

Evaluating the Effect of Low Intensity Laser Therapy on Chronic Wound Pain

A Proof of Concept Study

November 2011

Dr. Leila Karimi¹, Charne Miller², Dr. Lisa Donohue²,
Russell Nunn², Assoc. Prof. William McGuinness³,
Tina Czech⁴, Dr. Carolyn A. Arnold⁵, & Janine Sunderland⁶

A research study supported by:
The William Buckland Foundation

Published by:

Helen Macpherson Smith Institute of Community Health
Royal District Nursing Service
Melbourne, Australia
ABN 49 052 1088 717

© ROYAL DISTRICT NURSING SERVICE LIMITED 2011

ISBN: 978-0-9806380-8-0

No part of this publication may be reproduced, copied or transmitted without the prior written permission of Royal District Nursing Service Limited or in accordance with the provisions of the Australian Copyright Act.

Contents

Acknowledgements	vii
Disclosures	ix
Study teams and groups	xi
Executive summary	1
Background	1
Design	1
Results	2
Recommendations and implications for practice	3
1.0 Introduction	5
1.1 Chronic wounds & LILT	5
1.1.1 Wound healing.....	5
1.1.2 Wound pain.....	6
1.2 Proof of concept study	6
2.0 Materials & Method	7
2.1 Participants eligibility	7
2.2 Recruitment	7
2.3 Data Collection & Measures.....	8
2.4 Treatment Protocol.....	9
2.5 Statistical Analysis.....	11
3.0 Results: Pain, Wound Healing QoL, and K10	13
3.1 Sample	14
3.2 Pain interference with daily activity.....	15
3.3 Pain severity	16
3.4 Effect & sample size estimates.....	19
3.5 Pain Medication	20
3.6 Wound healing	21
3.7 Quality of life & psychological distress.....	22
4.0 Results: Feedback from Clients, Nurses, and Study Contributors	23
4.1 Client Satisfaction Survey Results.....	23
4.2 Feedback from Wound Management Clinical Nurse Consultants	27
4.2.1 LILT training and study education.....	27
4.2.2 Using LILT	27
4.2.3 Wounds improved and pain reduced but was it LILT?.....	28
4.2.4 Study participant reactions.....	28
4.2.5 Research Protocols.....	29
4.3 Research method review	30
4.3.1 Design.....	30
4.3.2 Eligibility	30
4.3.3 Data collection.....	30
4.3.4 Data entry & analysis	31
4.3.5 Management.....	31
5.0 Discussion	33
5.1 Efficacy of LILT.....	33
5.2 Trial feasibility & methodological considerations	34
5.3 Study Limitations.....	35
5.4 Conclusion	35
6.0 Recommendations for research & practice	37
Appendices	39

Appendix 1: Plain Language Statement	39
Appendix 2: Consent Form	43
Appendix 3: LILT Protocols	45
References	47

List of figures

Figure 2.1 Administering the Polylaser Trion™ (hand held laser)	10
Figure 2.2 Administering the Photonic 500 Acumed™ (scanning laser).....	11
Figure 3.1 Participant flow diagram	13
Figure 3.2 Estimated mean BPI Interference Scores by Treatment Group.....	16
Figure 3.3 Estimated mean BPI severity scores by treatment group.....	18
Figure 4.1 Satisfaction with convenience of visits	25
Figure 4.2 Satisfaction with professionalism of staff.....	25
Figure 4.3 Overall satisfaction with nursing care	25
Figure 4.4 Satisfaction with clinic reception / waiting facilities	25
Figure 4.5 Satisfaction with privacy of clinic	26

List of tables

Table 3.1 Demographics and health status by treatment group	14
Table 3.2 Wound and pain characteristics by treatment group	15
Table 3.3 Pain interference scores by treatment group.....	17
Table 3.4 Pain severity scores for the treatment groups.....	18
Table 3.5 Effect and sample size estimates.....	19
Table 3.6 Medication use to manage pain	20
Table 3.7 Healing rate scores for the treatment groups.....	21
Table 3.8 Logistic regression predicting healing (n=48).....	22
Table 3.9 Quality of Life and Psychological Distress Score by Treatment Group	22
Table 4.1 Satisfaction with assessment and care (n=44).....	24
Table 4.2 Satisfaction with laser treatment (n=31).....	26

Acknowledgements

The authors of this report would like to gratefully acknowledge the contribution from the following:

- The William Buckland Foundation for the funding to conduct this study.
- The nurses who facilitated the clinical aspects of this research and their dedication to the search for evidence of ways to improve outcomes for their wounded clients.
- The clients who participated in this research and kindly shared their time and experience.
- The Research Study Reference Group who critically appraised and informed the study's implementation which enhanced the outcomes that were achieved.
- The RDNS Service Delivery Executive who supported the implementation of this study.
- Home and Community Care (HACC) services provided by RDNS are jointly funded by the Victorian and Australian Governments.

Disclosures

Philanthropic funding was obtained from The William Buckland Foundation to conduct this research study. Tina Czech is the Director of the Australian Institute of Laser Therapy who contributed two days of LILT education to RDNS prior to commencement of the study. Ms Czech receives royalties from laser therapy education. Other contributions from study partners, beyond the work completed by staff funded by the philanthropic monies received, were provided inkind. There are no other conflicts of interest to declare.

Study teams and groups

Research study team

Dr. Leila Karimi (Study Manager)	Lecturer, School of Public Health, La Trobe University
Janine Sunderland	Wound Management Clinical Nurse Consultant, Royal District Nursing Service
Russell Nunn	Research Officer, Royal District Nursing Service Helen Macpherson Smith Institute of Community Health

Research study management group

Dr. Lisa Donohue	General Manager, Royal District Nursing Service Helen Macpherson Smith Institute of Community Health
Charne Miller	Research Fellow, Royal District Nursing Service Helen Macpherson Smith Institute of Community Health

Research study reference group

Dr. Carolyn A. Arnold	Director, Caulfield Pain Management and Research Centre, Caulfield General Medical Centre
Margaret Aston	Layperson / Community representative
Lynda Clark	Site Manager, Royal District Nursing Service
Tina Czech	Director & Educator, Australian Institute of Laser Therapy
Dr. Lisa Donohue (Chair)	General Manager, Royal District Nursing Service Helen Macpherson Smith Institute of Community Health
Terry Gliddon	Research and Development Manager, Royal District Nursing Service Helen Macpherson Smith Institute of Community Health
Suzanne Kapp	Research Fellow, Royal District Nursing Service Helen Macpherson Smith Institute of Community Health
Dr. Leila Karimi (Study Manager)	Lecturer, School of Public Health, La Trobe University
Associate Professor William McGuinness	A/C Head, Division of Nursing & Midwifery, LaTrobe University
Charne Miller	Research Fellow, Royal District Nursing Service Helen Macpherson Smith Institute of Community Health
Jenny Pilgrim	Educator, Royal District Nursing Service Helen Macpherson Smith Institute of Community Health
Glenda Valentine	Site Manager, Royal District Nursing Service
Martin Wischer	Director of Nursing, South / East Region, Royal District Nursing Service

Executive summary

Background

Pain associated with chronic wounds is a significant issue; more than half the people living with a chronic wound report significant and unremitting pain (Baker & Stacey, 1994) and wound pain is a known reason for non-adherence to best practice leg ulcer care (Dereure, Vin, Lazareth, & Bohbot, 2005; Edwards, 2003; Moffatt, Kommala, Dourdin, & Choe, 2009). Given the volume of wound care attended by community nursing services, it is an imperative to ensure effective wound pain management to facilitate improved client outcomes and quality of life and to optimise the efficiency of their healthcare provision.

Low Intensity Laser Therapy (LILT) is a form of phototherapy producing a power output in the milliwatt range (mW) enabling very low intensities of light energy to be delivered through the skin's surface. LILT is believed to stimulate or modulate biological processes created by the interaction of electromagnetic radiation with tissue (Basford, 1989). The therapeutic use of LILT began in the latter part of the 1960's and since then, LILT has been utilised by a range of care providers and for a range of applications (Bashford, 1995). The effectiveness of LILT on pain has been examined in relation to Carpal Tunnel Syndrome, nerve pain, rheumatoid arthritis, neck pain, and acute wound and surgical injury pain (Basford, 1993).

Research exploring the application of LILT to chronic wound management is limited, and is compromised by small samples and interventions that have not been methodically controlled or described. A proof of concept study was conducted to address the lack of rigorous evidence regarding the efficacy of LILT to resolve chronic leg wound pain. The feasibility of a Randomised Controlled Trial (RCT) was examined and more precise effect size estimates generated upon which power analyses for large clinical trials could be based.

Design

A non-blinded, RCT was conducted in a large Australian community nursing service. Clients were eligible to participate in the study if they were receiving care for a chronic wound healing by secondary intention [wound healing is delayed and occurs by a process of granulation, contraction and epithelialisation; (Carville, 2005)] and for which wound pain ≥ 1 on a 0-10 numeric pain rating scale was experienced for more than two weeks. Participants were randomised to one of the three study groups—control, Poly laser Trion™ (hand held laser), and Photonic 500 Acumed™ (scanning laser)—during a 14 month recruitment period (2008-2009). Both lasers were listed with the Therapeutic Goods Administration of Australia. The trial was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12608000503325) and ethics approval was received from the organisation's Human Research Ethics Committee.

A sample size of 60 participants was sought (20 participants per study group). Screening, recruitment, treatment and data collection were co-ordinated at two community nursing service sites by study trained Wound Management Clinical Nurse Consultants (WMCNCs). The primary outcome measure for this study was the reduction of pain assessed using the Brief Pain Inventory (BPI - Short Form) (copyright C.S. Cleeland & Pain Research Group, 1991) which generates two scores (domains) of pain; severity and interference. Secondary measures included wound healing rate, the number of wounds healed, quality of life, and psychological distress.

The 12 weeks of study participation included two phases; LILT Treatment Phase (0-6 weeks) and Monitoring Phase (6-12 weeks). For the first 6 weeks, participants randomised to either of the LILT groups received LILT three times each week during usual wound treatments in a clinic setting. Participants in the control group received twice weekly wound care unless more frequent standard care treatment was indicated. During the Monitoring Phase, participants attended the clinic every two weeks for wound care and data collection. Other wound care was attended as determined by the individual client's care plan either in the home or clinic as per the client's preference.

Pain data were gathered at each treatment session. Quality of life and psychological distress measures were assessed twice during the study period; at baseline and at the end of the 12 weeks monitoring phase or upon healing if it occurred first.

The Statistical Package for the Social Sciences (SPSS) for Windows Release 19.0 (SPSS Inc., 2010) was used to analyse these data. Data were analysed using linear mixed models and analyses of covariance (ANCOVA), with effect sizes for pain interference and severity generated from the adjusted means and standard deviations produced by the ANCOVA tests. Data were double checked and analyses reviewed by an independent statistical consultant.

