _____
7 pm _____
8 pm _____
9 pm _____
10 pm _____
11 pm _____
12 midnight _____

Usual activity level for day □ **Yes** □ **Less** □ **More**

Physical functioning after treatment for bone or soft tissue sarcoma

Activity Diary
Version1.0, 26st August 2013

Study ID: _____

Thank you for your help with this study. Please use this booklet to record when you have removed the monitor for any reason. Please record the time and reason for removal. For example,

6 am – Put monitor on rising from bed
8 pm – Removed monitor for 30 minutes to shower
10 pm – Removed monitor for night

Please also note on the diary if your daily activity has been an average day for that day of the week by ticking either yes or no in the boxes at the bottom of the page.

Usual activity level for day □ **Yes** □ **Less** □ **More**

If you do feel you have done more activity, please make a note on this page about this activity and the time period it covered. For example,
10 am to 2 pm – Went to watch football match / shopping
On the last page of the diary you are asked to give any feedback about your experience of wearing the monitor. Any comments will be greatly appreciated and will help in the design of future studies.

16. Appendix 16.0: Letter thanking participants

Orthopaedic Research Department
Department of Orthopaedic Surgery
Date:

«title» «forename» «surname»
«address1»
«address2»
«address3»
«postcode»

Thank you for participating in our research study of physical functioning after treatment for bone or soft tissue tumours.

Dear «title» «surname»,

We are writing to you to thank you for participating in the research study "Evaluation of Physical Functioning after treatment for Lower Extremity Bone and Soft tissue Tumours – A Feasibility Study of New technologies", in Newcastle Upon Tyne Hospitals NHS Foundation Trust.

We would be very interested to know what you thought of the devices that were used, and therefore would ask if you could fill in the feedback form enclosed and return it in the stamped addressed envelope enclosed.

If you have any other questions about the study please contact the Chief Investigator, Mr Craig Gerrand, Consultant Orthopaedic Surgeon via Sherron Furtado, Research Physiotherapist, Orthopaedic Research Department, Freeman Hospital, Newcastle Upon Tyne on 0191 22 31514 or 0191 21 39199.

Yours sincerely

Sherron Furtado.
Sarcoma Research Physiotherapist.
Orthopaedic Research Department.
Level 1, Room 22
Freeman Hospital
Tel: 0191 21 39199

Bone and Soft tissue Tumour Study Letter thanking the participant adult version 1.0, 26th August 2013

17. Appendix 17.0: Feedback forms to assess acceptability and comfort using these devices

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FEEDBACK FORM FOR ADULTS

Evaluation of Physical Functioning after treatment for Lower Extremity Bone and Soft tissue Tumours – A Feasibility Study of New Technologies

You are being asked to fill this feedback form, as you kindly agreed to participate in this Study. By you filling this form we hope to gain an overview of your experience and acceptability of the use of these technologies in patients with bone and soft tissue tumours.

We have added a short description at the bottom of this form to remind you about these devices.

A. Please answer Yes/No for the following questions:

1. Do you think you were comfortable using the following devices?

a. Xsens	Yes/No
b. Activity Monitor in clinic	Yes/No
c. Activity Monitor at home	Yes/No
d. Kinect	Yes/No

If you answered No:

Please explain:_____

2. Did your find the new devices acceptable?

a. Xsens	Yes/No
b. Activity Monitor in clinic	Yes/No
c. Activity Monitor at home	Yes/No
d. Kinect	Yes/No

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If you answered No:

Please explain: _____

3. Do you think we could have done anything better in the use of these devices in clinic or home?

Yes/No

If you answered Yes:

Please explain:_____

B. Please mark as many options

Which devices did you think were most user-friendly for you?

1. Activity Monitor
2. Xsens
3. Kinect

Please add any other comments:

_____
_____
_____
_____

Thank you for taking part in the study and taking time to fill thus feedback form.

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These pictures remind you what the devices look like:

1) Xsens: The device with black straps and wires – We helped you to wear it during the clinic visit.

2) Activity Monitor: 3 small monitors. We used them in the clinic visit and then handed you 2 monitors to take home. You were asked to send them back in a self addressed envelope.

3) Xbox Kinect: In the clinic you were asked to do some activities in front of this device.

18. Appendix 18.0: Derivation of balance outcomes from a BWM during standing (balance) test

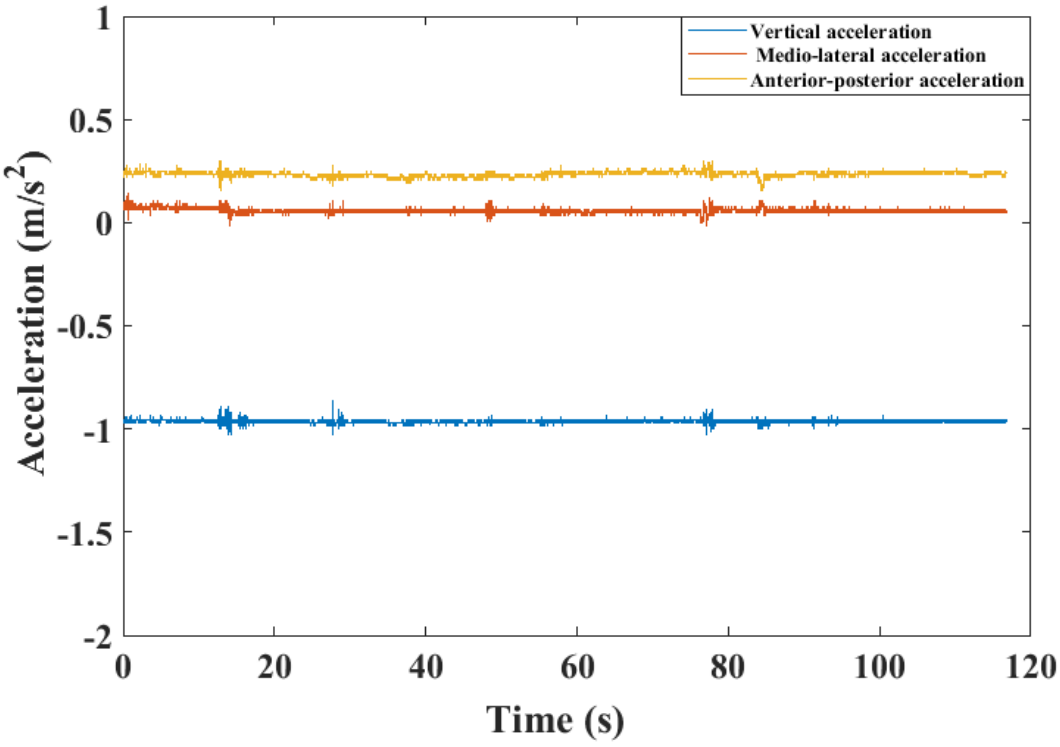

Figure 1: Example of a raw BWM acceleration signal during the standing (balance) test from a patient who underwent LSS for a lower extremity musculoskeletal tumour . This was analysed in MATLAB® (R2012a) program to derive balance outcomes

19. Appendix 19.0: Derivation of gait outcomes from a BWM during intermittent fast walk test

First, the vertical acceleration (Figure 1) was integrated, and then differentiated utilising a Gaussian CWT. From this, IC's were identified as the times of minimum acceleration (minima) of the first derivative. A further differentiation was then applied, to obtain a second derivative, from which FC's were identified as the times of maximum peaks (maxima). The pink diamond dots represent the initial contact and the red dots represent the final contact (Figure 2). An initial check revealed false IC events (non-IC events) from signal traces, suspected to be an artefact from contact with clothing. Hence, the algorithm was refined to restrict the IC peaks within a predetermined timed interval (0.25–2.25 s) (Najafi *et al.*, 2003), to optimise accuracy.

Previously the McCamley algorithm only estimated step time and stride time, however for this study to gather complete information on all events of the gait cycle, the IC/FC events were also used to estimate stance time and swing time (Figure 3) (Del Din *et al.*, 2015). This was calculated by analysing the sequence of IC and FC events , in relationship to the double support phase in the gait cycle.

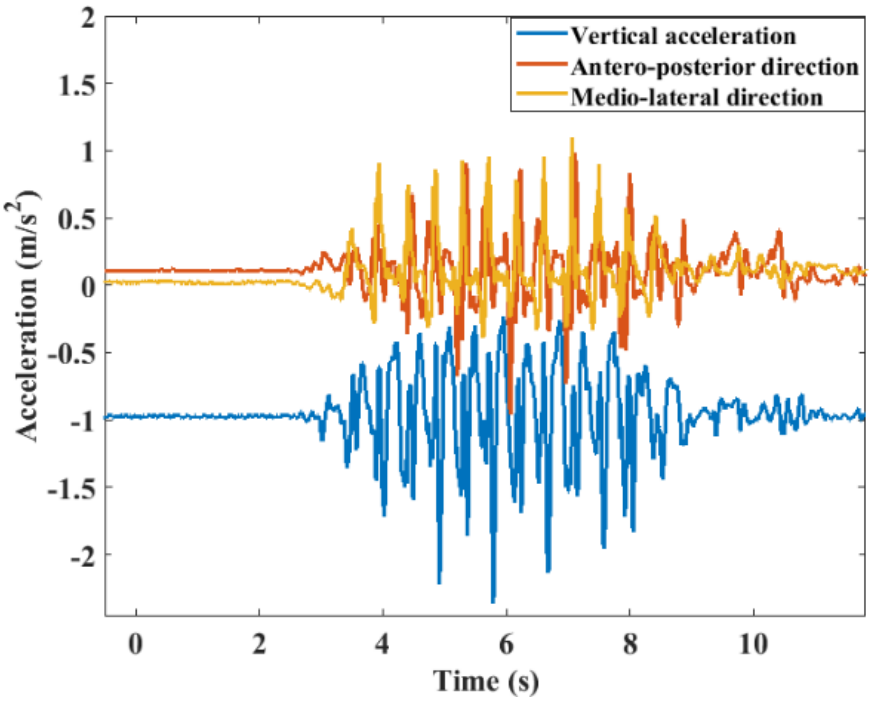

Figure 1: Raw acceleration signal obtained from BWM during the intermittent fast walk test: Orange lines is the acceleration measured in AP direction, yellow lines in ML direction and blue lines in vertical direction.

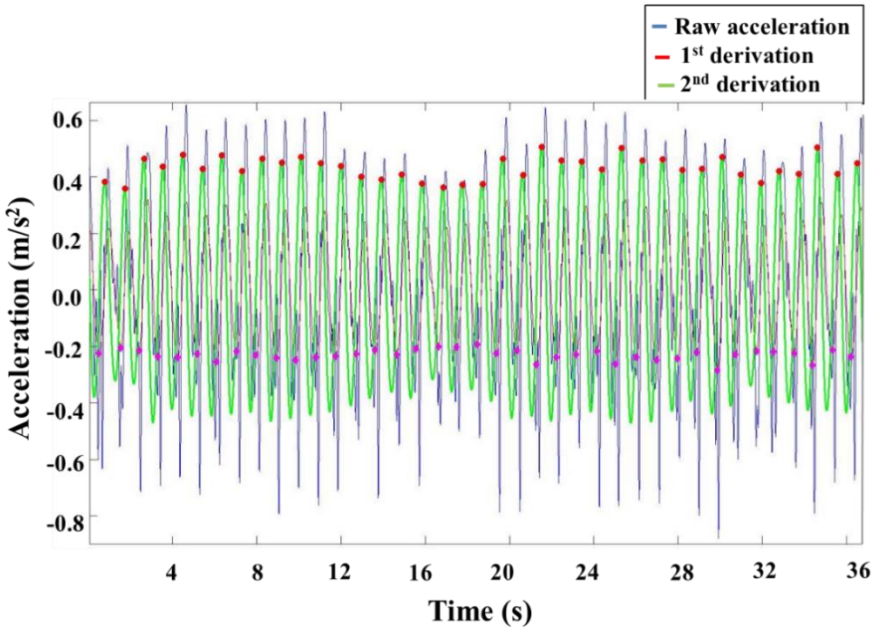

Figure 2: Raw Vertical Acceleration signal, 1st derivative, 2nd derivative, IC and FC event.