The RCT was supplemented by a survey of clients to ascertain impressions of LILT (for those randomised to either the hand held or scanning laser), feedback from the WMCNCs administering LILT, and comment by members of the study team regarding the implementation of the trial.

Results

Fifty-seven participants were recruited to the study during the recruitment timeframe established by the trial. Data from 54 participants were included in the primary analysis (scores on the BPI Interference measure) representing a high follow-up of participants (95%).

Participants were on average 79.29 years of age ($SD=11.58$) and two thirds were female (66.1%). Participants required some assistance with four ADLs or IADLs on average ($SD=3.31$). Most wounds were classified as a venous ulcer (35.2%) or mixed venous arterial ulcer (35.2%), had a duration of 9.48 months on average ($SD=13.43$), and had multiple signs of infection / critical colonisation ($M=3.30$, $SD=1.48$). Participants had experienced pain for several months prior to the commencement of the study ($M=7.29$, $SD=7.98$). Most study participants (77.4%) used pain medication.

The treatment groups were comparable on all baseline characteristics with the exception of pain duration which approached significance [$F(2,51)=3.15$, $p=0.05$]. This variable was controlled for where possible in the main statistical analyses.

Pain reduced significantly for both the BPI interference [$F(6,193.91)=5.08$, $P<0.00$] and BPI severity [$F(3,104.52)=7.55$, $P<0.00$] scores across the 12 weeks of monitoring. The lack of significant differences in pain scores between the study groups for BPI interference [$F(2,59.12)=0.32$, $P=0.73$] and BPI severity [$F(2,55.41)=0.99$, $P=0.38$] was not unexpected as the study was not powered to determine significance. Instead, the study has produced effect sizes that indicate the clinical significance of differences between the study groups and the sample size required to find a significant difference in further clinical trials.

Effect sizes were calculated from baseline to 3rd fortnight (representing the LILT Treatment Phase), baseline to 6th fortnight (inclusive of the LILT Treatment and Monitoring Phases), and also from baseline to 1st fortnight given that the differences in pain scores for the groups appeared largest at this initial assessment point. Due to missing data for the BPI severity outcome measure, effect and sample size estimates were only possible for the LILT Treatment Phase. Effects were further calculated for two models; 1) three trial groups (control, hand held, and scanning), and 2) two trial groups (control and hand held). This second model was pursued because the direction of clinical effects observed in this study favoured the hand held laser.

The power analyses revealed medium effect sizes in the 1st fortnight favouring a greater reduction in pain on both interference and severity scales for the hand held group. The required sample sizes estimates are corresponding low; between 20-34 participants per group depending on the model and pain measure considered. The effect sizes applicable for the LILT treatment phase (0-3rd fortnight) were small, suggesting per group sample sizes of approximately 90 participants for BPI interference and 50 participants for BPI severity. A very small effect size was observed for the pain interference measure after 12 weeks of follow-up. This finding implies an effect with limited clinical relevance for which an excessive sample size renders further clinical trials impractical.

The use of medication to manage pain declined from 77.4% of the sample at baseline to 26.4% at the last visit. Although both the LILT groups demonstrated swift reduction in the use of pain medication compared to the control group, the differences between the groups were significant only at fortnight one ($\chi^2(2)=6.73$, $p=0.04$) where fewer scanning laser clients were using pain medications (47.4%) compared to the hand held laser (61.1%) and high use amongst the control group (88.2%). Controlling for pain medication use at fortnight one did not, however, alter the lack of significance associated with or the effect size of the study groups on pain interference scores.

Eighteen wounds (37.5%) healed during the study. The distribution of healed and not healed wounds were comparable for the study groups; 5 (35.7%) for the control group, 6 (35.3%) for the hand held laser group, and 7 (41.2%) for the scanning laser group [$\chi^2(2)=0.15$, $P=0.93$]. Logistic regression further confirmed that study group was not a significant predictor of wound healing. There were also no significant main effects of study group on a wound healing rate, either quality of life scores (the EQ-5D utility score and the EQ-5D VAS current health state), or psychological distress.

Feedback from study participants indicated that LILT was an acceptable treatment. Clinicians and members of the study team provided feedback about the LILT and study education and the trial protocols that could be readily adopted into future trials. Clinicians attributed improvements in pain and healing to a number of aspects of their clinical care that were distinct from the LILT intervention and present for all study participants regardless of treatment randomisation. These included the expertise offered by wound management clinical nurse consultants, continuity of care, use of best practice wound products due to staffing expertise and access to wound product funding, and improved communications with the broader healthcare team including the participant's general practitioner.

Given the study design and the modest evidence of study group effects, other explanations need to be considered for the reduction of the persistent pain participants experienced upon entry to the study. A plausible explanation for a reduction in wound pain is the changed model of care. LILT was evaluated in a clinic setting outside usual homecare wound management. The clinic setting for the study enabled consistency in care, continuity of care, improved access to best practice care through staffing expertise and product funding, improved communication with the healthcare team and specifically the client's general practitioner regarding pain management education. These attributes are perhaps more likely to explain the study effects.

There was one aspect of LILT which was incongruent with usual wound management practice and for which efforts were continuing to discern an acceptable clinical management response; the duration of wound bed exposure which becomes prolonged during the LILT treatment compared to usual care.

Recommendations and implications for practice

Small to moderate effect sizes provide provisional support of a short term clinical benefit from the use of the hand held laser compared to the scanning laser and control groups. This finding requires substantiation. The following steps are recommended:

1. As a precursor to a large clinical trial, an in-home evaluation of the hand held laser is conducted to:
 - a. Establish the safe use of the hand held laser in the home setting and to develop guidelines supporting this implementation
 - b. Confirm/refine effect sizes based on information arising from the in-home application of the hand held laser with comparison to a home-based care control group.
2. The study protocol is revised for future clinical trials in light of the specific comments outlined throughout the report and specifically noted in Chapter Two, with respect to participant eligibility, data collection, and project management.
3. Methods of managing prolonged wound bed exposure are established to promote the best environment for wound healing.
4. A homogenous sample with respect to wound aetiology is sought by:
 - a. Excluding clients with arterial disease
 - b. Either adopting a focus on participants with Diabetes Mellitus or excluding this group
 - c. Targeting wound aetiologies that are associated with the most chronic and unresolved pain and/or highly prevalent wound types that are also painful.
5. Large clinical trials are conducted comparing pain reduction associated with the hand held laser and a control group for home based nursing clients. Given less evidence of efficacy associated with the scanning laser and the obvious logistic difficulty using this laser in a homecare setting, further testing of the scanning laser is optional for this population.

In light of the improvements observed in persistent chronic wound pain as a result of study participation that are not necessarily attributable to the intervention, it is recommended that:

6. Pain management is reviewed within the lead organisation commencing with an audit of pain assessment and management to inform future approaches to pain management including staff education; staffing skill mix and utilisation; systems and procedures; and new pain management initiatives (e.g. models of inter-disciplinary pain management, psychosocial education with clients).

1.0 Introduction

Low Intensity Laser Therapy (LILT) is a form of phototherapy producing a power output in the milliwatt range (mW) enabling very low intensities of light energy to be delivered through the skin's surface. LILT is believed to stimulate or modulate biological processes created by the interaction of electromagnetic radiation with tissue (Basford, 1989). The absorption of photon energy is believed to accelerate electron transfer (Karu, Ryabykh, & Letokhov, 1997), initiate folding of protein and subsequent activity on enzymes (Pasher, Ghesick, Winkler, & Gray, 1996), exert increased immune response, vasodilation and circulation, induce anti-inflammatory effects and improve nerve function (Campara et al., 1999; Lievens, 1988; Rochkind et al., 1989; Takaduma, 1993).

The therapeutic use of LILT, or 'low energy', 'low level', 'low intensity' or 'cold laser,' began in the latter part of the 1960's examining the impact of LILT on hair growth in mice (Mester, Szende, & Tota, 1967). Since then, LILT has been utilised by a range of care providers and for a range of applications (Bashford, 1995). Ear, nose and throat specialists have used LILT to treat chronic ear conditions including tinnitus, hearing loss, cochlear dysfunction, rhinitis and sinusitis. Neurological applications have included the stimulation of neural growth and recovery of nerve function. Though the effectiveness of LILT on pain has been examined in relation to Carpal Tunnel Syndrome, nerve pain, rheumatoid arthritis, neck pain, and acute wound and surgical injury pain (Basford, 1993), research exploring the application of LILT to chronic wound management is limited.

1.1 Chronic wounds & LILT

Chronic wounds have a profound impact on an individual's health and quality of life (Baker & Stacey, 1994; Dereure et al., 2005; Edwards, 2003; Flemming & Cullum, 2008; Moffatt et al., 2009). More than half the people living with a chronic wound report significant and unremitting pain (Baker & Stacey, 1994) with wound pain a reason for non-adherence to best practice leg ulcer care (Dereure et al., 2005; Edwards, 2003; Moffatt et al., 2009). The majority of studies conducted to date examining the effectiveness of LILT in relation to wounds have focused on wound healing as the primary outcome.

1.1.1 Wound healing

Systematic reviews of the impact of LILT on wound healing have reached markedly different conclusions (Flemming & Cullum, 2008; Woodruff et al., 2004). A Cochrane review examining the effects of LILT on venous leg ulcers included four of 14 randomised controlled trials (RCT) in their meta-analysis (Flemming & Cullum, 2008). All studies included small samples (≤ 46 participants), randomisation method was either inadequate or unclear, and none completed intention-to-treat analysis. The authors concluded there was no evidence of any benefit of LILT on venous ulcer healing with the exception of a small study in which the combination of laser and infrared light promoted healing (Bihari & Mester, 1989).

Another systematic review considering 24 aggregate human and animal studies concluded that laser therapy is an effective tool for promoting wound repair (Woodruff et al., 2004). Though the significant benefits were strongest for animal studies, they remained positive when considering the human studies separately (Woodruff et al., 2004). The review included trials considering 'bed sores' (pressure and decubitus ulcers), venous ulcers, diabetic ulcers, and surgical wounds: however, the results were not presented separately by wound aetiology.

The differing conclusions emerging from systematic reviews regarding the efficacy of LILT reflect variations in the selection criteria. It would seem probable that LILT can influence the healing process; however, it is unclear what the size of this clinical benefit is and which types of wounds would benefit most, with evidence of a benefit for venous leg ulcers presently limited.

In a small and more recent RCT, LILT produced faster healing for superficial abrasions compared to abrasions not treated with LILT (Hopkins, McLoda, Seegmiller, & Baxter, 2004). In other non-experimental, evaluation studies LILT has been associated with wound size reduction (James, 1994; McNulty, 1997; Vice, Walters, & Robinson, 1991), reduced oedema and inflammation (James, 1994), increased exudate and improved vascular granulation (Vice et al., 1991).

Although these results are noteworthy, they have largely failed to establish standard criteria for the particular laser, dosage, number, frequency, or duration of treatment (Posten et al., 2005) or have been undermined by small sample sizes and compromised clinical protocols (Flemming & Cullum, 2008; Posten et al., 2005).

1.1.2 Wound pain

Promising findings have emerged from clinical trials for the effectiveness of LILT in the treatment of nerve pain (Conti, 1997), pain associated with arteriosclerosis (El-Kasef & Attia, 1999), rheumatoid arthritis (Palmgren, Jensen, Kaae, Windelin, & Colov, 1989), and neck pain (Chow, Barnsley, Heller, & Siddall, 2004). In a systematic review of the effect of LILT on pain associated with acute injuries or surgical wounds, evidence emerging from laboratory studies which linked LILT with modulating inflammatory pain was also observed in blinded human trials (Bjordal, Johnson, Iversen, Aimbire, & Lopes-Martins, 2006). Eight of nine included trials observed that LILT performed significantly better than placebo in at least one of the outcomes assessed.

Few studies have considered the effectiveness of LILT in relation to chronic wound pain. These reports include case study or small sample single arm pre and post evaluations suggesting pain reduction for malignant external ulceration (Humaz & Diamantopoulos, 1993), chronic venous leg ulcers (Surgrue et al., 1990), and for people with Buerger's Disease (Schindl, Kainz, & Kern, 1991).

Furthermore, few studies have explored the safe and efficacious application of LILT to resolve wound pain in the home healthcare setting even though the prevalence of wound care delivery by these services has been estimated to range between 25-36% (Carville & Lewin, 1998; Pieper, 1999). Of the two nurse-led and community-based studies conducted, LILT was used safely and wound size was found to reduce; however, these were small evaluation studies that included only 7 and 8 participants respectively (James, 1994; McNulty, 1997).

Given the paucity of research available, the use of small samples, and interventions that have not been systematically controlled or described, there is presently insufficient or inadequate evidence to guide practice regarding the use of LILT to address chronic wound pain management.

1.2 Proof of concept study

Research funding was obtained to undertake a proof of concept study to address the lack of rigorous evidence regarding the efficacy of LILT to resolve chronic leg wound pain. Specifically, the goal of this investigation was to examine the feasibility of a Randomised Controlled Trial (RCT) and to generate more precise effect size estimates upon which power analyses for future research could be based.

A number of hypotheses were stated as the basis for conducting the RCT:

Hypothesis 1: Participants receiving LILT will report significantly lower levels of wound pain compared to participants in the control group.

Hypothesis 2: Participants receiving LILT will report a significantly quicker healing rate and more wounds healed compared to participants in the control group.

Hypothesis 3: Participants receiving LILT will report a significant reduction in psychological distress compared to participants in the control group.

Hypothesis 4: Participants receiving LILT will report a significant improvement in quality of life compared to participants in the control group.

2.0 Materials & Method

Using a non-blinded, RCT study design, eligible clients from two Australian community nursing service sites (providing in-home nursing services to two geographic regions) were randomised to one of the three study groups—control, Poly laser Trion™ (hand held laser), and Photonic 500 Acumed™ (scanning laser)—during a 14 month recruitment period (2008-2009). The trial was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12608000503325) and ethics approval was received from the organisation's Human Research Ethics Committee.

2.1 Participants eligibility

Inclusion criteria:

- (1) Aged ≥ 18 years.
- (2) Receiving care for a chronic leg wound (the study wound¹) of either pressure, venous, arterial, mixed venous/arterial, injury, burn, or vasculitis aetiology.
- (3) The wound was older than 6 weeks, ≤ 10 cms in diameter, and ≤ 2 cms in depth.
- (4) The wound was healing by secondary intention².
- (5) Had wound pain (≥ 1 on a 0-10 numeric pain rating scale).
- (6) Experienced wound pain at times other than (but could be in addition to) wound dressing changes.
- (7) The wound pain had not responded to a minimum of two weeks of standard pain management.
- (8) The client was willing to attend a clinic setting for their care during the study period.

Exclusion criteria:

- (1) Diagnosis of, or in receipt of treatment for, a malignancy (wound or other).
- (2) Lack of support for client participation from the local medical officer / wound specialist.
- (3) Any planned absences during the 12 week study period.

A sample size of 60 participants was sought (20 participants per study group) to achieve a sample which was sufficient to enable consideration of the study aim; a proof of concept evaluation of the efficacy of LILT on unresolved wound pain.

2.2 Recruitment

Prior to commencing recruitment, a two hour Wound Pain Management Education Program was delivered to all nursing staff at the study sites by study-trained Wound Management Clinical Nurse Consultants (WMCNCs) which established a standardised and comprehensive level of pain management care. The program sought to reinforce standardised assessment, care planning and evaluation of pain management.

Screening, recruitment, treatment and data collection were co-ordinated at two community nursing service sites by WMCNCs. Clients were identified as eligible for the study by general nurses, who provided them with a plain language statement and consent form. The client was subsequently contacted by a WMCNC by telephone to ascertain initial interest and answer any questions. If they were interested the clients attended one of two clinics operated by the service in their geographic region where the client's eligibility was re-assessed by a WMCNC and written informed consent obtained. Interpreters were engaged as necessary, and carers and guardians involved as appropriate.

¹ If a client had multiple wounds, only the wound that was the most painful was considered.

² Wound healing is delayed and occurs by a process of granulation, contraction and epithelialisation (Carville, 2005)

Participants were then randomly allocated to one of the three study groups (control, hand held laser, and scanning laser). Randomisation lists were generated using the random number function in Microsoft Excel™ and randomisation allocation was completed using sealed, opaque envelopes.

During the study participants received all wound dressing products at no cost and taxi vouchers were provided if required to assist participants to attend the clinics for treatment and data collection.

2.3 Data Collection & Measures

The primary outcome measure for this study was the reduction of pain. Secondary measures included wound healing rate, the number of wounds healed, quality of life and psychological distress.

This paper presents pain data at baseline and every fortnight (approximately 14 days) until the completion of the 12 weeks study participation period or less if the wound healed. Pain was assessed using the Brief Pain Inventory (BPI - Short Form) (copyright C.S. Cleeland & Pain Research Group, 1991) which generates two scores (domains) of pain; severity and interference. Four items are used to generate a pain severity score. Items are scored on a 0 ('no pain') to 10 ('pain as bad as you can imagine') scale and are asked in relation to the 'worst' pain in the last 24 hours, 'least' pain in the last 24 hours, 'average' pain and pain 'right now'. The composite score is the mean of these four items. The pain interference domain uses seven items to generate a composite score. Items are scored on a 0 ('does not interfere') to 10 ('completely interferes') scale for how pain has interfered over the last 24 hours with general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. The BPI interference score is reported for every fortnight for the 12 week study period. Due to one missed item from the BPI severity scale, this measure can only be reported for the LILT Treatment Phase (baseline to 6 weeks).

Wound size measurements were gathered using SilhouetteMobile™ (ARANZ Medical Ltd.), a portable imaging and measurement device. SilhouetteMobile™ obtains a digital image of the wound and a stylus is then used to trace its wound margins to produce a total wound surface area. This device has demonstrated high intra- and inter- rater reliability (Miller, Karimi, Donohue, & Kapp, accepted for publication). Wound measurements were obtained at baseline and every two weeks. The percentage change between fortnightly wound size measures was divided by the number of days between wound measures producing a daily healing rate that is standardised for slight variations in the timing of visits. Whether the wound healed and the date of wound healing was also recorded.

Quality of Life (QoL) was measured using the EuroQol 5D (EQ-5D), a validated self-report measure of health outcomes which was developed by the EuroQol group [Rotterdam, The Netherlands (www.euroqol.org)]. The EQ-5D comprises a five-part questionnaire which generates a generic health index or 'utility' score, and a 100 point visual analogue self-rating scale (VAS). The EQ-5D utility score is generated given the pattern of responses to the five-part questionnaire with a range of 1 which indicates full health and -0.59 reflecting that the respondent is at the bottom level of each dimension. The 100 point VAS scale is positively framed with 100 representing the 'best imaginable health state' and 0 representing the 'worst imaginable health state'. The scale has been shown to be suitable for measuring health status in a very elderly population (Holland, Smith, Harvey, Swift, & Lenaghan, 2004).

The Kessler Psychological Distress Scale (K10) was originally developed at the University of Michigan (1992) for screening populations for psychological distress. This 10-item questionnaire yields a global measure of distress based on questions about anxiety and depressive symptoms that a person has experienced in the most recent 30 days. The responses range from 1 "none of the time" to 5 "all of the time". The scores on the 10 items are summed to produce a composite score ranging from 10 to 50, with higher scores signifying higher levels of psychological distress. It has been widely used in the United States as well as in Australia where it has been validated in a large national sample of people aged 18 years and older (Andrew & Slade, 2001).

Additional measures were used to compare the study groups at baseline. Included in these data were measures of Activities of Daily Living (ADL's) (Katz, Ford, Moskowitz, Jackson, & Jaffe, 1963) and Instrumental Activities of Daily Living (IADL) (Lawton & Brody, 1969) that were modified in accordance with minimum data set requirements for Home and Community Care Services in Victoria, Australia. Clinical signs of infection or critical colonisation were collected according to published guidelines and assessment tools (Cutting, 1994; Gardner, 2001; World Union of Wound Healing Societies, 2008). Nutritional risk was assessed using the 11 item HACC Nutritional Risk Screening and Monitoring Tool (Department of Human Services, 2001).

Participants attended a clinic to receive their wound treatment and data collection for 12 weeks or less if their wound healed. Pain data were gathered at each treatment session, though reported herewith are the pre-treatment pain data that corresponds with the fortnightly data collection of wound measurements. Quality of life and psychological distress measures were assessed twice during the study period; at baseline and at the end of the 12 weeks monitoring phase or upon healing if it occurred first. Data collection was attended by study-trained WMCNCs.

Study participants were provided with a client survey and reply paid envelope either upon healing, discharge from the service, or upon completion of the study. The survey sought ratings of a number of aspects of their assessment and ongoing nursing service, attendance and provision of care at the clinic, and for those clients who were randomised to receive LILT, of the experience receiving the LILT treatment. The survey instrument was custom designed assessing areas determined by the study team to be of relevance to the appraisal of the service, clinic or LILT, was two pages in length and was administered in hard copy format. Questions relating to the nursing service or care provision at the clinic were assessed on a 5-point likert scale (scale including poor, fair, good, very good, and excellent). Three statements were made regarding the laser treatment (e.g. The wound was comfortable during laser application?) and were also assessed on a 5-point likert scale (scale including completely disagree, disagree, not sure, agree, completely agree). Participants were also asked if they would be willing to have the laser treatment again (yes/ no).