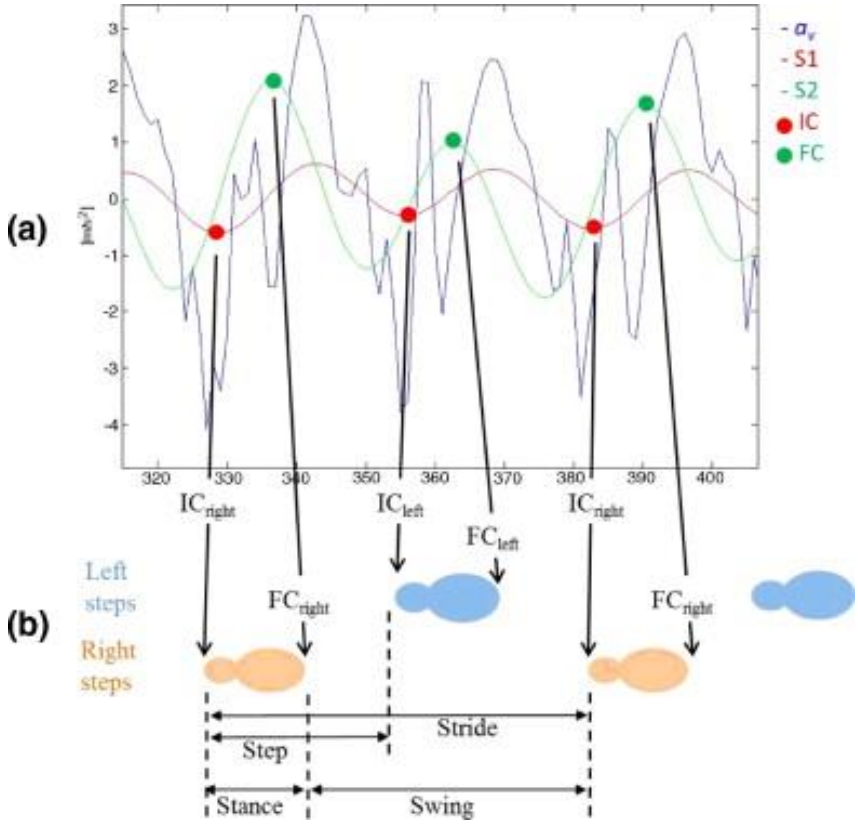

Figure 3: Derived temporal gait measures (step time, stride time, stance time, swing time). Figures adapted from Validation of an accelerometer to quantify a comprehensive battery of gait characteristics in healthy older adults and Parkinson's disease: toward clinical and at home use. By S Del Din, A Godfrey, L Rochester. "IEEE J Biomedical Health Informatics", Volume 20, Issue 3 page number 2168-2194. © 2015 Published by IEEE (Del Din *et al.*, 2015).

20. Appendix 20.0: Derivation of ambulatory PA outcomes from a BWM during free-living monitoring

In order to eliminate shorter stepping episodes and to define periods of walking or ambulatory bouts (Del Din *et al.*, 2016c), a threshold of 3 s was applied between these short stepping bouts, to group bouts before and after a short bout of standing. This is also referred to as the maximum resting period (MRP) used in previous research (Godfrey *et al.*, 2016).

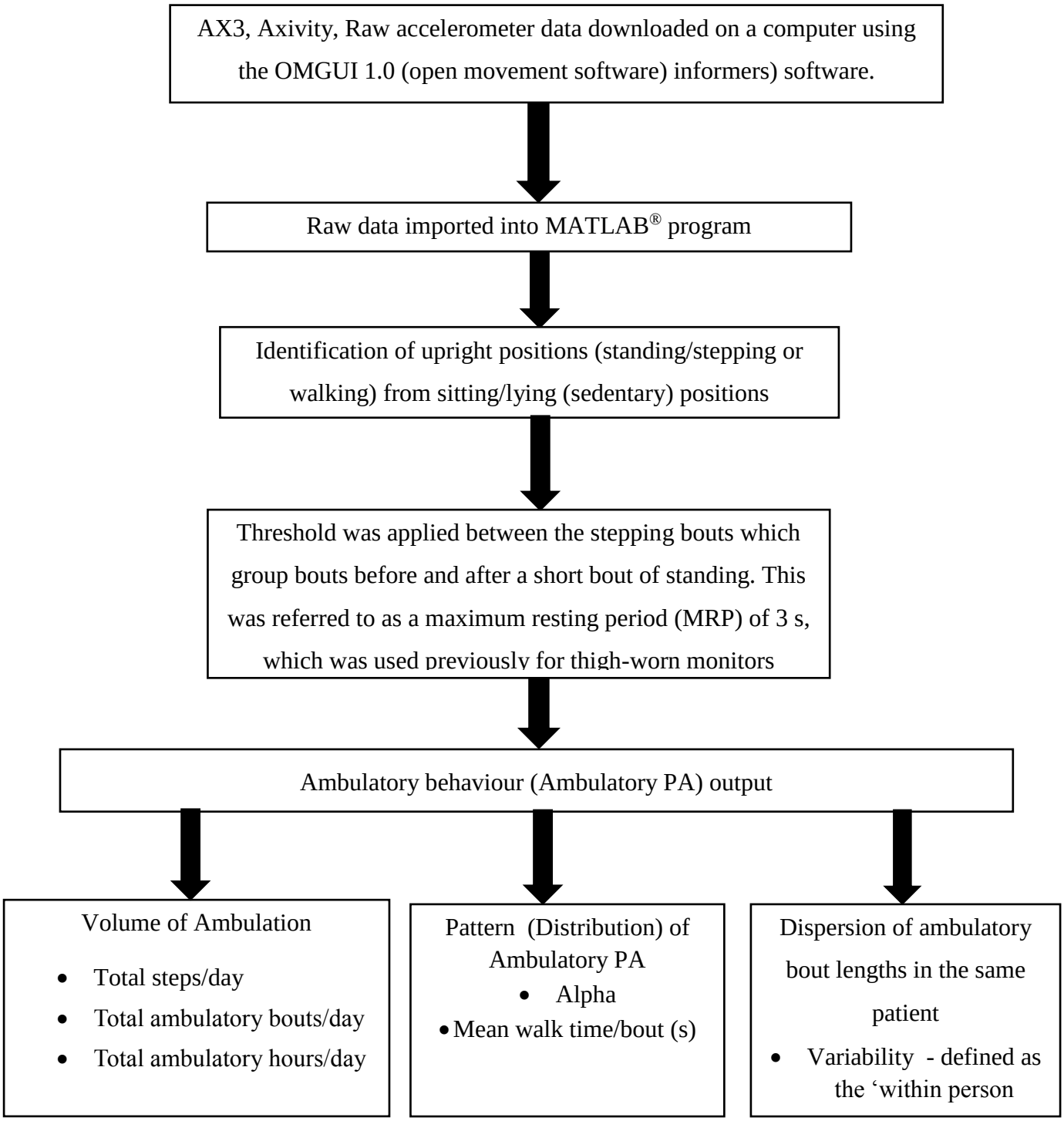

Figure 1: Flowchart of data downloading and data processing to obtain Ambulatory PA outcomes.

21. Appendix 21.0: Normality tests to investigate distribution of balance outcomes in tumour patients

Table 1: Distribution of balance outcomes in patients

Balance measures	Kolmogorov-Smirnova			Shapiro-Wilk		
	Statistic	Sample number	p-value (Sig*)	Statistic	Sample number	p-value (Sig*)
Ellipsis	0.298	**n=33**	<0.001*	0.609	**n=33**	<0.001*
Jerk	0.279		<0.001*	0.677		<0.001*
Jerk_AP	0.400		<0.001*	0.393		<0.001*
Jerk_ML	0.273		<0.001*	0.680		<0.001*
RMS	0.255		<0.001*	0.575		<0.001*
RMS_AP	0.211		0.001*	0.776		<0.001*
RMS_ML	0.191		0.004*	0.768		<0.001*
f95ML	0.194	**n=32**	0.003*	0.809	**n=32**	<0.001*
f95AP	0.121		0.200	0.930		0.038*

*=If p<0.05, as determined by Shapiro-Wilk test, data is not normally distributed, classed as non-parametric data.

22. Appendix 22.0: Sub-group analysis by age - Significant differences in balance outcomes between patients and controls

Table 2.1: Significant differences in RMS and f95_AP between young patients and young controls (age: 20-35 years old)($p<0.05$)

Comparison test	Mann-Whitney U test			Independent t test
Balance measures	RMS (m/s^2)	RMS_AP (m/s^2)	RMS_ML (m/s^2)	f95_AP (Hz)
Patients (n=11)	0.0018 (0.0015-0.0027)	0.0015 (0.0012-0.0022)	0.0009 (0.0007- 0.0011)	1.4582 ± 0.8423
Controls (n=6)	0.0059 (0.0038-0.0098)	0.0076 (0.0058 -0.0180)	0.0102 (0.0073 - 0.0199)	2.7361± 1.0349
Z or t statistic	Z = -3.216	Z = -3.317	Z =- 3.333	T = 2.764
p-value	0.001*	0.001*	0.001*	0.014*

p-value – difference between groups (*=statistically significant)

Table 2.2: Significant Differences in Jerk between young patients and young controls (age: 20-35 years old) ($p<0.05$)

Mann-Whitney U test	Jerk (m^2/s^5)	Jerk_AP (m^2/s^5)	Jerk_ML (m^2/s^5)
Patients (n=11)	0.1049 (0.0356 - 0.1168	0.0423 (0.0285 - 0.0570)	0.0518 (0.0356 - 0.1168)
Controls (n=6)	0.0354 (0.0270 - 0.0391)	0.0142 (0.0121 - 0.0172)	0.0182 (0.0151 - 0.0240)
Z statistic	-3.317	-3.116	-3.319
p-value	0.001*	0.002*	0.001*

p-value – difference between groups (*=statistically significant)

Table 2.3: Differences between middle-aged + elderly patients and middle-aged + elderly controls (age: 36-89 years old) (p<0.05)

Mann-Whitney U	Ellipsis (m^2/s^4)	RMS (m/s^2)	RMS_AP (m/s^2)	RMS_ML (m/s^2)
Patients (n=18)	0.0484	0.0020	0.0013	0.00125
	(0.0254- 0.1428)	(0.0016 - 0.0048)	(0.0012 - 0.0035)	(0.0008 - 0.0019)
Controls (n=15)	0.0004	0.0008	0.0008	0.0003
	(0.0002 - 0.0015)	(0.0007 - 0.0010)	(0.0007 - 0.0009)	(0.0007 - 0.0019)
Z-statistic	-5.2048	-4.903	-4.823	-4.721
p-value	<0.001*	0.000001*	0.000001*	0.000002*

p-value – difference between groups (*=statistically significant)

23. Appendix 23.0: Normality tests to investigate distribution of gait outcomes in tumour patients

Table 3: Distribution of gait outcomes in patients

BWM fast walk measures	Kolmogorov-Smirnova			Shapiro-Wilk		
	Statistic	Sample number	p-value (Sig*)	Statistic	Sample number	p-value (Sig*)
Step time(s)	0.193	**n=29**	0.007*	0.832	**n=29**	<0.001*
Stride time(s)	0.193		0.007*	0.830		<0.001*
Stance time(s)	0.134		0.197*	0.913		0.020*
Swing time(s)	0.228		<0.001*	0.790		<0.001*
Total time (s)	0.188		0.010*	0.862		0.001*
Step length(m)	0.125		0.200	0.966		0.450
Step velocity (m/s)	0.121		0.200	0.958		0.296

*= If p<0.05, as determined by Shapiro-Wilk test, data is not normally distributed, classified as non-parametric data.

24. Appendix 24.0: Sub-group analysis by age - Significant differences in gait outcomes between patients and controls

Table 4.1: Differences in temporal gait outcomes between young patients and young controls (age: 20-35 years old)($p<0.05$)

Mann-Whitney U	Step time (s)	Stance time (s)	Swing time (s)
Patients (n=10)	0.562 (0.503 - 0.601)	0.688 (0.650 - 0.774)	0.385 (0.360 - 0.4605)
Controls (n=9)	0.461 (0.418 - 0.497)	0.590 (0.536 - 0.663)	0.307 (0.2988 - 0.3350)
Z-statistic	-3.184	-2.736	-3.429
p-value	0.001*	0.006*	0.001*

* = $p<0.05$ indicates significant differences between groups

Table 4.2: Independent t test – Differences in spatial and spatio-temporal gait outcomes between young patients and young controls (age: 20-35 years old)($p<0.05$)

Independent t test	Step Length (m)	Step Velocity (m/s)
Patients (n=10)	0.699 ±0.0457	1.276±0.137
Controls (n=9)	0.665±0.107	1.453±0.184
T-statistic	0.914	-2.395
p-value	0.374	0.028*

* = $p<0.05$ indicates significant differences between groups

Table 4.3: Differences in temporal gait outcomes between middle-aged + elderly patients and middle-aged + elderly controls (age: >43 and ≤89 years old) ($p<0.05$)

Mann-Whitney U	Step time (s)	Stance time (s)	Swing time (s)
Patients (n=10)	0.55 (0.47 - 0.57)	0.69 (0.61 - 0.72)	0.38 (0.33 - 0.42)
Controls (n=19)	0.49 (0.47 - 0.52)	0.64 (0.61 - 0.68)	0.34 (0.32 - 0.38)
Z-statistic	-1.582	-1.419	-1.622
p-value	0.120	0.164	0.110

p-value – difference between groups (*=statistically significant)

Table 4.4: Differences between spatial and spatio-temporal gait between middle-aged + elderly patients and middle-aged + elderly controls (age: >43 and ≤89 years old) ($p<0.05$)

Independent t test	Step Length (m)	Step Velocity (m/s)
Patients (n=12)	0.60467±0.107401	1.14±0.218
Controls (n=19)	0.70586±0.108672	1.47±0.273
T-statistic	-2.536	-3.518
p-value	0.017*	0.001*

p-value – difference between groups (*=statistically significant)

25. Appendix 25.0: Normality tests to investigate distribution of iTUG outcomes

Table 5: Distribution of iTUG outcomes in patients

iTUG measure	Kolmogorov-Smirnova			Shapiro-Wilk		
	Statistic	Sample number	p-value (Sig*)	Statistic	Sample number	p-value (Sig*)
iTUG time	0.162	n = 33	0.027*	0.863	n = 33	0.001*

*= If $p<0.05$, as determined by Shapiro-Wilk test, data is not normally distributed, classified as non-parametric data.

26. Appendix 26.0: Ambulatory PA outcomes for individual sarcoma patients and data loss

Patient	Thigh Sensor Data	No. of Days Extracted	No. of Days of Gait Data Extracted	Data used for analysis (Y=Yes, N=No)
SC01	Y	7	5	Y
SC02	Y	7	7	Y
SC03	Y	7	7	Y
SC04	Y	7	7	Y
SC05	Y	6	3	Y
SC06	Y	7	7	Y
SC07	Y	7	7	Y
SC08	Y	5	5	Y
SC09	Y	5	5	N
SC10	Y	5	5	N
SC11	Y	7	7	Y
SC12	Y	7	7	Y
SC13	Y	7	7	Y
SC14	Y	7	5	Y
SC15	Y	7	7	Y
SC16	Y	6	6	Y
SC17	Y	7	7	Y
SC18	Monitors not returned	No data	No data	N
SC19	Y	3	3	Y
SC20	Y	7	7	Y
SC21	Y	7	7	Y
SC22	Y	7	7	Y
SC23	Y	7	7	Y
SC24	Y	4	4	Y
SC25	Y	6	6	Y
SC26	Y	3	3	Y
SC27	Y	2	2	Y
SC28	Y	1	1	N
SC29	Y	1	1	N
SC30	Y	7	7	Y
SC31	Y	7	7	Y
SC32	Y	7	7	Y
SC33	Unable to extract	-	-	N (Data not extracted)
SC34	Y	7	7	Y
SC35	Y	7	7	Y
SC36	Y	7	7	Y
SC37	Y	6	6	Y
SC38	Y	7	7	Y
SC39	Y	7	7	Y
SC40	Y	7	7	Y

27. Appendix 27.0: Normality tests to investigate distribution of ambulatory PA outcomes

Table 7: Distribution of Ambulatory PA outcomes in patients

	Kolmogorov-Smirnov			Shapiro-Wilk		
	Statistic	Sample number	p-value (Sig*)	Statistic	Sample number	p-value (Sig*)
Total steps/day	0.128	n=32	0.200	0.970	n=32	0.584
Total ambulatory bouts/day	0.157		0.076	0.922		0.040*
Total ambulatory hours walked/day	0.096		0.200	0.976		0.739
Mean walk time per bout (s)	0.116		0.200	0.927		0.053
Alpha	0.241		<0.001*	0.839		0.001*
Variability	0.083		0.200	0.986		0.964

*=If p<0.05, as determined by Shapiro-Wilk test, data is not normally distributed, classed as non-parametric data.

References

(CCSS), T.C.C.S.S. (2017) *The Childhood Cancer Survivor Study (CCSS)*. Available at: https://ccss.stjude.org/ (Accessed: 12/02/2017).

(CSP), C.S.o.P. (2012) *Evidence Based Clinical Guidelines for the Physiotherapy Management of Adults with Lower Limb Prostheses* Chartered Society of Physiotherapy (CSP)http://www.csp.org.uk/publications/evidence-based-clinical-guidelines-physiotherapy-management-adults-lower-limb-prosthese.

(NCIN), N.C.I.N. (2017a) 'NCIN - Data Briefing', *Bone Sarcomas: incidence and survival rates in England - NCIN Data Briefing*. Available at: http://www.ncin.org.uk/publications/data_briefings/bone_sarcomas_incidence_and_survival (Accessed: 12/02/2017).

(NCIN), N.C.I.N. (2017b) 'NCIN Data Briefing', *Soft Tissue Sarcomas: incidence and survival rates in England*. Available at: http://www.ncin.org.uk/publications/data_briefings/soft_tissue_sarcoma (Accessed: 06.03.2017).

(WHO), W.H.O. (2002) *Towards a Common Language for Functioning, Disability and Health*. Available at: http://www.who.int/classifications/icf/en/ (Accessed: 06/02/2016).

Aksnes, L.H., Bauer, H.C., Jebsen, N.L., Folleras, G., Allert, C., Haugen, G.S. and Hall, K.S. (2008) 'Limb-sparing surgery preserves more function than amputation: a Scandinavian sarcoma group study of 118 patients', *J Bone Joint Surg Br*, 90(6), pp. 786-94.

Anderson, E. and Shivakumar, G. (2013) 'Effects of exercise and physical activity on anxiety', *Front Psychiatry*, 4, p. 27.

Angela Coulter, R.F., Jocelyn Cornwell (2009) *The Point of Care Measures of patients' experience in hospital: purpose, methods and uses*. [Online]. Available at: https://www.kingsfund.org.uk/sites/files/kf/Point-of-Care-Measures-of-patients-experience-in-hospital-Kings-Fund-July-2009.pdf.

Armstrong, R.A. (2014) 'When to use the Bonferroni correction', *Ophthalmic Physiol Opt*, 34(5), pp. 502-8.

Arnold, C.M., Sran, M.M. and Harrison, E.L. (2008) 'Exercise for fall risk reduction in community-dwelling older adults: a systematic review', *Physiother Can*, 60(4), pp. 358-72.

Bachlin, M., Plotnik, M., Roggen, D., Maidan, I., Hausdorff, J.M., Giladi, N. and Troster, G. (2010) 'Wearable assistant for Parkinson's disease patients with the freezing of gait symptom', *IEEE Trans Inf Technol Biomed*, 14(2), pp. 436-46.

Barbaric, M., Brooks, E., Moore, L. and Cheifetz, O. (2010) 'Effects of Physical Activity on Cancer Survival: A Systematic Review', *Physiotherapy Canada*, 62(1), pp. 25-34.

Barclay-Goddard, R., Stevenson, T., Poluha, W., Moffatt, M.E. and Taback, S.P. (2004) 'Force platform feedback for standing balance training after stroke', *Cochrane Database Syst Rev*, (4), p. Cd004129.

Barrera, M., Teall, T., Barr, R., Silva, M. and Greenberg, M. (2012) 'Health related quality of life in adolescent and young adult survivors of lower extremity bone tumors', *Pediatr Blood Cancer*, 58(2), pp. 265-73.

Barry, E., Galvin, R., Keogh, C., Horgan, F. and Fahey, T. (2014) 'Is the Timed Up and Go test a useful predictor of risk of falls in community dwelling older adults: a systematic review and meta-analysis', *BMC Geriatr*, 14, p. 14.

Bartlett, J.W. and Frost, C. (2008) 'Reliability, repeatability and reproducibility: analysis of measurement errors in continuous variables', *Ultrasound Obstet Gynecol*, 31(4), pp. 466-75.

Basso, M.R., Bornstein, R.A. and Lang, J.M. (1999) 'Practice effects on commonly used measures of executive function across twelve months', *Clin Neuropsychol*, 13(3), pp. 283-92.

Bauman, A., Smith, B., Stoker, L., Bellew, B. and Booth, M. (1999) 'Geographical influences upon physical activity participation: evidence of a 'coastal effect'', *Australian and New Zealand Journal of Public Health*, 23(3), pp. 322-324.

Beebe, K., Song, K.J., Ross, E., Tuy, B., Patterson, F. and Benevenia, J. (2009) 'Functional Outcomes After Limb-Salvage Surgery and Endoprosthetic Reconstruction With an Expandable Prosthesis: A Report of 4 Cases', *Archives of Physical Medicine and Rehabilitation*, 90(6), pp. 1039-1047.

Bekkering, W.P., Vlieland, T., Koopman, H.M., Schaap, G.R., Beishuizen, A., Anninga, J.K., Wolterbeek, R., Nelissen, R. and Taminiau, A.H.M. (2012a) 'A prospective study on quality of life and functional outcome in children and adolescents after malignant bone tumor surgery', *Pediatric Blood & Cancer*, 58(6), pp. 978-985.

Bekkering, W.P., Vlieland, T., Koopman, H.M., Schaap, G.R., Schreuder, H.W.B., Beishuizen, A., Jutte, P.C., Hoogerbrugge, P.M., Anninga, J.K., Nelissen, R. and Taminiau, A.H.M. (2011) 'Functional Ability and Physical Activity in Children and Young Adults After Limb-Salvage or Ablative Surgery for Lower Extremity Bone Tumors', *Journal of Surgical Oncology*, 103(3), pp. 276-282.

Bekkering, W.P., Vlieland, T.P., Koopman, H.M., Schaap, G.R., Schreuder, H.W., Beishuizen, A., Tissing, W.J., Hoogerbrugge, P.M., Anninga, J.K. and Taminiau, A.H. (2009) 'The Bt-DUX: development of a subjective measure of health-related quality of life in patients who underwent surgery for lower extremity malignant bone tumor', *Pediatr Blood Cancer*, 53(3), pp. 348-55.

Bekkering, W.P., Vliet Vlieland, T.P., Koopman, H.M., Schaap, G.R., Beishuizen, A., Anninga, J.K., Wolterbeek, R., Nelissen, R.G. and Taminiau, A.H. (2012b) 'A prospective study on quality of life and functional outcome in children and adolescents after malignant bone tumor surgery', *Pediatr Blood Cancer*, 58(6), pp. 978-85.

Beltran Valls, M.R., Dimauro, I., Brunelli, A., Tranchita, E., Ciminelli, E., Caserotti, P., Duranti, G., Sabatini, S., Parisi, P., Parisi, A. and Caporossi, D. (2014) 'Explosive type of moderate-resistance training induces functional, cardiovascular, and molecular adaptations in the elderly', *Age (Dordr)*, 36(2), pp. 759-72.

Benedetti, M.G., Di Gioia, A., Conti, L., Berti, L., Esposti, L.D., Tarrini, G., Melchionda, N. and Giannini, S. (2009) 'Physical activity monitoring in obese people in the real life environment', *J Neuroeng Rehabil*, 6, p. 47.

Benini, L., Farella, E. and Guiducci, C. (2006) 'Wireless sensor networks: Enabling technology for ambient intelligence', *Microelectronics Journal*, 37(12), pp. 1639-1649.

Bidargaddi, N., Klingbeil, L., Sarela, A., Boyle, J., Cheung, V., Yelland, C., Karunanithi, M. and Gray, L. (2007) 'Wavelet based approach for posture transition estimation using a waist worn accelerometer', *Conf Proc IEEE Eng Med Biol Soc*, 2007, pp. 1884-7.

Bird, M.L., Hill, K., Ball, M. and Williams, A.D. (2009) 'Effects of resistance- and flexibility-exercise interventions on balance and related measures in older adults', *J Aging Phys Act*, 17(4), pp. 444-54.

Borghouts, J.A., Koes, B.W. and Bouter, L.M. (1998) 'The clinical course and prognostic factors of non-specific neck pain: a systematic review', *Pain*, 77(1), pp. 1-13.

Bornbaum, C.C., Doyle, P.C., Skarakis-Doyle, E. and Theurer, J.A. (2013) 'A critical exploration of the International Classification of Functioning, Disability, and Health (ICF) framework from the perspective of oncology: recommendations for revision', *J Multidiscip Healthc*, 6, pp. 75-86.

Bosmans, J., Geertzen, J. and Dijkstra, P.U. (2009) 'Consumer satisfaction with the services of prosthetics and orthotics facilities', *Prosthet Orthot Int*, 33(1), pp. 69-77.

Brodie, M., Lord, S., Coppens, M., Annegarn, J. and Delbaere, K. (2015) 'Eight weeks remote monitoring using a freely worn device reveals unstable gait patterns in older fallers', *IEEE Transac Bio-Med Eng*, 62(11), pp. 2588-94.