Qualitative feedback was obtained from the five WMCNCs and study team regarding the implementation of this research study. A focus group discussion was convened with the five WMCNCs after data collection for all study participants was complete. The discussion was conducted face-to-face, with one WMCNC tele-conferencing into the meeting. A semi-structured guide was developed and used by the Study Manager who facilitated the discussion to prompt comment on: the LILT education; ease, time and feasibility of using LILT; client reactions to LILT; application of LILT to home nursing service; and overall impressions. The discussion was digitally recorded and subsequently transcribed. Broad categories of feedback were determined from the transcript content and agreed upon by two researchers employed by the Institute managing the proof of concept study who were involved in aspects of the study implementation.

A review of the research method was conducted by three study contributors at the end of this proof of concept study to assist in making recommendations for a future larger trial. A list of areas identified as either working effectively in the proof of concept study which should be integrated into future trials, and those areas requiring further consideration and refinement were circulated and consolidated. A report of these comments was developed and re-circulated to reaffirm that items were adequately addressed and described. The report was then circulated for critique by remaining study collaborators.

2.4 Treatment Protocol

The 12 weeks of study participation included two phases; LILT Treatment Phase (0-6 weeks) and Monitoring Phase (6-12 weeks). For the first 6 weeks, participants randomised to either of the LILT groups received LILT three times each week during usual wound treatments. Participants in the control group received twice weekly wound care unless more frequent treatment was indicated. The LILT treatment was discontinued if pain was resolved for two weeks or upon the conclusion of the six week treatment phase. During the Monitoring Phase, participants attended the clinic every two weeks for wound care and data collection. Other wound care was attended as determined by the individual client's care plan either in the home or clinic as per the client's preference.

For the purposes of this study, care during the Treatment Phase, and fortnightly care during the Monitoring Phase was attended in a clinic setting. For most clients this differed to their usual in-home care with treatment being provided by advanced WMCNCs rather than generalist nurses. This variation was adopted to ensure participant and clinician safety given the use of LILT was a novel treatment in the community nursing service. As the scanning laser is not a portable device, it required clinic administration.

Study-trained WMCNCs completed an accredited three day course in LILT and received certification following formal examination. WMCNCs accessed clinical supervision and telephone support as needed from an experienced LILT clinician (TC). A LILT treatment guideline was created for use in the study to standardise practice (Appendix 1).

This study included two types of lasers; a Poly laser Trion™ hand held cluster laser and a Photonic 500 Acumed™ scanning laser (Reimers & Janssen GmbH). They are semiconductor diode lasers with a gallium aluminium arsenide medium and are classified as Class 3b lasers, emitting power outputs in the milliwatt (mW) range below 1 watt. Both lasers are listed with the Therapeutic Goods Administration of Australia for use in photo induced biomodulation, which is non-thermal in its effects.

The Poly laser Trion™ Hand held cluster laser (hand held laser) is comprised of 12 laser diodes. Consisting of 4 X 655nm visible red light with a power output of 5mW and 4X 655nm visible red light at 40mW power and 4X 785nm infra-red wavelength at 55mW power output (Figure 2.1). The hand held laser was selected for the study for its portability; a feature which could conceivably permit future exploration of providing in-home laser therapy.



Figure 2.1 Administering the Poly laser Trion™ (hand held laser)

The Photonic 500 Acumed™ (scanning laser) version is a free standing scanning laser simultaneously emitting 655nm visible red laser light at a power output of 50mW and 810nm infra-red laser wavelength, at a power output of 500mW (Figure 2.2). This laser was selected for its ability to deliver laser light energy at specific pulse repetition rates that support photobiomodulation (Karu, Andreichuk, & Ryabykh, 1993). Although offering more power and a greater range of functions in contrast to the hand held laser, some of which is reflected in the treatment protocol, the full extent of the options provided by the scanning laser were not exercised in this study due to the need to standardise and simplify its application in this setting for research transparency in reporting and repeatability. The hands-free aspect of delivering treatment to large wound areas is advantageous in a clinical setting as it allows the clinician to perform other tasks while the treatment is taking place.



Figure 2.2 Administering the Photonic 500 Acumed™ (scanning laser)

2.5 Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) for Windows Release 19.0 (SPSS Inc., 2010) was used to analyse these data. Data were checked for out of range values and assumptions of the statistical tests used prior to analysis. An alpha level of 0.05 was used to classify findings as significant.

The effect of treatment group on change in pain severity, interference and healing rate were analysed using linear mixed models (LMM). LMM has the advantage of allowing all available data to be utilised irrespective of the number of completed follow-ups. This approach is considered appropriate for wound research given that the event of wound healing often results in missing data. Analyses of Covariance (ANCOVA) were conducted assessing differences between treatment groups at each fortnight for pain and wound healing. Differences between the adjusted means and standard deviations from the ANCOVA analysis for pain were used to compute effect and sample size estimates. The K10, EQ-5D Utility score, and EQ-5D VAS were analysed using Repeated Measures Analysis of Covariance (RMANCOVA). Pain duration was included as a covariate in all LMM, ANCOVA and RMANCOVA analyses.

3.0 Results: Pain, Wound Healing QoL, and K10

Fifty-seven participants were recruited to the study. Their progress from recruitment through to analysis is shown in Figure 3.1. Data from 54 participants were included in the primary analysis (scores on the BPI Interference measure) representing a high follow-up of participants (95%). Data are not presented for the 3 respondents excluded from the primary analysis and, given that this was a small number of respondents to be excluded, statistical comparisons between the analysed sample and excluded cases were not pursued. Data were not gathered regarding the size of the population screened for eligibility for the trial, the percentage of clients excluded given the eligibility criteria, or who declined to participate in the trial.

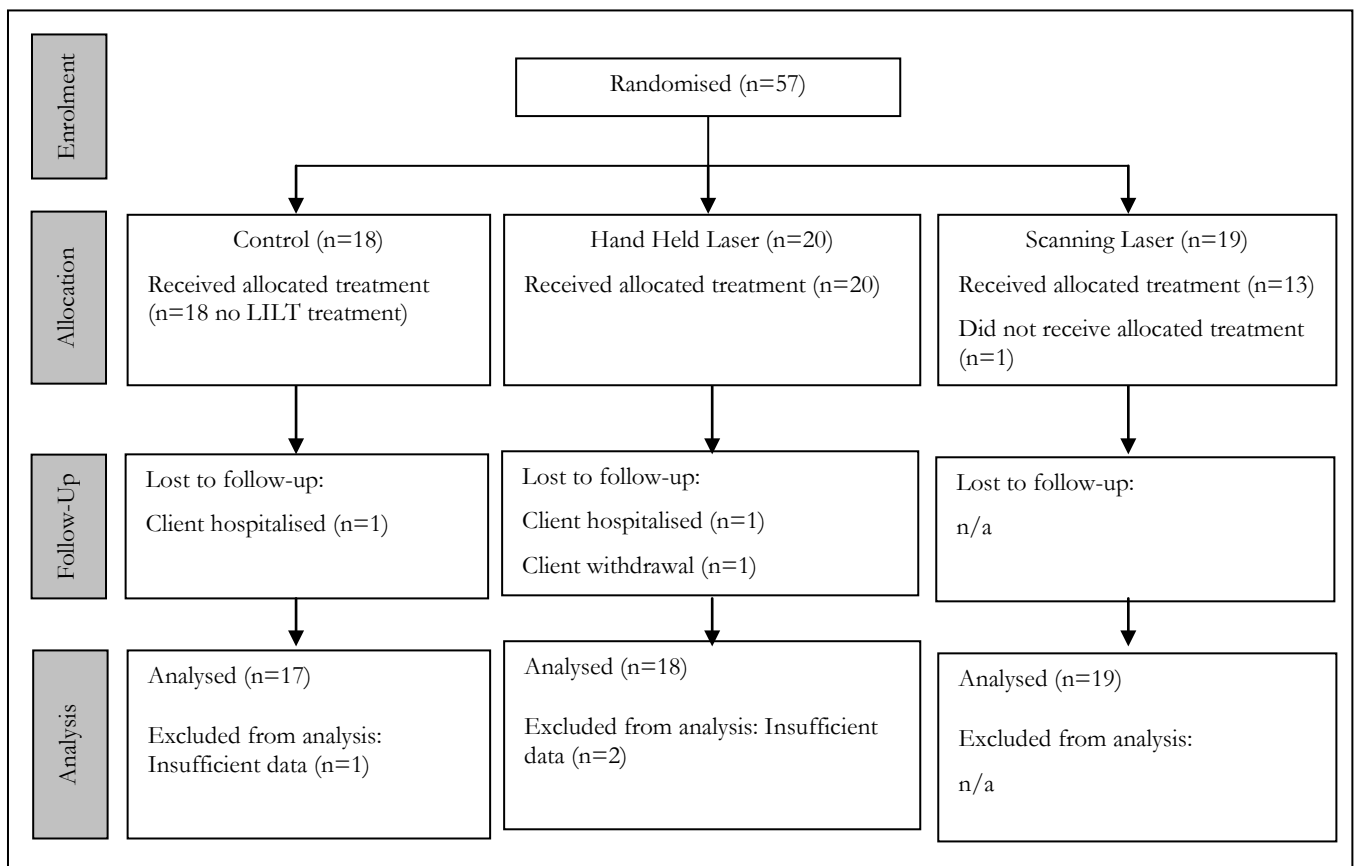


Figure 3.1 Participant flow diagram

Participants who failed to receive >3 of their randomised laser sessions (of a possible 18 sessions) were classified as 'did not receive allocated treatment'. This classification only applied to one participant who declined ongoing treatment with the scanning laser after 3 sessions. There were another 5 instances where participants missed 1-2 LILT sessions (distributed equally across the LILT treatment groups), a participant received a lower dose treatment for 2 sessions, and a participant allocated to the hand held laser group received one scanning laser treatment in error. Reasons for laser treatments being missed included participants being unable to attend the clinic and staff unavailability.

Analysis was conducted where possible as intention-to-treat and, thus, according to the randomised treatment and all participants for whom data were available. Analysis was also repeated removing the participant who did not receive the allocated treatment. Due to missing data, this participant was not included in the pain and healing outcome measures, and so the analysis was only repeated for the quality of life and psychological distress measures. Comparable results were observed with this participant excluded.

Although no adverse events were officially reported during the trial, subsequent interviews with the WMCNCs administering the LILT identified an instance where exposure to the air whilst the LILT treatment was being delivered resulted in pain and may have contributed to the decision by one participant to withdraw from the trial. There were three instances of hospitalisation associated with a deterioration in the study wound; one instance in each of the control, hand held, and scanning laser groups.

3.1 Sample

The sample included in the BPI interference analysis is used to describe the baseline characteristics of the groups to enable appraisal of the comparability of trial groups included in the primary analysis (Dumville, Torgerson, & Hewitt, 2006).

The treatment groups were comparable on all baseline characteristics with the exception of pain duration which approached significance [$F(2,51)=3.15, p=0.05$]. Participants in the scanning laser group reported longer pain duration ($M=10.84$ months, $SD=9.63$) than the control ($M=5.44$ months, $SD=5.59$) or hand held laser ($M=5.28$ months, $SD=7.00$) groups. Given evidence of significant associations between pain duration and both primary and secondary outcome variables, and the theoretical relevance of pain duration to the study aim, this variable was controlled for where possible in the main statistical analyses.

The demographic and clinical characteristics of the participants are presented in Table 3.1. Participants were on average 79.29 years of age ($SD=11.58$) and two thirds were female (66.1%). Participants required some assistance with four ADLs or IADLs on average ($M=4.00, SD=3.31$). Although three quarters of the sample (74.1%) were classified as being at nutritional risk as indicated by an affirmative response to any of the 11 items of the tool, participants indicated fewer than two areas on average for which they were at risk ($M=1.83, SD=1.73$).

Table 3.1 Demographics and health status by treatment group

	Control (n=17)	Hand Held Laser (n=18)	Scanning Laser (n=19)	Total (n=54)	Sig. (P=)
Gender (% female)	77.8 (n=14)	63.2 (n=12)	57.9 (n=11)	66.1 (n=37)	P=0.42
Age (Years; M \pm SD)	79.61 \pm 14.72	81.05 \pm 8.45	77.21 \pm 11.22	79.29 \pm 11.58	P=0.60
Has Diabetes Mellitus diagnosis (%) [*]	6.3 (n=1)	6.3 (n=1)	23.5 (n=4)	12.2 (n=6)	n/a [^]
Nutritional risk (% at risk)	64.7 (n=11)	77.8 (n=14)	78.9 (n=15)	74.1 (n=40)	n/a [^]
(M \pm SD)	1.59 \pm 1.66	1.61 \pm 1.38	2.26 \pm 2.05	1.83 \pm 1.73	P=0.41
Number ADL/IADL dependent	3.77 \pm 3.38	4.17 \pm 3.57	4.05 \pm 3.15	4.00 \pm 3.31	P=0.94

* Sample size variations are due to missing data

[^] Insufficient sample to conduct statistical analysis

Wound and pain characteristics of participants are presented in Table 3.2. Most wounds were classified as a venous ulcer (35.2%) or mixed venous arterial ulcer (35.2%), had a duration of 9.48 months on average ($SD=13.43$), and had multiple signs of infection / critical colonisation ($M=3.30, SD=1.48$). Participants had experienced pain for several months prior to the commencement of the study ($M=7.29, SD=7.98$) and, as already noted, the treatment groups differed for the duration of pain. Most study participants (77.4%) used pain medication.

Table 3.2 Wound and pain characteristics by treatment group

	Control (n=17)	Hand Held Laser (n=18)	Scanning Laser (n=19)	Total (n=54)	Sig.
Wound duration (Months, M \pm SD)*	6.59 \pm 5.68	8.00 \pm 12.57	13.61 \pm 18.27	9.48 \pm 13.43	P=0.26
Wound size (cm ²) (M \pm SD)*	12.81 \pm 13.98	10.67 \pm 24.31	14.24 \pm 17.86	12.60 \pm 18.95	P=0.85
Wound depth (mm) (M \pm SD)*	1.40 \pm 1.44	1.27 \pm 2.04	0.98 \pm 1.81	1.20 \pm 1.74	P=0.79
Number of signs of infection / critical colonisation (M \pm SD)	3.59 \pm 1.23	3.17 \pm 1.45	3.16 \pm 1.86	3.30 \pm 1.48	P=0.62
Wound Type (%)					
Venous Leg Ulcer	29.4 (n=5)	50.0 (n=9)	26.3 (n=5)	35.2 (n=19)	n/a ^
Mixed Venous / Arterial Leg ulcer	47.1 (n=8)	33.3 (n=6)	26.3 (n=5)	35.2 (n=19)	
Arterial Leg ulcer	17.6 (n=3)	5.6 (n=1)	21.1 (n=4)	14.8 (n=8)	
Other diagnosis	5.9 (n=1)	11.1 (n=2)	26.3 (n=5)	14.8 (n=8)	
Pain duration (Months, M \pm SD)	5.44 \pm 5.59	5.28 \pm 7.00	10.84 \pm 9.63	7.29 \pm 7.98	P=0.05
Pain medication used (% yes)*	82.4 (n=14)	76.5 (n=13)	73.7 (n=14)	77.4 (n=41)	n/a ^

* Sample size variations due to missing data

^ Insufficient sample to conduct statistical analysis

3.2 Pain interference with daily activity

The average score on the BPI interference scale is reported for the treatment groups at baseline and every fortnightly assessment (Table 3.3). Linear Mixed Model (LMM) analysis, including pain duration as a covariate [F(1,53.35)=5.00, P=0.03], showed a significant overall decline in pain interference throughout the study period [F(6,193.91)=5.08, P<0.00] and a significant treatment group by fortnight interaction [F(12,194.34)=1.99, P=0.03]. However, no overall difference between treatment groups was observed [F(2,59.12)=0.32, P=0.73] (Figure 3.2). ANCOVA tests, controlling for pain duration, conducted at each fortnightly assessment identified no significant differences between the study groups for BPI interference (see Table 3.3).

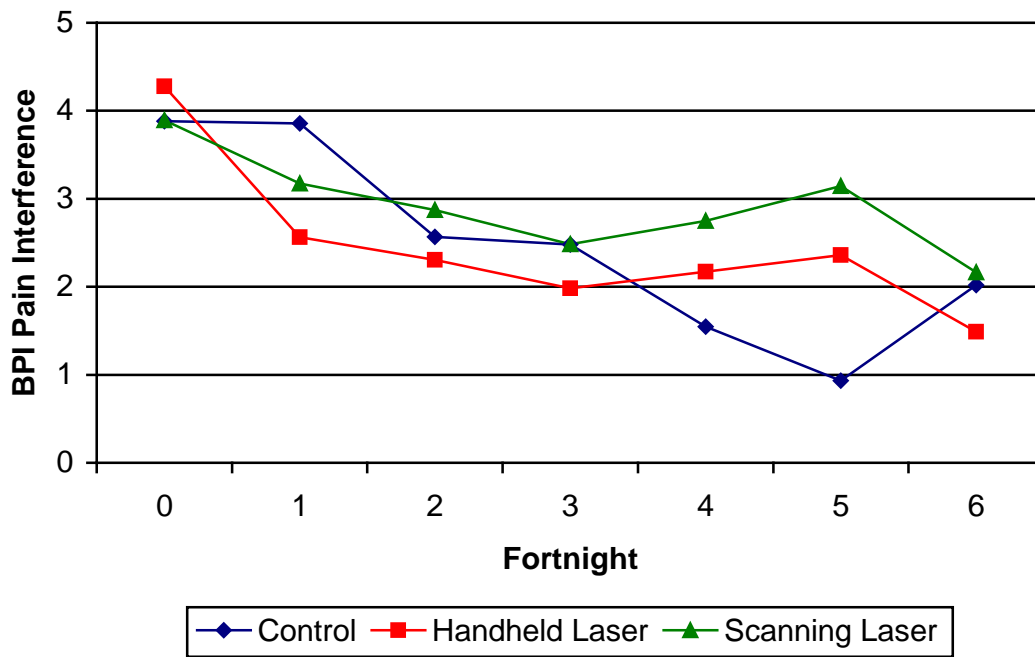


Figure 3.2 Estimated mean BPI Interference Scores by Treatment Group

3.3 Pain severity

BPI severity scale scores are reported at baseline and fortnightly during the LILT treatment phase (Table 3.4). LMM analysis, with pain duration as a covariate [$F(1,53.69)=0.63, P=0.43$], showed a significant reduction in pain severity over the study period [$F(3,104.52)=7.55, P<0.00$], however, there was no significant main effect for treatment group [$F(2,55.41)=0.99, P=0.38$] or treatment group by time interaction [$F(6,104.47)=1.23, P=0.30$] (Figure 3.3). ANCOVA tests, controlling for pain duration, identified no significant differences between the study groups for BPI severity at any of the fortnightly assessments during the LILT Treatment Phase (Table 3.4).

Table 3.3 Pain interference scores by treatment group*

Study period	Assessment point	Control	Hand Held Laser	Scanning Laser	ANCOVA
LILT Treatment Period	Baseline	(M ± SE) 3.88 ± 0.56 (n=17)	4.28 ± 0.55 (n=18)	3.89 ± 0.55 (n=19)	F(2,51)=1.74, P=0.19
	FN 1	(M ± SE) 3.86 ± 0.58 (n=16)	2.56 ± 0.56 (n=17)	3.18 ± 0.57 (n=16)	F(2,46)=0.15, P=0.86
	FN 2	(M ± SE) 2.57 ± 0.60 (n=13)	2.30 ± 0.58 (n=15)	2.87 ± 0.57 (n=17)	F(2,42)=0.65, P=0.53
	FN 3	(M ± SE) 2.48 ± 0.62 (n=13)	1.98 ± 0.63 (n=12)	2.48 ± 0.59 (n=15)	F(2,37)=1.81, P=0.18
	FN 4	(M ± SE) 1.55 ± 0.70 (n=8)	2.17 ± 0.67 (n=10)	2.75 ± 0.65 (n=11)	F(2,26)=0.57, P=0.57
	FN 5	(M ± SE) 0.94 ± 0.71 (n=10)	2.36 ± 0.66 (n=12)	3.14 ± 0.71 (n=9)	F(2,28)=1.78, P=0.19
Monitoring Period (no LILT)	FN 6	(M ± SE) 2.02 ± 0.77 (n=8)	1.49 ± 0.70 (n=10)	2.16 ± 0.75 (n=9)	F(2,24)=1.69, P=0.21

* The reported mean and standard errors were generated using linear mixed model analysis.