Brodie, M.A., Coppens, M.J., Lord, S.R., Lovell, N.H., Gschwind, Y.J., Redmond, S.J., Del Rosario, M.B., Wang, K., Sturnieks, D.L., Persiani, M. and Delbaere, K. (2016) 'Wearable pendant device monitoring using new wavelet-based methods shows daily life and laboratory gaits are different', *Med Biol Eng Comput*, 54(4), pp. 663-74.

Brown, K., Topp, R., Brosky, J.A. and Lajoie, A.S. (2012) 'Prehabilitation and quality of life three months after total knee arthroplasty: a pilot study', *Percept Mot Skills*, 115(3), pp. 765-74.

BSRM (2003) 'Amputee and Prosthetic Rehabilitation – Standards and Guidelines (2 nd Edition)'.

Butler, P., Engelbrecht, M., Major, R.E., Tait, J.H., Stallard, J. and Patrick, J.H. (1984) 'Physiological cost index of walking for normal children and its use as an indicator of physical handicap', *Dev Med Child Neurol*, 26(5), pp. 607-12.

Campbell, W.B., Marriott, S., Eve, R., Mapson, E., Sexton, S. and Thompson, J.F. (2001) 'Factors influencing the early outcome of major lower limb amputation for vascular disease', *Annals of The Royal College of Surgeons of England*, 83(5), pp. 309-314.

Carty, C.P., Bennett, M.B., Dickinson, I.C. and Steadman, P. (2009a) 'Assessment of kinematic and kinetic patterns following limb salvage procedures for bone sarcoma', *Gait Posture*, 30(4), pp. 547-51.

Carty, C.P., Bennett, M.B., Dickinson, I.C. and Steadman, P. (2010a) 'Electromyographic assessment of Gait function following limb salvage procedures for bone sarcoma', *Journal of Electromyography and Kinesiology*, 20(3), pp. 502-507.

Carty, C.P., Bennett, M.B., Dickinson, I.C. and Steadman, P. (2010b) 'Electromyographic assessment of Gait function following limb salvage procedures for bone sarcoma', *J Electromyogr Kinesiol*, 20(3), pp. 502-7.

Carty, C.P., Dickinson, I.C., Watts, M.C., Crawford, R.W. and Steadman, P. (2009b) 'Impairment and disability following limb salvage procedures for bone sarcoma', *Knee*, 16(5), pp. 405-8.

Chastin, S.F., Baker, K., Jones, D., Burn, D., Granat, M.H. and Rochester, L. (2010) 'The pattern of habitual sedentary behavior is different in advanced Parkinson's disease', *Mov Disord*, 25(13), pp. 2114-20.

Colterjohn, N.R., Davis, A.M., O'Sullivan, B., Catton, C.N., Wunder, J.S. and Bell, R.S. (1997) 'Functional outcome in limb-salvage surgery for soft tissue tumours of the foot and ankle', *Sarcoma*, 1(2), pp. 67-74.

Costa, G. and Gaffuri, E. (1975) '[The perception of physical performance in different work conditions (author's transl)]', *Lav Um*, 27(5), pp. 129-38.

COT (2011) *Occupational therapy with people who have had lower limb amputations: evidence-based guidelines*. College of Occupation Therapy (COT)https://www.cot.co.uk/publication/z-listing/occupational-therapy-people-who-have-had-lower-limb-amputations-evidence-bas-0.

Cowing, M., Davino-Ramaya, C.M., Ramaya, K. and Szmerekovsky, J. (2009) 'Health Care Delivery Performance: Service, Outcomes, and Resource Stewardship', *The Permanente Journal*, 13(4), pp. 72-78.

Culhane, K.M., O'Connor, M., Lyons, D. and Lyons, G.M. (2005) 'Accelerometers in rehabilitation medicine for older adults', *Age Ageing*, 34(6), pp. 556-60.

Daigeler, A., Lehnhardt, M., Khadra, A., Hauser, J., Steinstraesser, L., Langer, S., Goertz, O. and Steinau, H.-U. (2009) 'Proximal major limb amputations – a retrospective analysis of 45 oncological cases', *World Journal of Surgical Oncology*, 7, pp. 15-15.

Davidson, D., Barr, R.D., Riad, S., Griffin, A.M., Chung, P.W., Catton, C.N., O'Sullivan, B., Ferguson, P.C., Davis, A.M. and Wunder, J.S. (2016) 'Health-related quality of life following treatment for extremity soft tissue sarcoma', *J Surg Oncol*, 114(7), pp. 821-827.

Davis, A.M. (1999) 'Functional outcome in extremity soft tissue sarcoma', *Seminars in Radiation Oncology*, 9(4), pp. 360-368.

Davis, A.M., Devlin, M., Griffin, A.M., Wunder, J.S. and Bell, R.S. (1999a) 'Functional outcome in amputation versus limb sparing of patients with lower extremity sarcoma: a matched case-control study', *Arch Phys Med Rehabil*, 80(6), pp. 615-8.

Davis, A.M., O'Sullivan, B., Bell, R.S., Turcotte, R., Catton, C.N., Wunder, J.S., Chabot, P., Hammond, A., Benk, V., Isler, M., Freeman, C., Goddard, K., Bezjak, A., Kandel, R.A., Sadura, A., Day, A., James, K., Tu, D., Pater, J. and Zee, B. (2002) 'Function and health status outcomes in a randomized trial comparing preoperative and postoperative radiotherapy in extremity soft tissue sarcoma', *J Clin Oncol*, 20(22), pp. 4472-7.

Davis, A.M., Punniyamoorthy, S., Griffin, A.M., Wunder, J.S. and Bell, R.S. (1999b) 'Symptoms and their relationship to disability following treatment for lower extremity tumours', *Sarcoma*, 3(2), pp. 73-77.

Davis, A.M., Sennik, S., Griffin, A.M., Wunder, J.S., O'Sullivan, B., Catton, C.N. and Bell, R.S. (2000) 'Predictors of functional outcomes following limb salvage surgery for lower-extremity soft tissue sarcoma', *J Surg Oncol*, 73(4), pp. 206-11.

Davis, A.M., Wright, J.G., Williams, J.I., Bombardier, C., Griffin, A. and Bell, R.S. (1996) 'Development of a measure of physical function for patients with bone and soft tissue sarcoma', *Qual Life Res*, 5(5), pp. 508-16.

de Bruin, E.D., Najafi, B., Murer, K., Uebelhart, D. and Aminian, K. (2007) 'Quantification of everyday motor function in a geriatric population', *J Rehabil Res Dev*, 44(3), pp. 417-28.

de Visser, E., Deckers, J.A., Veth, R.P., Schreuder, H.W., Mulder, T.W. and Duysens, J. (2001) 'Deterioration of balance control after limb-saving surgery', *Am J Phys Med Rehabil*, 80(5), pp. 358-65.

De Visser, E., Mulder, T., Schreuder, H.W.B., Veth, R.P.H. and Duysens, J. (2000) 'Gait and electromyographic analysis of patients recovering after limb-saving surgery', *Clinical Biomechanics*, 15(8), pp. 592-599.

De Visser, E., Pauwels, J., Duysens, J.E.J., Mulder, T. and Veth, R.P.H. (1998) 'Gait adaptations during walking under visual and cognitive constraints: A study of patients recovering from limb-saving surgery of the lower limb', *American Journal of Physical Medicine and Rehabilitation*, 77(6), pp. 503-509.

de Visser, E., Veth, R.P., Schreuder, H.W., Duysens, J. and Mulder, T. (2003) 'Reorganization of gait after limb-saving surgery of the lower limb', *Am J Phys Med Rehabil*, 82(11), pp. 825-31.

Del Din, S., Godfrey, A., Coleman, S., Galna, B., Lord, S. and Rochester, L. (2016a) 'Time-dependent changes in postural control in early Parkinson's disease: what are we missing?', *Med Biol Eng Comput*, 54(2-3), pp. 401-10.

Del Din, S., Godfrey, A., Galna, B., Lord, S. and Rochester, L. (2016b) 'Free-living gait characteristics in ageing and Parkinson's disease: impact of environment and ambulatory bout length', *J Neuroeng Rehabil*, 13(1), p. 46.

Del Din, S., Godfrey, A., Galna, B., Lord, S. and Rochester, L. (2016c) 'Free-living gait characteristics in ageing and Parkinson’s disease: impact of environment and ambulatory bout length', *Journal of NeuroEngineering and Rehabilitation*, 13(1), p. 46.

Del Din, S., Godfrey, A., Mazzà, C., Lord, S. and Rochester, L. (2016d) 'Free-living monitoring of Parkinson's disease: Lessons from the field', *Movement Disorders*, 31(9), pp. 1293-313.

Del Din, S., Godfrey, A. and Rochester, L. (2015) 'Validation of an accelerometer to quantify a comprehensive battery of gait characteristics in healthy older adults and Parkinson's disease: toward clinical and at home use', *IEEE J Biomed Health Inform*, 20(3), pp. 838-847.

Den Oudsten, B.L., Van Heck, G.L. and De Vries, J. (2007) 'Quality of life and related concepts in Parkinson's disease: a systematic review', *Mov Disord*, 22(11), pp. 1528-37.

DeSantis, C.E., Lin, C.C., Mariotto, A.B., Siegel, R.L., Stein, K.D., Kramer, J.L., Alteri, R., Robbins, A.S. and Jemal, A. (2014) 'Cancer treatment and survivorship statistics, 2014', *CA Cancer J Clin*, 64(4), pp. 252-71.

DiCaprio, M.R. and Friedlaender, G.E. (2003) 'Malignant bone tumors: limb sparing versus amputation', *J Am Acad Orthop Surg*, 11(1), pp. 25-37.

Din, S.D., Hickey, A., Woodman, S., Hiden, H., Morris, R., Watson, P., Nazarpour, K., Catt, M., Rochester, L. and Godfrey, A. (2016) *2016 IEEE Statistical Signal Processing Workshop (SSP)*. 26-29 June 2016.

Donati, D., D'Apote, G., Boschi, M., Cevolani, L. and Benedetti, M.G. (2012) 'Clinical and functional outcomes of the saddle prosthesis', *Journal of Orthopaedics and Traumatology : Official Journal of the Italian Society of Orthopaedics and Traumatology*, 13(2), pp. 79-88.

Dozza, M., Chiari, L., Chan, B., Rocchi, L., Horak, F.B. and Cappello, A. (2005) 'Influence of a portable audio-biofeedback device on structural properties of postural sway', *J Neuroeng Rehabil*, 2, p. 13.

Dyer, D., Bouman, B., Davey, M. and Ismond, K.P. (2008) 'An intervention program to reduce falls for adult in-patients following major lower limb amputation', *Healthc Q*, 11(3 Spec No.), pp. 117-21.

Edwardson, C.L., Rowlands, A.V., Bunnewell, S., Sanders, J., Esliger, D.W., Gorely, T., O'Connell, S., Davies, M.J., Khunti, K. and Yates, T. (2016) 'Accuracy of Posture Allocation Algorithms for Thigh- and Waist-Worn Accelerometers', *Med Sci Sports Exerc*, 48(6), pp. 1085-90.

Eiser, C., Cool, P., Grimer, R.J., Carter, S.R., Cotter, I.M., Ellis, A.J. and Kopel, S. (1997) 'Quality of Life in Children Following Treatment for a Malignant Primary Bone Tumour Around the Knee', *Sarcoma*, 1(1), pp. 39-45.

Eiser, C., Darlington, A.-S.E., Stride, C.B. and Grimer, R. (2001) 'Quality of Life Implications as a Consequence of Surgery: Limb Salvage, Primary and Secondary Amputation', *Sarcoma*, 5(4), pp. 189-195.

Elm, E.v., Altman, D.G., Egger, M., Pocock, S.J., Gøtzsche, P.C. and Vandenbroucke, J.P. (2007) 'Strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies', *BMJ*, 335(7624), pp. 806-808.

Enneking, W.F. (1987) 'Limb Salvage in Musculoskeletal Oncology. New York (YK): Churchill Livingston; Modification of the system for functional evaluation in the surgical management of musculoskeletal tumors', pp. 626–39 [Online].

Enneking, W.F., Dunham, W., Gebhardt, M.C., Malawar, M. and Pritchard, D.J. (1993) 'A system for the functional evaluation of reconstructive procedures after surgical treatment of tumors of the musculoskeletal system', *Clin Orthop Relat Res*, (286), pp. 241-6.

Escorpizo, R., Stucki, G., Cieza, A., Davis, K., Stumbo, T. and Riddle, D.L. (2010) 'Creating an interface between the International Classification of Functioning, Disability and Health and physical therapist practice', *Phys Ther*, 90(7), pp. 1053-63.

Feito, Y., Bassett, D.R. and Thompson, D.L. (2012) 'Evaluation of activity monitors in controlled and free-living environments', *Med Sci Sports Exerc*, 44(4), pp. 733-41.