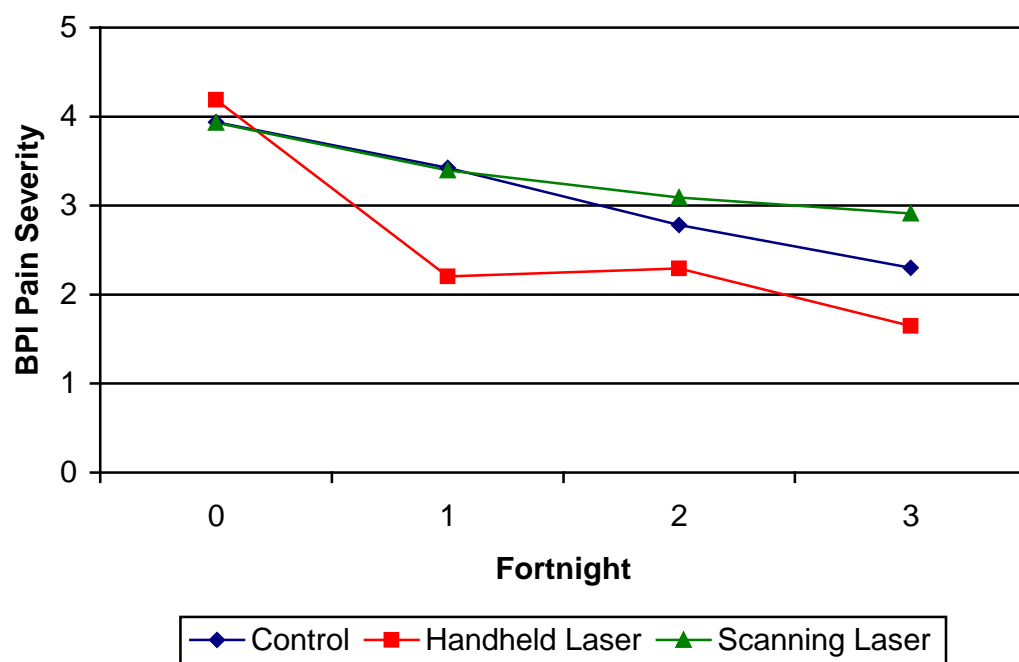


Figure 3.3 Estimated mean BPI severity scores by treatment group

Table 3.4 Pain severity scores for the treatment groups*

Study period	Assessment point	Control	Hand Held Laser	Scanning Laser	ANCOVA
LJLT Treatment Period	Baseline (M ± SE)	3.94 ± 0.51	4.19 ± 0.47	3.93 ± 0.52	F(2,38)=1.05, P=0.36
	(n=)	(n=13)	(n=17)	(n=14)	
	FN 1 (M ± SE)	3.42 ± 0.49	2.20 ± 0.51	3.40 ± 0.50	F(2,41)=0.01, P=0.99
	(n=)	(n=16)	(n=13)	(n=15)	
	FN 2 (M ± SE)	2.78 ± 0.52	2.29 ± 0.51	3.09 ± 0.51	F(2,37)=0.50, P=0.61
	(n=)	(n=13)	(n=14)	(n=14)	
	FN 3 (M ± SE)	2.30 ± 0.59	1.65 ± 0.55	2.91 ± 0.59	F(2,29)=1.24, P=0.31
	(n=)	(n=10)	(n=12)	(n=10)	

*The reported mean and standard errors were generated using linear mixed model analysis.

3.4 Effect & sample size estimates

Effect sizes were determined using means and standard deviations generated by the ANCOVA analyses (see Table 3.5). These data were used to conduct power analyses for both BPI interference and BPI severity scores computing the size of the sample required to find a significant difference between the treatment groups. Power estimates were calculated using G*Power Version 3.0.10 software (Franz Faul, Universitat Kiel, Germany) using an ANOVA fixed effects, omnibus, one-way test, $\alpha=0.05$, $\text{power}=0.90$. Effect sizes were calculated from baseline to 3rd fortnight (representing the LILT Treatment Phase), baseline to 6th fortnight (inclusive of the LILT Treatment and Monitoring Phases), and also from baseline to 1st fortnight given that the differences in pain scores for the groups appeared largest at this initial assessment point. Due to missing data for the BPI severity outcome measure, effect and sample size estimates were only possible for the LILT Treatment Phase.

Effects were calculated for two models; 1) three trial groups (control, hand held, and scanning), and 2) two trial groups (control and hand held). This second model was pursued because the direction of clinical effects observed in this study favoured the hand held laser. Future clinical trials may also wish to consolidate efforts to establish clinical effectiveness for just one laser application in comparison to a control group. Effect sizes were interpreted using Cohen's (1988) description of small (0.2-0.3), medium (0.5), and large (>0.8) effects (Cohen, 1988).

Table 3.5 Effect and sample size estimates

		Effect size	Per group n=	Total n=
BPI Interference				
3 groups	0-1 fortnight	0.36	34	102
	0-3 rd fortnight (treatment)	0.22	89	267
	0-6 th fortnight (total)	0.16	168	504
2 groups	0-2 weeks	0.44	29	58
	0-3 rd fortnight (treatment)	0.24	93	186
	0-6 th fortnight (total)	0.10	484	968
BPI Severity				
3 groups	0-1 fortnight	0.43	24	72
	0-3 rd fortnight (treatment)	0.29	51	153
2 groups	0-1 fortnight	0.53	20	40
	0-3 rd fortnight (treatment)	0.34	48	96

The power analyses revealed medium effect sizes in the first fortnight favouring a greater reduction in pain on both interference and severity scales for the hand held group. The required sample size estimates are corresponding low; between 20-34 participants per group depending on the model and pain measure considered. The effect sizes applicable for the LILT treatment phase (0-3rd fortnight) were small, suggesting per group sample sizes of approximately 90 participants for BPI interference and 50 participants for BPI severity. A very small effect size was observed for the pain interference measure after 12 weeks of follow-up. This finding implies an effect with limited clinical relevance for which an excessive sample size renders further clinical trials impractical.

These calculations represent the required sample per group during analysis. As such, general trial attrition (5% in this trial) as well as data collection/treatments that cannot be attended must be considered when deliberating on the initial sample size targets to achieve the final required sample.

3.5 Pain Medication

The use of medication to manage pain declined from 77.4% of the sample at baseline to 26.4% at the last visit. Medication use was contrasted across the treatment groups at baseline and every fortnight utilising the sample available for the primary analysis (pain interference) (Table 3.6). Although both the LILT groups demonstrated swift reduction in the use of pain medication compared to the control group, the differences between groups was significant only at fortnight 1 ($\chi^2(2)=6.73$, $p=0.04$) where fewer scanning laser participants were using pain medications (47.4%) compared to the hand held laser (61.1%) and high use amongst the control group (88.2%).

Table 3.6 Medication use to manage pain

Study period	Assessment point	Control	Hand Held Laser	Scanning Laser	χ^2
LILT Treatment Period	Baseline	82.4 (n=17)	76.5 (n=17)	73.7 (n=19)	$\chi^2(2)=0.40$, $p=0.82$
	% (yes) (n=)				
	FN 1	88.2 (n=17)	61.1 (n=18)	47.4 (n=19)	$\chi^2(2)=6.73$, $p=0.04$
	% (yes) (n=)				
	FN 2	68.8 (n=16)	50.0 (n=16)	52.6 (n=19)	$\chi^2(2)=1.37$, $p=0.51$
	% (yes) (n=)				
Monitoring Period (no LILT)	FN 3	52.9 (n=17)	31.3 (n=16)	42.1 (n=19)	$\chi^2(2)=1.59$, $p=0.45$
	% (yes) (n=)				
	FN 4	43.8 (n=16)	33.3 (n=15)	31.6 (n=19)	$\chi^2(2)=0.63$, $p=0.73$
	% (yes) (n=)				
	FN 5	47.1 (n=17)	47.1 (n=17)	36.8 (n=19)	$\chi^2(2)=0.52$, $p=0.77$
	% (yes) (n=)				
FN 6	35.3 (n=17)	23.5 (n=17)	21.1 (n=19)	$\chi^2(2)=1.04$, $p=0.59$	
% (yes) (n=)					

As a moderate, significant relationship was found between medication use and pain interference scores at this fortnight ($r=-0.44$, $p=0.00$), the ANCOVA test was repeated controlling for medication use to ensure changes in medication were not masking study group effects. While both pain duration [$F(1,46)=4.97$, $P<0.00$] and medication use [$F(1,46)=9.28$, $P<0.00$] emerged as significant covariates in this model, the significance and effect size of the study group was unchanged [$F(1,46)=0.965$, $P<0.00$]. A larger clinical trial would possibly resolve study group differences or permit further exploration of these effects.

3.6 Wound healing

Healing rates are reported for baseline and during the LILT Treatment and Monitoring Phases (Table 3.7). LMM analysis, with pain duration as a covariate [$F(1,69.28)=1.97$, $P=0.17$], revealed a significant overall change in healing rate throughout the study period [$F(5,158.59)=2.40$, $P=0.04$]; however, the variable pattern of change makes this result difficult to interpret. There was no significant main effect for treatment group [$F(2,76.43)=0.86$, $P=0.43$] or treatment group by time interaction [$F(10,154.81)=0.46$, $P=0.91$]. ANCOVA tests controlling for pain duration found no significant difference in healing rate between the study groups for fortnights one through five. The difference between the groups approached significance at fortnight six [$F(2,15)=3.80$, $P=0.05$]. As shown in Table 6, the mean and standard errors show that comparable healing rates were observed at fortnight six for the control ($M=2.33$, $SE=1.94$) and hand held laser groups ($M=2.70$, $SE=2.28$) in contrast to a negative healing rate for the scanning laser group ($M=-1.51$, $SE=2.13$).

Table 3.7 Healing rate scores for the treatment groups*

Study period	Assessment point	Control	Hand Held Laser	Scanning Laser	ANCOVA	
LILT Treatment Period	FN 1	(M ± SE)	1.90 ± 1.37	1.58 ± 1.28	1.12 ± 1.21	F(2,44)=1.32, P=0.28
		(n=)	(n=14)	(n=15)	(n=18)	
	FN 2	(M ± SE)	-0.83 ± 1.49	0.40 ± 1.42	-1.92 ± 1.37	F(2,36)=1.60, P=0.22
		(n=)	(n=12)	(n=13)	(n=14)	
	FN 3	(M ± SE)	2.88 ± 1.48	4.50 ± 1.70	2.52 ± 1.37	F(2,32)=0.23, P=0.80
		(n=)	(n=12)	(n=19)	(n=14)	
Monitoring Period (no LILT)	FN 4	(M ± SE)	1.22 ± 1.70	-0.34 ± 2.08	0.61 ± 1.33	F(2,27)=0.83, P=0.45
		(n=)	(n=9)	(n=6)	(n=15)	
	FN 5	(M ± SE)	-0.50 ± 1.81	1.79 ± 1.93	1.98 ± 1.83	F(2,20)=1.49, P=0.25
		(n=)	(n=8)	(n=7)	(n=8)	
	FN 6	(M ± SE)	2.33 ± 1.94	2.70 ± 2.28	-1.51 ± 2.13	F(2,15)=3.80, P=0.05
		(n=)	(n=7)	(n=5)	(n=6)	

* The reported mean and standard errors were generated using linear mixed model analysis.