Fernie, G.R., Gryfe, C.I., Holliday, P.J. and Llewellyn, A. (1982) 'The relationship of postural sway in standing to the incidence of falls in geriatric subjects', *Age Ageing*, 11(1), pp. 11-6.

Ferrell, B.R., Dow, K.H. and Grant, M. (1995) 'Measurement of the quality of life in cancer survivors', *Qual Life Res*, 4(6), pp. 523-31.

Fidler, M.M., Frobisher, C., Guha, J., Wong, K., Kelly, J., Winter, D.L., Sugden, E., Duncan, R., Whelan, J., Reulen, R.C. and Hawkins, M.M. (2015) 'Long-term adverse outcomes in survivors of childhood bone sarcoma: the British Childhood Cancer Survivor Study', *British Journal of Cancer*, 112(12), pp. 1857-1865.

Fitzpatrick, A.L., Buchanan, C.K., Nahin, R.L., Dekosky, S.T., Atkinson, H.H., Carlson, M.C. and Williamson, J.D. (2007) 'Associations of gait speed and other measures of physical function with cognition in a healthy cohort of elderly persons', *J Gerontol A Biol Sci Med Sci*, 62(11), pp. 1244-51.

Frederiks, J.P. and Visagie, S. (2013) 'The rehabilitation programme and functional outcomes of persons with lower limb amputations at a primary level rehabilitation centre', *South African Journal of Occupational Therapy*, 43, pp. 18-28.

Fukumothi, D.K., Pupo, H., Reganin, L.A., Matte, S.R.F., Lima, B.S.d. and Mattos, C.A.d. (2016) 'Functional assessment of endoprosthesis in the treatment of bone tumors()', *Revista Brasileira de Ortopedia*, 51(5), pp. 569-573.

Furtado, S., Briggs, T., Fulton, J., Russell, L., Grimer, R., Wren, V., Cool, P., Grant, K. and Gerrand, C. (2016a) 'Patient experience after lower extremity amputation for sarcoma in England: a national survey', *Disabil Rehabil*, pp. 1-20.

Furtado, S., Errington, L., Godfrey, A., Rochester, L. and Gerrand, C. (2016b) 'Objective clinical measurement of physical functioning after treatment for lower extremity sarcoma – A systematic review', *European Journal of Surgical Oncology*, 43(6), pp. 968-993.

Furtado, S., Grimer, R.J., Cool, P., Murray, S.A., Briggs, T., Fulton, J., Grant, K. and Gerrand, C.H. (2015) 'Physical functioning, pain and quality of life after amputation for musculoskeletal tumours: a national survey', *Bone Joint J*, 97-b(9), pp. 1284-90.

Gadotti, I.C., Vieira, E.R. and Magee, D.J. (2006) 'Importance and clarification of measurement properties in rehabilitation', *Brazilian Journal of Physical Therapy*, 10, pp. 137-146.

Ganz, D.A., Bao, Y., Shekelle, P.G. and Rubenstein, L.Z. (2007) 'Will my patient fall?', *Jama*, 297(1), pp. 77-86.

Garratt, A.M., Ruta, D.A., Abdalla, M.I., Buckingham, J.K. and Russell, I.T. (1993) 'The SF36 health survey questionnaire: an outcome measure suitable for routine use within the NHS?', *Bmj*, 306(6890), pp. 1440-4.

Gerrand, C.H., Wunder, J.S., Kandel, R.A., O'Sullivan, B., Catton, C.N., Bell, R.S., Griffin, A.M. and Davis, A.M. (2004) 'The Influence of Anatomic Location on Functional Outcome in Lower-Extremity Soft-Tissue Sarcoma', *Annals of Surgical Oncology*, 11(5), pp. 476-482.

Ghasemi, A. and Zahediasl, S. (2012) 'Normality tests for statistical analysis: a guide for non-statisticians', *Int J Endocrinol Metab*, 10(2), pp. 486-9.

Gilchrist, L.S., Galantino, M.L., Wampler, M., Marchese, V.G., Morris, G.S. and Ness, K.K. (2009) 'A framework for assessment in oncology rehabilitation', *Phys Ther*, 89(3), pp. 286-306.

Ginsberg, J.P., Rai, S.N., Carlson, C.A., Meadows, A.T., Hinds, P.S., Spearing, E.M., Zhang, L., Callaway, L., Neel, M.D., Rao, B.N. and Marchese, V.G. (2007) 'A comparative analysis of functional outcomes in adolescents and young adults with lower-extremity bone sarcoma', *Pediatr Blood Cancer*, 49(7), pp. 964-9.

Godfrey, A., Lara, J., Munro, C.A., Wiuff, C., Chowdhury, S.A., Del Din, S., Hickey, A., Mathers, J.C. and Rochester, L. (2015) 'Instrumented assessment of test battery for physical capability using an accelerometer: a feasibility study', *Physiol Meas*, 36(5), pp. N71-83.

Godfrey, A., Lord, S., Galna, B., Mathers, J.C., Burn, D.J. and Rochester, L. (2014) 'The association between retirement and age on physical activity in older adults', *Age Ageing*, 43(3), pp. 386-93.

Godfrey, A., Morris, R., Hickey, A. and Del Din, S. (2016) 'Beyond the front end: Investigating a thigh worn accelerometer device for step count and bout detection in Parkinson's disease', *Med Eng Phys*, 38(12), pp. 1524-1529.

Godi, M., Franchignoni, F., Caligari, M., Giordano, A., Turcato, A.M. and Nardone, A. (2013) 'Comparison of reliability, validity, and responsiveness of the mini-BESTest and Berg Balance Scale in patients with balance disorders', *Phys Ther*, 93(2), pp. 158-67.

Gray, D.B. and Hendershot, G.E. (2000) 'The ICIDH-2: developments for a new era of outcomes research', *Arch Phys Med Rehabil*, 81(12 Suppl 2), pp. S10-4.

Grimer, R., Judson, I., Peake, D. and Seddon, B. (2010) 'Guidelines for the management of soft tissue sarcomas', *Sarcoma*, 2010, p. 506182.

Grimer, R.J., Chandrasekar, C.R., Carter, S.R., Abudu, A., Tillman, R.M. and Jeys, L. (2013) 'Hindquarter amputation: is it still needed and what are the outcomes?', *Bone Joint J*, 95-b(1), pp. 127-31.

Grubbs, F.E. (1969) 'Procedures for detecting outlying observations in samples', *Technometrics*, 11, pp. 1-21.

Guest, J.F., Sladkevicius, E., Gough, N., Linch, M. and Grimer, R. (2013) 'Utility Values for Advanced Soft Tissue Sarcoma Health States from the General Public in the United Kingdom', *Sarcoma*, 2013, p. 863056.

Gusi, N., Olivares, P.R. and Rajendram, R. (2010) 'The EQ-5D Health-Related Quality of Life Questionnaire', in Preedy, V.R. and Watson, R.R. (eds.) *Handbook of Disease Burdens and Quality of Life Measures*. New York, NY: Springer New York, pp. 87-99.

Henderson, C., Knapp, M., Fernández, J.-L., Beecham, J., Hirani, S.P., Cartwright, M., Rixon, L., Beynon, M., Rogers, A., Bower, P., Doll, H., Fitzpatrick, R., Steventon, A., Bardsley, M., Hendy, J. and Newman, S.P. (2013) 'Cost effectiveness of telehealth for patients with long term conditions (Whole Systems Demonstrator telehealth questionnaire study): nested economic evaluation in a pragmatic, cluster randomised controlled trial', *BMJ : British Medical Journal*, 346, p. f1035.

Hepple, R.T., Mackinnon, S.L., Goodman, J.M., Thomas, S.G. and Plyley, M.J. (1997) 'Resistance and aerobic training in older men: effects on VO2peak and the capillary supply to skeletal muscle', *J Appl Physiol (1985)*, 82(4), pp. 1305-10.

Hetzler, R.K., Stickley, C.D., Lundquist, K.M. and Kimura, I.F. (2008) 'Reliability and accuracy of handheld stopwatches compared with electronic timing in measuring sprint performance', *J Strength Cond Res*, 22(6), pp. 1969-76.

Hickey, A., Stuart, S., O'Donovan, K. and Godfrey, A. (2017) 'Walk on the wild side: the complexity of free-living mobility assessment', *J Epidemiol Community Health*, 71(6), p. 624.

Hillmann, A., Rosenbaum, D., Schroter, J., Gosheger, G., Hoffmann, C. and Winkelmann, W. (2000) 'Electromyographic and gait analysis of forty-three patients after rotationplasty', *J Bone Joint Surg Am*, 82(2), pp. 187-96.

Hinds, P.S., Gattuso, J.S., Billups, C.A., West, N.K., Wu, J., Rivera, C., Quintana, J., Villarroel, M. and Daw, N.C. (2009) 'Aggressive treatment of non-metastatic osteosarcoma improves health-related quality of life in children and adolescents', *Eur J Cancer*, 45(11), pp. 2007-14.

Hodt-Billington, C., Helbostad, J.L., Vervaat, W., Rognsvag, T. and Moe-Nilssen, R. (2011) 'Changes in gait symmetry, gait velocity and self-reported function following total hip replacement', *Journal of Rehabilitation Medicine*, 43(9), pp. 787-93.

Hopyan, S., Tan, J.W., Graham, H.K. and Torode, I.P. (2006) 'Function and upright time following limb salvage, amputation, and rotationplasty for pediatric sarcoma of bone', *J Pediatr Orthop*, 26(3), pp. 405-8.

Horak, F., King, L. and Mancini, M. (2015a) 'Role of Body-Worn Movement Monitor Technology for Balance and Gait Rehabilitation', *Physical Therapy*, 95(3), pp. 461-470.

Horak, F., King, L. and Mancini, M. (2015b) 'Role of body-worn movement monitor technology for balance and gait rehabilitation', *Phys Ther*, 95(3), pp. 461-70.

Horak, F.B. (1987) 'Clinical measurement of postural control in adults', *Phys Ther*, 67(12), pp. 1881-5.

Horak, F.B. (1997) 'Clinical assessment of balance disorders', *Gait & Posture*, 6(1), pp. 76-84.

Horak, F.B. (2006) 'Postural orientation and equilibrium: what do we need to know about neural control of balance to prevent falls?', *Age Ageing*, 35 Suppl 2, pp. ii7-ii11.

Horak, F.B., Wrisley, D.M. and Frank, J. (2009) 'The Balance Evaluation Systems Test (BESTest) to differentiate balance deficits', *Phys Ther*, 89(5), pp. 484-98.

Ishida, Y., Honda, M., Kamibeppu, K., Ozono, S., Okamura, J., Asami, K., Maeda, N., Sakamoto, N., Inada, H., Iwai, T., Kakee, N. and Horibe, K. (2011) 'Social outcomes and quality of life of childhood cancer survivors in Japan: a cross-sectional study on marriage, education, employment and health-related QOL (SF-36)', *Int J Hematol*, 93(5), pp. 633-44.

Johansson, J., Nordstrom, A., Gustafson, Y., Westling, G. and Nordstrom, P. (2017) 'Increased postural sway during quiet stance as a risk factor for prospective falls in community-dwelling elderly individuals', *Age Ageing*, pp. 1-6.

Johnson, M. (2015) 'Activity Monitors Step Count Accuracy in Community-Dwelling Older Adults', *Gerontology and geriatric medicine*, 1, p. 2333721415601303.

Kawai, A., Backus, S.I., Otis, J.C., Inoue, H. and Healey, J.H. (2000) 'Gait characteristics of patients after proximal femoral replacement for malignant bone tumour', *Journal of Bone & Joint Surgery - British Volume*, 82(5), pp. 666-9.

Khoo, T.K., Yarnall, A.J., Duncan, G.W., Coleman, S., O'Brien, J.T., Brooks, D.J., Barker, R.A. and Burn, D.J. (2013) 'The spectrum of nonmotor symptoms in early Parkinson disease', *Neurology*, 80(3), pp. 276-81.

Kitabayashi, T., Demura, S. and Noda, M. (2003) 'Examination of the factor structure of center of foot pressure movement and cross-validity', *J Physiol Anthropol Appl Human Sci*, 22(6), pp. 265-72.

Klein, P.D.a.R. (2004) *The NHS Improvers - A study of the Commission for Health Improvement*. London: Fund, K.s. [Online]. Available at: https://www.kingsfund.org.uk/sites/files/kf/field/field_publication_file/nhs-improvers-study-commission-health-improvement-day-klein-feb04.pdf.

Koo, T.K. and Li, M.Y. (2016) 'A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research', *Journal of Chiropractic Medicine*, 15(2), pp. 155-163.

Ku, P.X., Abu Osman, N.A. and Wan Abas, W.A. (2014) 'Balance control in lower extremity amputees during quiet standing: a systematic review', *Gait Posture*, 39(2), pp. 672-82.

Kuijpers, T., van der Windt, D.A., van der Heijden, G.J. and Bouter, L.M. (2004) 'Systematic review of prognostic cohort studies on shoulder disorders', *Pain*, 109(3), pp. 420-31.

Kun, L., Inoue, Y., Shibata, K. and Enguo, C. (2011) 'Ambulatory estimation of knee-joint kinematics in anatomical coordinate system using accelerometers and magnetometers', *IEEE Transactions on Biomedical Engineering*, 58(2), pp. 435-42.

Kwong, T.N., Furtado, S. and Gerrand, C. (2014) 'What do we know about survivorship after treatment for extremity sarcoma? A systematic review', *Eur J Surg Oncol*, 40(9), pp. 1109-24.

Ladha C, J.D., Ladha K, Olivier P. (2013) 'Shaker table validation of OpenMovement AX3 accelerometer. ', *Ahmerst (ICAMPAM 2013 AMHERST): In 3rd International Conference on Ambulatory Monitoring of Physical Activity and Movement.* pp. 69-70.

Lara, J., O'Brien, N., Godfrey, A., Heaven, B., Evans, E.H., Lloyd, S., Moffatt, S., Moynihan, P.J., Meyer, T.D., Rochester, L., Sniehotta, F.F., White, M. and Mathers, J.C. (2016) 'Pilot Randomised Controlled Trial of a Web-Based Intervention to Promote Healthy Eating, Physical Activity and Meaningful Social Connections Compared with Usual Care Control in People of Retirement Age Recruited from Workplaces', *PLoS One*, 11(7), p. e0159703.

Laucis, N.C., Hays, R.D. and Bhattacharyya, T. (2015) 'Scoring the SF-36 in Orthopaedics: A Brief Guide', *The Journal of Bone and Joint Surgery. American volume*, 97(19), pp. 1628-1634.

Lepage, C., Noreau, L. and Bernard, P.M. (1998) 'Association between characteristics of locomotion and accomplishment of life habits in children with cerebral palsy', *Phys Ther*, 78(5), pp. 458-69.

Lewis, R.A., Neal, R.D., Williams, N.H., France, B., Hendry, M., Russell, D., Hughes, D.A., Russell, I., Stuart, N.S., Weller, D. and Wilkinson, C. (2009) 'Follow-up of cancer in primary care versus secondary care: systematic review', *Br J Gen Pract*, 59(564), pp. e234-47.

Lord, S., Godfrey, A., Galna, B., Mhiripiri, D., Burn, D. and Rochester, L. (2013) 'Ambulatory activity in incident Parkinson's: more than meets the eye?', *J Neurol*, 260(12), pp. 2964-72.

MacDermid, J.C., Grewal, R. and MacIntyre, N.J. (2009) 'Using an evidence-based approach to measure outcomes in clinical practice', *Hand Clin*, 25(1), pp. 97-111, vii.

Macmillan (2008) *Two million reasons. The cancer survivorship agenda.* Available at: http://www.macmillan.org.uk/getinvolved/campaigns/weareaforceforchange/survivorship/two_million_reasons.aspx (Accessed: 07.02.2017).

Malek, F., Somerson, J.S., Mitchel, S. and Williams, R.P. (2012a) 'Does limb-salvage surgery offer patients better quality of life and functional capacity than amputation?', *Clin Orthop Relat Res*, 470(7), pp. 2000-6.

Malek, F., Somerson, J.S., Mitchel, S. and Williams, R.P. (2012b) 'Does Limb-salvage Surgery Offer Patients Better Quality of Life and Functional Capacity than Amputation?', *Clinical Orthopaedics and Related Research®*, 470(7), pp. 2000-2006.

Mancini, M., Horak, F.B., Zampieri, C., Carlson-Kuhta, P., Nutt, J.G. and Chiari, L. (2011) 'Trunk accelerometry reveals postural instability in untreated Parkinson's disease', *Parkinsonism Relat Disord*, 17(7), pp. 557-62.

Mancini, M., Salarian, A., Carlson-Kuhta, P., Zampieri, C., King, L., Chiari, L. and Horak, F.B. (2012) 'ISway: a sensitive, valid and reliable measure of postural control', *Journal of NeuroEngineering and Rehabilitation*, 9, pp. 59-59.

Mansfield, E.D., Ducharme, N. and Koski, K.G. (2012) 'Individual, social and environmental factors influencing physical activity levels and behaviours of multiethnic socio-economically disadvantaged urban mothers in Canada: A mixed methods approach', *International Journal of Behavioral Nutrition and Physical Activity*, 9(1), p. 42.

Marchese, V.G., Ogle, S., Womer, R.B., Dormans, J. and Ginsberg, J.P. (2004) 'An examination of outcome measures to assess functional mobility in childhood survivors of osteosarcoma', *Pediatr Blood Cancer*, 42(1), pp. 41-5.

Marchese, V.G., Rai, S.N., Carlson, C.A., Hinds, P.S., Spearing, E.M., Zhang, L., Callaway, L., Neel, M.D., Rao, B.N. and Ginsberg, J.P. (2007) 'Assessing functional mobility in survivors of lower-extremity sarcoma: reliability and validity of a new assessment tool', *Pediatr Blood Cancer*, 49(2), pp. 183-9.

Mason, G.E., Aung, L., Gall, S., Meyers, P.A., Butler, R., Krug, S., Kim, M., Healey, J.H. and Gorlick, R. (2013) 'Quality of life following amputation or limb preservation in patients with lower extremity bone sarcoma', *Front Oncol*, 3, p. 210.

Mathias, S., Nayak, U.S. and Isaacs, B. (1986) 'Balance in elderly patients: the "get-up and go" test', *Arch Phys Med Rehabil*, 67(6), pp. 387-9.

Matthew Francis, N.D., Jackie Charman, Gill Lawrence, Rob Grimer (2013) *Bone and Soft Tissue Sarcomas. UK Incidence and Survival: 1996 to 2010* (Version 2.0) (Version 2.0). West Midlands: 2013, P.K.I.T.W.M. [Online]. Available at: http://www.ncin.org.uk/publications/.

Matthews, C.E., Hagströmer, M., Pober, D.M. and Bowles, H.R. (2012) 'BEST PRACTICES FOR USING PHYSICAL ACTIVITY MONITORS IN POPULATION-BASED RESEARCH', *Medicine and science in sports and exercise*, 44(1 Suppl 1), pp. S68-S76.

Mavrogenis, A.F., Abati, C.N., Romagnoli, C. and Ruggieri, P. (2012) 'Similar survival but better function for patients after limb salvage versus amputation for distal tibia osteosarcoma', *Clin Orthop Relat Res*, 470(6), pp. 1735-48.

Mayagoitia, R.E., Lotters, J.C., Veltink, P.H. and Hermens, H. (2002) 'Standing balance evaluation using a triaxial accelerometer', *Gait Posture*, 16(1), pp. 55-9.

McCambridge, J., Witton, J. and Elbourne, D.R. (2014) 'Systematic review of the Hawthorne effect: New concepts are needed to study research participation effects()', *Journal of Clinical Epidemiology*, 67(3), pp. 267-277.

McCamley, J., Donati, M., Grimpampi, E. and Mazza, C. (2012) 'An enhanced estimate of initial contact and final contact instants of time using lower trunk inertial sensor data', *Gait Posture*, 36(2), pp. 316-8.

McDougall, J., Wright, V. and Rosenbaum, P. (2010) 'The ICF model of functioning and disability: incorporating quality of life and human development', *Dev Neurorehabil*, 13(3), pp. 204-11.

Mei, J., Zhu, X.Z., Wang, Z.Y. and Cai, X.S. (2014) 'Functional outcomes and quality of life in patients with osteosarcoma treated with amputation versus limb-salvage surgery: a systematic review and meta-analysis', *Arch Orthop Trauma Surg*, 134(11), pp. 1507-16.

Melzer, I., Benjuya, N. and Kaplanski, J. (2004) 'Postural stability in the elderly: a comparison between fallers and non-fallers', *Age Ageing*, 33(6), pp. 602-7.

Moe-Nilssen, R. (1998a) 'A new method for evaluating motor control in gait under real-life environmental conditions. Part 1: The instrument', *Clin Biomech (Bristol, Avon)*, 13(4-5), pp. 320-327.

Moe-Nilssen, R. (1998b) 'Test-retest reliability of trunk accelerometry during standing and walking', *Archives of Physical Medicine and Rehabilitation*, 79(11), pp. 1377-1385.

Moe-Nilssen, R. and Helbostad, J.L. (2002) 'Trunk accelerometry as a measure of balance control during quiet standing', *Gait & Posture*, 16(1), pp. 60-68.

Moghadam, M., Ashayeri, H., Salavati, M., Sarafzadeh, J., Taghipoor, K.D., Saeedi, A. and Salehi, R. (2011) 'Reliability of center of pressure measures of postural stability in healthy older adults: effects of postural task difficulty and cognitive load', *Gait Posture*, 33(4), pp. 651-5.

Mols, F., Vingerhoets, A.J.J.M., Coebergh, J.W. and van de Poll-Franse, L.V. (2005) 'Quality of life among long-term breast cancer survivors: A systematic review', *European Journal of Cancer*, 41(17), pp. 2613-2619.

Murphy, S.L., Lyden, A.K., Clary, M., Geisser, M.E., Yung, R.L., Clauw, D.J. and Williams, D.A. (2011) 'Activity pacing for osteoarthritis symptom management: study design and methodology of a randomized trial testing a tailored clinical approach using accelerometers for veterans and non-veterans', *BMC Musculoskeletal Disorders*, 12, p. 177.

Myung, I.J. (2003) 'Tutorial on maximum likelihood estimation', *Journal of Mathematical Psychology*, 47(1), pp. 90-100.

Nagarajan, R., Clohisy, D.R., Neglia, J.P., Yasui, Y., Mitby, P.A., Sklar, C., Finklestein, J.Z., Greenberg, M., Reaman, G.H., Zeltzer, L. and Robison, L.L. (2004a) 'Function and quality-of-life of survivors of pelvic and lower extremity osteosarcoma and Ewing's sarcoma: the Childhood Cancer Survivor Study', *Br J Cancer*, 91(11), pp. 1858-65.

Nagarajan, R., Clohisy, D.R., Neglia, J.P., Yasui, Y., Mitby, P.A., Sklar, C., Finklestein, J.Z., Greenberg, M., Reaman, G.H., Zeltzer, L. and Robison, L.L. (2004b) 'Function and quality-of-life of survivors of pelvic and lower extremity osteosarcoma and Ewing's sarcoma: the Childhood Cancer Survivor Study', *British Journal of Cancer*, 91(11), pp. 1858-1865.

Nagarajan, R., Kamruzzaman, A., Ness, K.K., Marchese, V.G., Sklar, C., Mertens, A., Yasui, Y., Robison, L.L. and Marina, N. (2011) 'Twenty years of follow-up of survivors of childhood osteosarcoma: a report from the Childhood Cancer Survivor Study', *Cancer*, 117(3), pp. 625-34.

Nagarajan, R., Neglia, J.P., Clohisy, D.R. and Robison, L.L. (2002) 'Limb salvage and amputation in survivors of pediatric lower-extremity bone tumors: what are the long-term implications?', *J Clin Oncol*, 20(22), pp. 4493-501.

Nagarajan, R., Neglia, J.P., Clohisy, D.R., Yasui, Y., Greenberg, M., Hudson, M., Zevon, M.A., Tersak, J.M., Ablin, A. and Robison, L.L. (2003) 'Education, employment, insurance, and marital status among 694 survivors of pediatric lower extremity bone tumors: a report from the childhood cancer survivor study', *Cancer*, 97(10), pp. 2554-64.

Najafi, B., Aminian, K., Paraschiv-Ionescu, A., Loew, F., Bula, C.J. and Robert, P. (2003) 'Ambulatory system for human motion analysis using a kinematic sensor: monitoring of daily physical activity in the elderly', *IEEE Trans Biomed Eng*, 50(6), pp. 711-23.

Napolitano, M.A., Borradaile, K.E., Lewis, B.A., Whiteley, J.A., Longval, J.L., Parisi, A.F., Albrecht, A.E., Sciamanna, C.N., Jakicic, J.M., Papandonatos, G.D. and Marcus, B.H. (2010) 'Accelerometer use in a physical activity intervention trial', *Contemp Clin Trials*, 31(6), pp. 514-23.

Narayanan, M.R., Lord, S.R., Budge, M.M., Celler, B.G. and Lovell, N.H. (2007) 'Falls management: detection and prevention, using a waist-mounted triaxial accelerometer', *Conf Proc IEEE Eng Med Biol Soc*, 2007, pp. 4037-40.