Eighteen wounds (37.5%) healed during the study. The distribution of healed and not healed wounds were comparable for the treatment groups [$\chi^2(2)=0.15$, $P=0.93$]; 5 (35.7%) for the control group, 6 (35.3%) for the hand held laser group, and 7 (41.2%) for the scanning laser group. Logistic regression was used to assess whether treatment group was a significant predictor of healing. Pain duration was included as a covariate in the regression model to account for differences between the study groups at baseline. The overall model was not significant [$G^2(3)=5.91$, $P=0.12$] and, as shown in Table 3.8, neither pain duration nor the laser treatments were significant predictors of whether a wound healed during the study.

Table 3.8 Logistic regression predicting healing (n=48)

	Wald (df)	Sig.	Odds ratio (HR)	95% CI for OR	
				Lower	Upper
Pain duration	3.37 (1)	0.07	0.88	0.77	1.01
Hand held laser	0.01 (1)	0.94	0.95	0.21	4.32
Scanning laser	1.13 (1)	0.29	2.46	0.47	12.98

3.7 Quality of life & psychological distress

The treatment groups were compared on two dimensions of quality of life—the EQ-5D utility score and the EQ-5D VAS current health state—and psychological distress as measured by the K10 (Table 3.9). Scores for these scales were obtained at baseline (time 1) and either upon conclusion of the study period or upon healing if this occurred first (time 2). RMANCOVA on the EQ-5D utility score revealed no significant main effects for time [$F(1,36)=1.90$, $P=0.18$], treatment group [$F(2,36)=1.49$, $P=0.24$] or time by treatment group interaction [$F(2,36)=0.07$, $P=0.93$]. The covariate, pain duration, was not significant [$F(1,36)=1.55$, $P=0.22$]. Analysis for EQ-5D VAS current health state revealed a significant improvement from time 1 to time 2 [$F(1,41)=5.76$, $P=0.02$], although no significant effect was observed for treatment group [$F(2,41)=0.40$, $P=0.67$], the time by treatment group interaction [$F(2,41)=0.18$, $P=0.84$], nor the covariate [$F(1,41)=0.99$, $P=0.33$]. Analysis of the K10 total score revealed no significant effects for time [$F(1,43)=0.39$, $P=0.53$], treatment group [$F(2,43)=0.05$, $P=0.95$], time by treatment group interaction [$F(2,43)=2.13$, $P=0.13$], or the covariate [$F(1,43)=2.77$, $P=0.10$].

Table 3.9 Quality of Life and Psychological Distress Score by Treatment Group

	Control	Hand Held Laser	Scanning Laser
EQ-5D Utility Score	(n=12)	(n=13)	(n=15)
Time 1 (M ± SE)*	0.53 ± 0.08	0.46 ± 0.08	0.39 ± 0.07
Time 2 (M ± SE)*	0.70 ± 0.07	0.60 ± 0.07	0.57 ± 0.07
EQ-5D VAS Score	(n=13)	(n=16)	(n=16)
Time 1 (M ± SE)*	60.25 ± 6.09	56.88 ± 5.70	51.79 ± 5.90
Time 2 (M ± SE)*	66.39 ± 5.18	66.65 ± 4.85	60.79 ± 5.02
K10 score	(n=14)	(n=17)	(n=16)
Time 1 (M ± SE)*	21.92 ± 1.87	20.41 ± 1.70	19.82 ± 1.81
Time 2 (M ± SE)*	16.64 ± 2.31	18.64 ± 2.10	20.38 ± 2.24

* Means and standard errors are estimated controlling for pain duration.

4.0 Results: Feedback from Clients, Nurses, and Study Contributors

In addition to gathering data to enable the generation of effect sizes upon which future clinical trials could base their power calculations to determine their sample size targets, this proof of concept study also conducted a brief survey of study participants to ascertain their satisfaction with the nursing service, attendance at the clinics for care, and the laser therapy. Comment about LILT was obtained from the clinicians involved in delivering the LILT treatment. Finally, members of the study team involved in data analysis and reporting contributed their reflections about the research method and implementation to inform the development and implementation of future trials. These results are summarised in this chapter.

4.1 Client Satisfaction Survey Results

Satisfaction questionnaires were completed by 44 clients (77% response rate). Responses to the questions concerning nursing assessment and care are displayed in Table 4.1. Feedback was highly positive with almost all clients giving ratings of 'Very Good' or 'Excellent' on all items.

Of the 44 clients who completed the satisfaction questionnaire, 13 were in the control group, 17 were in the hand held laser group and 14 were in the scanning laser group. The Kruskal-Wallis Test was used to test for overall differences between study groups on questions relating to satisfaction with assessment and care. Significant differences were observed for 'convenience of visits' ($\chi^2(2) = 6.79, p=0.03$), 'professionalism of staff' ($\chi^2(2) = 7.63, p=0.02$), 'overall satisfaction with nursing care' ($\chi^2(2) = 11.91, p=0.00$), 'clinic waiting / reception facilities' ($\chi^2(2) = 8.46, p=0.02$) and 'privacy of the clinic' ($\chi^2(2) = 7.38, p=0.03$) (see Figures 4.1 to 4.5).

Post-hoc testing to identify specific differences between study groups was conducted using the Mann-Whitney Test. The hand held laser received a higher satisfaction rating compared to the scanning laser on 'convenience of visits' ($Z=-2.65, p=0.01$), 'professionalism of staff' ($Z=-2.65, p=0.01$), 'overall satisfaction with nursing care' ($Z=-3.10, p=0.00$), 'clinic reception / waiting facilities' ($Z=-2.48, p=0.01$) and 'privacy of clinic' ($Z=-2.11, p=0.04$). In addition, the hand held laser group reported a higher satisfaction rating than the control group on 'clinic waiting / reception facilities' ($Z=-2.01, p=0.04$). The control group reported a higher satisfaction rating than the scanning laser group on 'overall satisfaction with nursing care' ($Z=-2.28, p=0.02$) and 'privacy of clinic' ($Z=-2.10, p=0.04$).

The most common means of travelling to the clinic was taxi (56.8%) followed by driving oneself (20.5%) and being driven by another person (11.4%). Thirty-one clients (70.5%) had received care from this organisation in the past. The overwhelming majority of participants would use this organisation again (97.7%) and would recommend it to family and friends (97.7%).

Thirty-one clients who were allocated to either the hand held or scanning laser groups answered additional questions on their satisfaction with the laser treatment (Table 4.2). Almost all clients found the laser treatment comfortable and acceptable; however, five study participants (16.1%) experienced at least some discomfort immediately following the laser treatment. Analyses using the Mann-Whitney Test revealed no significant differences between the hand held or scanning laser groups on level of satisfaction with the laser treatment. Almost all clients (90.3%) reported a willingness to have the same laser treatment again in the future.

These results reveal that on a variety of dimensions, although none relating to the actual laser treatment, study participants receiving the hand held laser were more satisfied than the scanning laser group, and to some extent the control group. There was, however, no related theme that could be drawn from the items where statistically significant differences were detected. More generally, study participants rated the nursing service, the clinic, and the laser treatment highly. The vast majority were willing to use and recommend this organisation and, for those who received LILT, to use LILT again.

Table 4.1 Satisfaction with assessment and care (n=44)

Item		Poor	Fair	Good	Very Good	Excellent	Missing / NA
Ease of arranging nursing care	%	-	-	9.1	29.5	56.8	4.5
	n=	0	0	4	13	25	2
How quickly nursing care started	%	-	-	9.1	34.1	54.5	2.3
	n=	0	0	4	15	24	1
Convenience of appointments / visits	%	-	-	6.8	29.5	59.1	4.5
	n=	0	0	3	13	26	2
Frequency of appointments / visits	%	2.3	-	6.8	29.5	59.1	2.3
	n=	1	0	3	13	26	1
Professionalism of staff	%	-	-	6.8	20.5	72.7	-
	n=	0	0	3	9	32	0
Number of staff involved in care	%	4.5	9.1	6.8	29.5	43.2	6.8
	n=	2	4	3	13	19	3
Communication with other healthcare providers	%	-	-	11.4	31.8	52.3	4.5
	n=	0	0	5	14	23	2
How well care coordinated	%	-	-	4.5	31.8	59.1	4.5
	n=	0	0	2	14	26	2
Value for money	%	-	2.3	2.3	27.3	61.4	6.8
	n=	0	1	1	12	27	3
Overall satisfaction with nursing care & services	%	-	-	4.5	20.5	75.0	-
	n=	0	0	2	9	33	0
Instructions / direction for 1 st visit	%	-	-	9.1	31.8	52.3	6.8
	n=	0	0	4	14	23	3
Ease of getting to clinic	%	-	2.3	4.5	36.4	47.7	9.1
	n=	0	1	2	16	21	4
Availability of parking	%	-	4.5	6.8	25.0	34.1	29.5
	n=	0	2	3	11	15	13
Ease of locating / signage at clinic	%	2.3	6.8	9.1	38.6	36.4	6.8
	n=	1	3	4	17	16	3
Hours of opening at clinic	%	-	2.3	4.5	40.9	45.5	6.8
	n=	0	1	2	18	20	3
Frequency of clinic appointments / visits	%	-	-	11.4	27.3	54.5	6.8
	n=	0	0	5	12	24	3
Reception and waiting facilities	%	-	4.5	6.8	31.8	47.7	9.1
	n=	0	2	3	14	21	4
Facilities within clinic room	%	-	2.3	9.1	25.0	56.8	6.8
	n=	0	1	4	11	25	3
Privacy of clinic	%	-	-	9.1	20.5	61.4	9.1
	n=	0	0	4	9	27	4
Overall satisfaction with clinic	%	-	-	4.5	15.9	68.2	11.4
	n=	0	0	2	7	30	5