Ness, K.K., Hudson, M.M., Ginsberg, J.P., Nagarajan, R., Kaste, S.C., Marina, N., Whitton, J., Robison, L.L. and Gurney, J.G. (2009) 'Physical performance limitations in the Childhood Cancer Survivor Study cohort', *J Clin Oncol*, 27(14), pp. 2382-9.

Ness, K.K., Neel, M.D., Kaste, S.C., Billups, C.A., Marchese, V.G., Rao, B.N. and Daw, N.C. (2014) 'A comparison of function after limb salvage with non-invasive expandable or modular prostheses in children', *European Journal of Cancer*, 50(18), pp. 3212-3220.

Nevitt, M.C., Cummings, S.R., Kidd, S. and Black, D. (1989) 'Risk factors for recurrent nonsyncopal falls. A prospective study', *Jama*, 261(18), pp. 2663-8.

Nilsson, H., Angeras, U., Bock, D., Borjesson, M., Onerup, A., Fagevik Olsen, M., Gellerstedt, M., Haglind, E. and Angenete, E. (2016) 'Is preoperative physical activity related to post-surgery recovery? A cohort study of patients with breast cancer', *BMJ Open*, 6(1), p. e007997.

O'Neill, B., McDonough, S.M., Wilson, J.J., Bradbury, I., Hayes, K., Kirk, A., Kent, L., Cosgrove, D., Bradley, J.M. and Tully, M.A. (2017) 'Comparing accelerometer, pedometer and a questionnaire for measuring physical activity in bronchiectasis: a validity and feasibility study?', *Respiratory Research*, 18, p. 16.

O'Sullivan, M., Blake, C., Cunningham, C., Boyle, G. and Finucane, C. (2009) 'Correlation of accelerometry with clinical balance tests in older fallers and non-fallers', *Age and Ageing*, 38(3), pp. 308-313.

Ostrosky, K.M., VanSwearingen, J.M., Burdett, R.G. and Gee, Z. (1994) 'A comparison of gait characteristics in young and old subjects', *Phys Ther*, 74(7), pp. 637-44; discussion 644-6.

Ottaviani, G., Robert, R.S., Huh, W.W., Palla, S. and Jaffe, N. (2013) 'Sociooccupational and physical outcomes more than 20 years after the diagnosis of osteosarcoma in children and adolescents: limb salvage versus amputation', *Cancer*, 119(20), pp. 3727-36.

Ozger, H., Bulbul, M. and Eralp, L. (2010) 'Complications of limb salvage surgery in childhood tumors and recommended solutions', *Strategies in Trauma and Limb Reconstruction*, 5(1), pp. 11-15.

Paillard, T. and Noe, F. (2015) 'Techniques and Methods for Testing the Postural Function in Healthy and Pathological Subjects', *Biomed Res Int*, 2015, p. Article ID 891390: 15 pages.

Pakulis, P.J., Young, N.L. and Davis, A.M. (2005) 'Evaluating physical function in an adolescent bone tumor population', *Pediatr Blood Cancer*, 45(5), pp. 635-43.

Pardasaney, P.K., Sullivan, P.E., Portney, L.G. and Mankin, H.J. (2006) 'Advantage of limb salvage over amputation for proximal lower extremity tumors', *Clin Orthop Relat Res*, 444, pp. 201-8.

Park, J.H., Mancini, M., Carlson-Kuhta, P., Nutt, J.G. and Horak, F.B. (2016) 'Quantifying effects of age on balance and gait with inertial sensors in community-dwelling healthy adults', *Exp Gerontol*, 85, pp. 48-58.

Parsons, J.A. and Davis, A.M. (2004) 'Rehabilitation and quality-of-life issues in patients with extremity soft tissue sarcoma', *Curr Treat Options Oncol*, 5(6), pp. 477-88.

Patel, S., Park, H., Bonato, P., Chan, L. and Rodgers, M. (2012) 'A review of wearable sensors and systems with application in rehabilitation', *Journal of NeuroEngineering and Rehabilitation*, 9(1), p. 21.

Peat, J.B., B (2005) *Medical statistics - A guide to data analysis and critical appraisal.* Blackwell Publishing.

Perneger, T.V. (1998) 'What's wrong with Bonferroni adjustments', *BMJ : British Medical Journal*, 316(7139), pp. 1236-1238.

Piirtola, M. and Era, P. (2006) 'Force platform measurements as predictors of falls among older people - a review', *Gerontology*, 52(1), pp. 1-16.

Podsiadlo, D. and Richardson, S. (1991) 'The timed "Up & Go": a test of basic functional mobility for frail elderly persons', *J Am Geriatr Soc*, 39(2), pp. 142-8.

Poquet, N. and Lin, C. (2016) 'The Brief Pain Inventory (BPI)', *Journal of Physiotherapy*, 62(1), p. 52.

Portney LG, W.M.P.H. (2000) *Foundations of clinical research: applications to practice.* New Jersey.

Prieto, T.E., Myklebust, J.B., Hoffmann, R.G., Lovett, E.G. and Myklebust, B.M. (1996) 'Measures of postural steadiness: differences between healthy young and elderly adults', *IEEE Trans Biomed Eng*, 43(9), pp. 956-66.

Prince, S.A., Adamo, K.B., Hamel, M.E., Hardt, J., Gorber, S.C. and Tremblay, M. (2008) 'A comparison of direct versus self-report measures for assessing physical activity in adults: a

systematic review', *The International Journal of Behavioral Nutrition and Physical Activity*, 5, pp. 56-56.

Rauch, A., Cieza, A. and Stucki, G. (2008) 'How to apply the International Classification of Functioning, Disability and Health (ICF) for rehabilitation management in clinical practice', *Eur J Phys Rehabil Med*, 44(3), pp. 329-42.

Renard, A.J., Veth, R.P., Schreuder, H.W., van Loon, C.J., Koops, H.S. and van Horn, J.R. (2000) 'Function and complications after ablative and limb-salvage therapy in lower extremity sarcoma of bone', *J Surg Oncol*, 73(4), pp. 198-205.

Richards, M., Corner, J. and Maher, J. (2011) 'The National Cancer Survivorship Initiative: new and emerging evidence on the ongoing needs of cancer survivors', *British Journal of Cancer*, 105(Suppl 1), pp. S1-S4.

Roach, K.E. (2006) 'Measurement of Health Outcomes: Reliability, Validity and Responsiveness', *JPO: Journal of Prosthetics and Orthotics*, 18(6), pp. P8-P12.

Robert, R.S., Ottaviani, G., Huh, W.W., Palla, S. and Jaffe, N. (2010a) 'Psychosocial and functional outcomes in long-term survivors of osteosarcoma: a comparison of limb-salvage surgery and amputation', *Pediatr Blood Cancer*, 54(7), pp. 990-9.

Robert, R.S., Ottaviani, G., Huh, W.W., Palla, S. and Jaffe, N. (2010b) 'Psychosocial and Functional Outcomes in Long-Term Survivors of Osteosarcoma: A Comparison of Limb-Salvage Surgery and Amputation', *Pediatric blood & cancer*, 54(7), pp. 990-999.

Robison, L.L. and Hudson, M.M. (2014) 'Survivors of childhood and adolescent cancer: life-long risks and responsibilities', *Nat Rev Cancer*, 14(1), pp. 61-70.

Rompen, J.C., Ham, S.J., Halbertsma, J.P. and van Horn, J.R. (2002) 'Gait and function in patients with a femoral endoprosthesis after tumor resection: 18 patients evaluated 12 years after surgery', *Acta Orthop Scand*, 73(4), pp. 439-46.

Rosenbaum, D., Brandes, M., Hardes, J., Gosheger, G. and Rodl, R. (2008a) 'Physical activity levels after limb salvage surgery are not related to clinical scores-objective activity assessment in 22 patients after malignant bone tumor treatment with modular prostheses', *J Surg Oncol*, 98(2), pp. 97-100.

Rosenbaum, D., Brandes, M., Hardes, J., Gosheger, G. and Rödl, R. (2008b) 'Physical activity levels after limb salvage surgery are not related to clinical scores - Objective activity assessment in 22 patients after malignant bone tumor treatment with modular prostheses', *Journal of Surgical Oncology*, 98(2), pp. 97-100.

Rubenstein, L.Z. and Josephson, K.R. (2002) 'The epidemiology of falls and syncope', *Clin Geriatr Med*, 18(2), pp. 141-58.

Rubenstein, L.Z. and Josephson, K.R. (2006) 'Falls and their prevention in elderly people: what does the evidence show?', *Med Clin North Am*, 90(5), pp. 807-24.

Rubenstein, L.Z., Powers, C.M. and MacLean, C.H. (2001) 'Quality indicators for the management and prevention of falls and mobility problems in vulnerable elders', *Ann Intern Med*, 135(8 Pt 2), pp. 686-93.

Rutkowski, P. and Ługowska, I. (2014) 'Follow-up in soft tissue sarcomas', *Memo*, 7(2), pp. 92-96.

Salarian, A., Horak, F.B., Zampieri, C., Carlson-Kuhta, P., Nutt, J.G. and Aminian, K. (2010) 'iTUG, a sensitive and reliable measure of mobility', *IEEE Trans Neural Syst Rehabil Eng*, 18(3), pp. 303-10.

Sanderson, S., Tatt, I.D. and Higgins, J.P. (2007) 'Tools for assessing quality and susceptibility to bias in observational studies in epidemiology: a systematic review and annotated bibliography', *Int J Epidemiol*, 36(3), pp. 666-76.

Sandroff, B.M., Motl, R.W., Pilutti, L.A., Learmonth, Y.C., Ensari, I., Dlugonski, D., Klaren, R.E., Balantrapu, S. and Riskin, B.J. (2014) 'Accuracy of StepWatch™ and ActiGraph Accelerometers for Measuring Steps Taken among Persons with Multiple Sclerosis', *PLoS ONE*, 9(4), p. e93511.

Schmid, A.A., Van Puymbroeck, M., Altenburger, P.A., Miller, K.K., Combs, S.A. and Page, S.J. (2013) 'Balance is associated with quality of life in chronic stroke', *Top Stroke Rehabil*, 20(4), pp. 340-6.

Schrack, J.A., Simonsick, E.M. and Ferrucci, L. (2013) 'The Relationship of the Energetic Cost of Slow Walking and Peak Energy Expenditure to Gait Speed in Mid-to-Late Life', *American journal of physical medicine & rehabilitation / Association of Academic Physiatrists*, 92(1), pp. 28-35.

Schuck, P. and Zwingmann, C. (2003) 'The 'smallest real difference' as a measure of sensitivity to change: a critical analysis', *Int J Rehabil Res*, 26(2), pp. 85-91.

Schwenk, M., Hauer, K., Zieschang, T., Englert, S., Mohler, J. and Najafi, B. (2014) 'Sensor-derived physical activity parameters can predict future falls in people with dementia', *Gerontology*, 60(6), pp. 483-92.

Serletti, J.M., Carras, A.J., O'Keefe, R.J. and Rosier, R.N. (1998) 'Functional outcome after soft-tissue reconstruction for limb salvage after sarcoma surgery', *Plast Reconstr Surg*, 102(5), pp. 1576-83; discussion 1584-5.

Shehadeh, A., El Dahleh, M., Salem, A., Sarhan, Y., Sultan, I., Henshaw, R.M. and Aboulafia, A.J. (2013) 'Standardization of rehabilitation after limb salvage surgery for sarcomas improves patients' outcome', *Hematol Oncol Stem Cell Ther*, 6(3-4), pp. 105-11.

Sheiko, M., Bjornson, K., Lisle, J., Song, K., Eary, J.F. and Conrad, E.U. (2012) 'Physical Activity Assessment in Adolescents with Limb Salvage', *Journal of Pediatrics*, 161(6), pp. 1138-1141.

Shepherd, C.W. and While, A.E. (2012) 'Cardiac rehabilitation and quality of life: a systematic review', *Int J Nurs Stud*, 49(6), pp. 755-71.

Shoup, J.A., Gattshall, M., Dandamudi, P. and Estabrooks, P. (2008) 'Physical activity, quality of life, and weight status in overweight children', *Qual Life Res*, 17(3), pp. 407-12.

Silver, J.K. (2015) 'Cancer prehabilitation and its role in improving health outcomes and reducing health care costs', *Semin Oncol Nurs*, 31(1), pp. 13-30.

Silver, J.K. and Baima, J. (2013) 'Cancer prehabilitation: an opportunity to decrease treatment-related morbidity, increase cancer treatment options, and improve physical and psychological health outcomes', *Am J Phys Med Rehabil*, 92(8), pp. 715-27.

Sim, J. and Arnell, P. (1993) 'Measurement validity in physical therapy research', *Phys Ther*, 73(2), pp. 102-10; discussion 110-5.

Singh, R., Hunter, J. and Philip, A. (2007) 'The rapid resolution of depression and anxiety symptoms after lower limb amputation', *Clin Rehabil*, 21(8), pp. 754-9.

Srivastava, K. and Chaudhury, S. (2014) 'Rehabilitation after Amputation: Psychotherapeutic Intervention Module in Indian Scenario', *The Scientific World Journal*, 2014, p. 6.

Stefanov, D.H., Bien, Z. and Bang, W.C. (2004) 'The smart house for older persons and persons with physical disabilities: structure, technology arrangements, and perspectives', *IEEE Trans Neural Syst Rehabil Eng*, 12(2), pp. 228-50.

Steiner, W.A., Ryser, L., Huber, E., Uebelhart, D., Aeschlimann, A. and Stucki, G. (2002) 'Use of the ICF model as a clinical problem-solving tool in physical therapy and rehabilitation medicine', *Phys Ther*, 82(11), pp. 1098-107.

Stevenson, J., Tsagkozis, P. and Grimer, R. (2016) 'Functional and quality of life outcomes in bone sarcoma following amputation, rotationplasty or limb-salvage', *Expert Review of Quality of Life in Cancer Care*, 1(4), pp. 303-312.

Stiller, C.A., Trama, A., Serraino, D., Rossi, S., Navarro, C., Chirlaque, M.D., Casali, P.G. and Group, R.W. (2013) 'Descriptive epidemiology of sarcomas in Europe: report from the RARECARE project', *Eur J Cancer*, 49(3), pp. 684 - 695.

Storm, F.A., Heller, B.W. and Mazzà, C. (2015) 'Step Detection and Activity Recognition Accuracy of Seven Physical Activity Monitors', *PLoS ONE*, 10(3), p. e0118723.

Studenski, S., Perera, S., Wallace, D., Chandler, J.M., Duncan, P.W., Rooney, E., Fox, M. and Guralnik, J.M. (2003) 'Physical performance measures in the clinical setting', *J Am Geriatr Soc*, 51(3), pp. 314-22.

Sugiura, H., Katagiri, H., Yonekawa, M., Sato, K., Yamamura, S. and Iwata, H. (2001) 'Walking ability and activities of daily living after limb salvage operations for malignant bone and soft-tissue tumors of the lower limbs', *Arch Orthop Trauma Surg*, 121(3), pp. 131-4.

Tabone, M.D., Rodary, C., Oberlin, O., Gentet, J.C., Pacquement, H. and Kalifa, C. (2005) 'Quality of life of patients treated during childhood for a bone tumor: assessment by the Child Health Questionnaire', *Pediatr Blood Cancer*, 45(2), pp. 207-11.

Tanaka, A., Yoshimura, Y., Aoki, K., Kito, M., Okamoto, M., Suzuki, S., Momose, T. and Kato, H. (2016) 'Knee extension strength and post-operative functional prediction in quadriceps resection for soft-tissue sarcoma of the thigh', *Bone & Joint Research*, 5(6), pp. 232-238.

Thijssens, K.M., Hoekstra-Weebers, J.E., van Ginkel, R.J. and Hoekstra, H.J. (2006) 'Quality of life after hyperthermic isolated limb perfusion for locally advanced extremity soft tissue sarcoma', *Ann Surg Oncol*, 13(6), pp. 864-71.

Tobias, K. and Gillis, T. (2015) 'Rehabilitation of the sarcoma patient-enhancing the recovery and functioning of patients undergoing management for extremity soft tissue sarcomas', *J Surg Oncol*, 111(5), pp. 615-21.

Troiano, R.P. and Dodd, K.W. (2008) 'Differences between objective and self-report measures of physical activity. What do they mean?', *The Korean Journal of Measurement and Evaluation in Physical Education and Sport Science*, 10(2), pp. 31-42.

Tsauo, J.Y., Li, W.C. and Yang, R.S. (2006) 'Functional outcomes after endoprosthetic knee reconstruction following resection of osteosarcoma near the knee', *Disability & Rehabilitation*, 28(1), pp. 61-6.

Tudor-Locke, C. and Bassett, D.R. (2004) 'How many steps/day are enough? Preliminary pedometer indices for public health', *Sports Medicine*, 34(1), pp. 1-8.

Tudor-Locke, C., Craig, C.L., Aoyagi, Y., Bell, R.C., Croteau, K.A., De Bourdeaudhuij, I., Ewald, B., Gardner, A.W., Hatano, Y. and Lutes, L.D. (2011a) 'How many steps/day are enough? For older adults and special populations', *Int J Behav Nutr Phys Act*, 8, p. 80.

Tudor-Locke, C., Craig, C.L., Beets, M.W., Belton, S., Cardon, G.M., Duncan, S., Hatano, Y., Lubans, D.R., Olds, T.S. and Raustorp, A. (2011b) 'How many steps/day are enough? For children and adolescents', *Int J Behav Nutr Phys Act*, 8, p. 78.

Turcot, K., Allet, L., Golay, A., Hoffmeyer, P. and Armand, S. (2009) 'Investigation of standing balance in diabetic patients with and without peripheral neuropathy using accelerometers', *Clinical Biomechanics*, 24(9), pp. 716-721.

Tyson, S.F., Hanley, M., Chillala, J., Selley, A.B. and Tallis, R.C. (2007) 'The relationship between balance, disability, and recovery after stroke: predictive validity of the Brunel Balance Assessment', *Neurorehabil Neural Repair*, 21(4), pp. 341-6.

van Dam, M.S., Kok, G.J., Munneke, M., Vogelaar, F.J., Vliet Vlieland, T.P. and Taminiau, A.H. (2001) 'Measuring physical activity in patients after surgery for a malignant tumour in the leg. The reliability and validity of a continuous ambulatory activity monitor', *J Bone Joint Surg Br*, 83(7), pp. 1015-9.

van der Geest, I.C.M., Knoop, H., Veth, R.P.H., Bart Schreuder, H.W. and Bleijenberg, G. (2013) 'High fatigue scores before and after surgical treatment of bone and soft tissue tumors', *Experimental and Therapeutic Medicine*, 5(1), pp. 205-208.

van Schooten, K.S., Rispens, S.M., Elders, P.J., Lips, P., van Dieen, J.H. and Pijnappels, M. (2015) 'Assessing physical activity in older adults: required days of trunk accelerometer measurements for reliable estimation', *J Aging Phys Act*, 23(1), pp. 9-17.

van Weert, E., Hoekstra-Weebers, J.E., May, A.M., Korstjens, I., Ros, W.J. and van der Schans, C.P. (2008) 'The development of an evidence-based physical self-management rehabilitation programme for cancer survivors', *Patient Educ Couns*, 71(2), pp. 169-90.

Varni, J.W., Lane, M.M., Burwinkle, T.M., Fontaine, E.N., Youssef, N.N., Schwimmer, J.B., Pardee, P.E., Pohl, J.F. and Easley, D.J. (2006) 'Health-related quality of life in pediatric patients with irritable bowel syndrome: a comparative analysis', *J Dev Behav Pediatr*, 27(6), pp. 451-8.

Vaught, S.L. (2001) 'Gait, Balance, and Fall Prevention', *The Ochsner Journal*, 3(2), pp. 94-97.

Velotta, J., Weyer, J., Ramirez, A., Winstead, J. and Bahamonde, R. (2011) *ISBS-Conference Proceedings Archive*.

Visser, J.E., Carpenter, M.G., van der Kooij, H. and Bloem, B.R. (2008) 'The clinical utility of posturography', *Clin Neurophysiol*, 119(11), pp. 2424-36.

Vissers, M.M., Bussmann, J.B.J., de Groot, I.B., Verhaar, J.A.N. and Reijman, M. (2011) 'Walking and chair rising performed in the daily life situation before and after total hip arthroplasty', *Osteoarthritis & Cartilage*, 19(9), pp. 1102-7.

Wai, A.A., Duc, P.D., Syin, C. and Zhang, H. (2014) 'iBEST: intelligent Balance assessment and Stability Training system using smartphone', *Conf Proc IEEE Eng Med Biol Soc*, 2014, pp. 3683-6.

Warburton, D.E.R., Nicol, C.W. and Bredin, S.S.D. (2006) 'Health benefits of physical activity: the evidence', *CMAJ : Canadian Medical Association Journal*, 174(6), pp. 801-809.

Whitney, S.L., Roche, J.L., Marchetti, G.F., Lin, C.C., Steed, D.P., Furman, G.R., Musolino, M.C. and Redfern, M.S. (2011) 'A comparison of accelerometry and center of pressure measures during computerized dynamic posturography: a measure of balance', *Gait Posture*, 33(4), pp. 594-9.

WHO (2013) *WHO Classification of Tumours of Soft Tissue and Bone*. Fourth edn. World Health Organisation (WHO).

Wickramasinghe, N.R., Clement, N.D., Singh, A. and Porter, D.E. (2014) 'Sarcoma Excision and Pattern of Complicating Sensory Neuropathy', *ISRN Oncology*, 2014, p. 168698.

Williams, E.N., Carroll, S.G., Reddihough, D.S., Phillips, B.A. and Galea, M.P. (2005) 'Investigation of the timed 'up & go' test in children', *Dev Med Child Neurol*, 47(8), pp. 518-24.

Winter, C., Muller, C., Brandes, M., Brinkmann, A., Hoffmann, C., Hardes, J., Gosheger, G., Boos, J. and Rosenbaum, D. (2009) 'Level of activity in children undergoing cancer treatment', *Pediatr Blood Cancer*, 53(3), pp. 438-43.

Winter, C.C., Muller, C., Hardes, J., Boos, J., Gosheger, G. and Rosenbaum, D. (2012) 'Pediatric patients with a malignant bone tumor: when does functional assessment make sense?', *Supportive Care in Cancer*, 20(1), pp. 127-33.

Winter, D.A. (1995) 'Human balance and posture control during standing and walking', *Gait & Posture*, 3(4), pp. 193-214.

Winter, D.A., Patla, A.E., Frank, J.S. and Walt, S.E. (1990) 'Biomechanical walking pattern changes in the fit and healthy elderly', *Phys Ther*, 70(6), pp. 340-7.

Yarnall, A.J., Breen, D.P., Duncan, G.W., Khoo, T.K., Coleman, S.Y., Firbank, M.J., Nombela, C., Winder-Rhodes, S., Evans, J.R. and Rowe, J.B. (2014) 'Characterizing mild cognitive impairment in incident Parkinson disease: the ICICLE-PD study', *Neurology*, 82.

Yelnik, A. and Bonan, I. (2008) 'Clinical tools for assessing balance disorders', *Neurophysiologie Clinique/Clinical Neurophysiology*, 38(6), pp. 439-445.

Yin, K., Liao, Q., Zhong, D., Ding, J., Niu, B., Long, Q. and Ding, D. (2012) 'Meta-analysis of limb salvage versus amputation for treating high-grade and localized osteosarcoma in patients with pathological fracture', *Exp Ther Med*, 4(5), pp. 889-894.

Youssef, N.N., Murphy, T.G., Langseder, A.L. and Rosh, J.R. (2006) 'Quality of life for children with functional abdominal pain: a comparison study of patients' and parents' perceptions', *Pediatrics*, 117(1), pp. 54-9.

Zampieri, C., Salarian, A., Carlson-Kuhta, P., Aminian, K., Nutt, J.G. and Horak, F.B. (2010) 'The instrumented timed up and go test: potential outcome measure for disease modifying therapies in Parkinson's disease', *J Neurol Neurosurg Psychiatry*, 81(2), pp. 171-6.

Zampieri, C., Salarian, A., Carlson-Kuhta, P., Nutt, J.G. and Horak, F.B. (2011) 'Assessing mobility at home in people with early Parkinson's disease using an instrumented Timed Up and Go test', *Parkinsonism Relat Disord*, 17(4), pp. 277-80.

Zeltzer, L.K., Lu, Q., Leisenring, W., Tsao, J.C., Recklitis, C., Armstrong, G., Mertens, A.C., Robison, L.L. and Ness, K.K. (2008) 'Psychosocial outcomes and health-related quality of life in adult childhood cancer survivors: a report from the childhood cancer survivor study', *Cancer Epidemiol Biomarkers Prev*, 17(2), pp. 435-46.

Zhao, Q., Zhang, B., Wang, J., Feng, W., Jia, W. and Sun, M. (2017) 'Improved method of step length estimation based on inverted pendulum model', *International Journal of Distributed Sensor Networks*, 13(4).

Zijlstra, W. and Hof, A.L. (2003) 'Assessment of spatio-temporal gait parameters from trunk accelerations during human walking', *Gait Posture*, 18(2), pp. 1-10.

Zohman, G.L., Boardman, D.L., Eckardt, J.J. and Lane, J.M. (1997) 'Stride analysis after proximal tibial replacement', *Clinical Orthopaedics & Related Research*, (339), pp. 180-4.