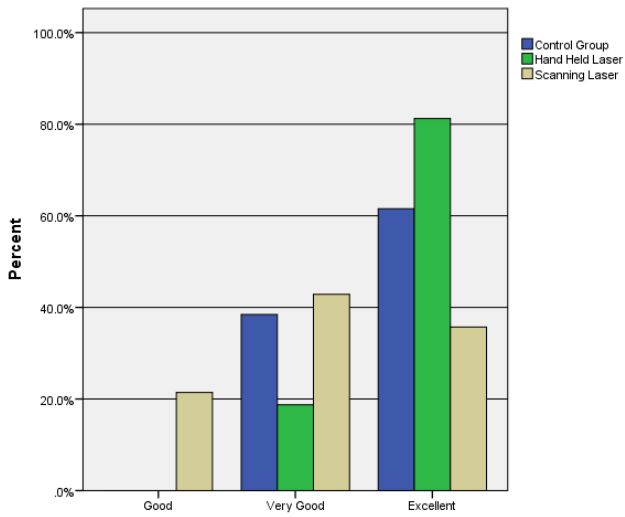


Figure 4.1 Satisfaction with convenience of visits

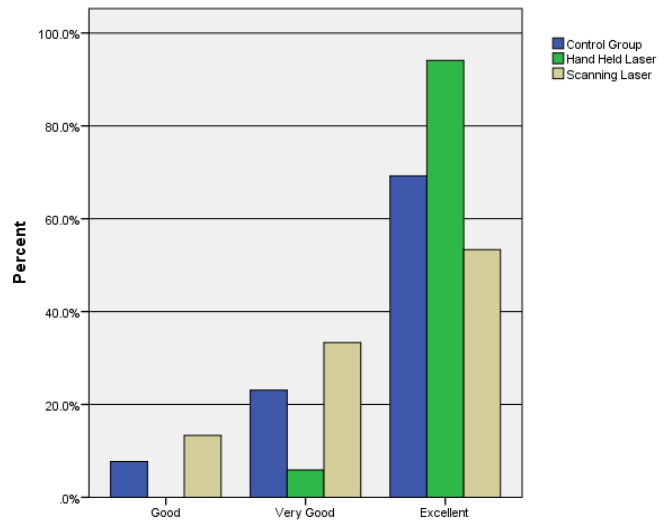


Figure 4.2 Satisfaction with professionalism of staff

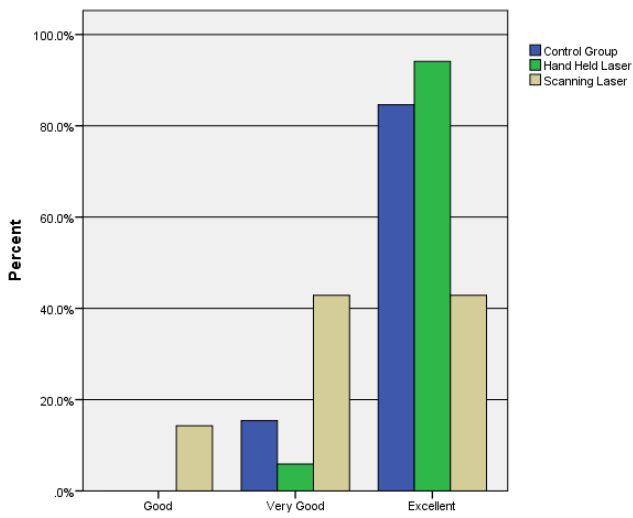


Figure 4.3 Overall satisfaction with nursing care

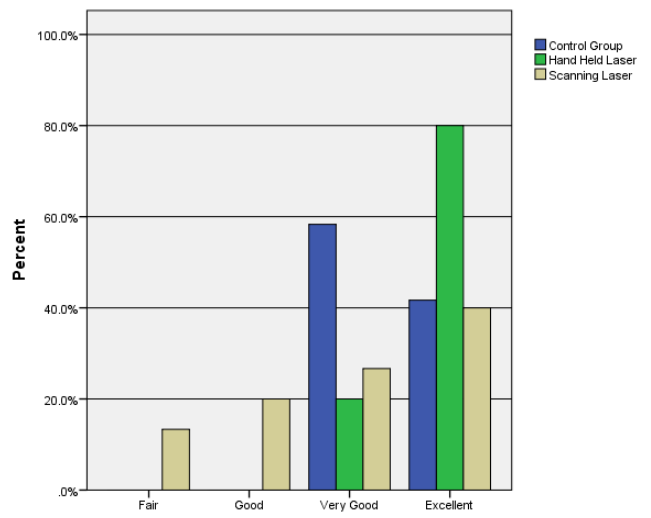


Figure 4.4 Satisfaction with clinic reception / waiting facilities

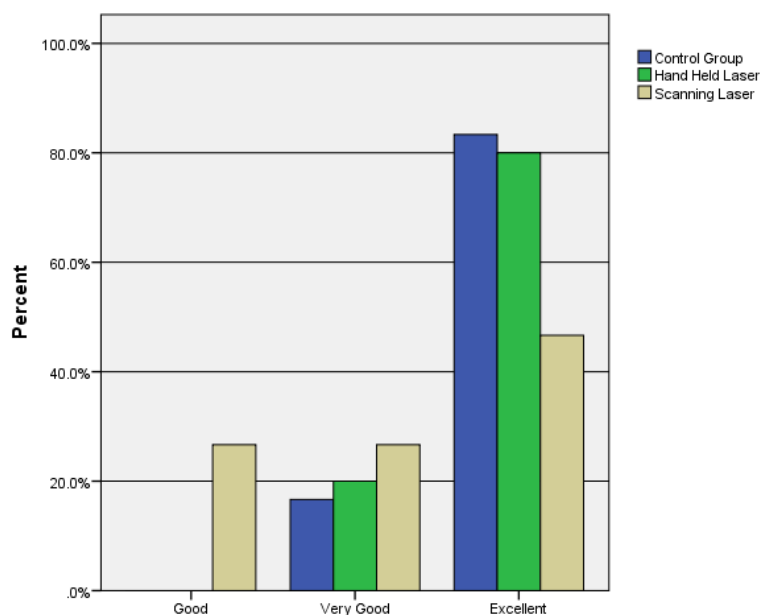


Figure 4.5 Satisfaction with privacy of clinic

Table 4.2 Satisfaction with laser treatment (n=31)

Item		Completely Disagree	Disagree	Not Sure	Agree	Completely Agree
Wound comfortable during laser application	%	-	3.2	-	48.4	48.4
	n=	0	1	0	15	15
Wound comfortable immediately after laser application	%	6.5	9.7	6.5	41.9	35.5
	n=	2	3	2	13	11
Overall, laser treatment was quite acceptable	%	-	-	9.7	32.3	58.1
	n=	0	0	3	10	18

4.2 Feedback from Wound Management Clinical Nurse Consultants

Feedback was obtained from five Wound Management Clinical Nurse Consultants (WMCNCs) who were trained to provide the LILT treatment and were responsible for recruitment, obtaining informed consent, and data collection during the proof of concept study. The feedback session was convened after data collection for all study participants was finished and was coordinated by the project manager. The discussion was conducted face-to-face, with one WMCNC tele-conferencing into the meeting. A semi-structured guide was developed to shape the discussion which was recorded and subsequently transcribed. Broad categories of feedback were determined from the transcript content and agreed upon by two project team members. These are now summarised.

4.2.1 LILT training and study education

WMCNCs identified a number of experiences associated with the training received which highlighted the importance for these clinicians of early hands-on supervision in delivering LILT.

1. Initial LILT training was well received and although mostly theoretical as was necessary for certification purposes, the practical application of LILT was reported by WMCNCs as the most useful education to ensure study readiness.
2. The practical clinic based education was indispensable. This education was required at the point of recruitment / data collection as knowledge was lost if not immediately applied.
3. The LILT trainer support transferred most information and established confidence within a few weeks. There was minimal requirement for direct face-to-face consultancy after this time.
4. Once trained, project personnel could deliver the practical training and support to other staff with greatly reduced reliance on the external LILT trainer.
5. Concurrent technology required for other data collection measures such as the wound imaging and measurement equipment was required and it would have assisted WMCNCs if more education regarding these technologies had been provided.

WMCNCs received three days of intensive LILT training to achieve certification, and were additionally supported by the presence in one of the study clinics by a LILT therapist. In the second clinic, the WMCNC who coordinated the study in Clinic 1 provided the in-person support while the LILT clinical consultant remained available for telephone consultation. Clinicians felt in-person support during the practical application of LILT was the most effective approach to build skills and confidence with respect to LILT. Using this approach LILT could be learnt quite swiftly and study trained personnel could then support other staff members using LILT during the study period.

4.2.2 Using LILT

WMCNCs generally felt confident using LILT given the availability of treatment guidelines to standardised practice. Differences between the two lasers were noted.

1. Treatment guidelines were essential for consistency and confidence in practice.
2. Learning how to operate the scanning laser took more time than the hand held laser.
3. The scanning laser technology didn't follow a logical sequence (deemed by clinicians to be a problem inherent in the manufacturing of the device). Clinicians adapted to this by translating the sequence into a step-by-step guide which made it easier for them to follow the protocol.
4. The scanning laser was more difficult to implement depending on the angle of the equipment to the wound, the wound location, or when there was no clear wound border. The hand held device offered greater capacity to reposition the laser which reduced these limitations for this device.
5. The scanning laser enabled better circulation of the leg (scanning up and down the leg) via its automated settings.
6. Once mastered, the free standing scanning laser permitted clinicians to multi-task during the treatment session (attending to preparation of the dressings, documentation) resulting in time efficiencies. Clinicians were required to hold the hand held laser throughout the treatment.

7. It was felt that the hand held laser could be used in a home environment if the home was clean and uncluttered.

The development and training according to treatment guidelines was not only essential from an empirical perspective, but these guidelines facilitated the learning, delivery and confidence in the LILT treatment. While there were some drawbacks to the free standing scanning laser with respect to positioning of the laser as well as learning its use, once mastered it freed the clinicians to attend to other aspects of the wound care session. These clinicians felt that the hand held laser could be feasibly used in the home environment.

4.2.3 Wounds improved and pain reduced but was it LILT?

WMCNCs observed improvement in wound pain levels and wound healing although they suggested a number of reasons for this change that were unrelated to the LILT treatment. Only a few study participants were thought to benefit from LILT although WMCNCs were awaiting the outcomes from the data analysis to base their final determination of LILT's efficacy. The specific areas of feedback were as follows:

1. WMCNCs who applied LILT to study participants deferred final comment on LILT's efficacy pending the study results as would be expected.
2. WMCNCs mentioned only a few participants that they perceived had directly benefited from LILT.
3. Improved clinical outcomes for most study participants were thought to result from other factors that included consistency in care, consistency in staffing, access to best practice treatments due to staffing expertise and wound product funding, and improved communication from staff with GPs regarding pain management medication.
4. The LILT treatment required the wound to be exposed for longer durations than usual for dressing changes/wound care. This feature of the treatment resulted in:
 - a. Concerns expressed by WMCNCs about the wound drying out, increased wound pain, and contamination.
 - b. Anxiety for WMCNCs who worried about the effects of exposure given this was incongruent with usual wound management practice.
 - c. Advice to cover the wound with glad wrap to stop it from drying was not successful as the glad wrap adhered to the wound. Damp gauze was subsequently used with more success.
5. There was difficulty discerning whether pain after the treatment was related to LILT, dressing change, or debridement, or a combination of these factors.
6. If LILT was shown to reduce pain, WMCNCs would accept its use despite the detractors of wound bed exposure or the time required to provide treatment.

4.2.4 Study participant reactions

WMCNCs provided comment as to what they heard or perceived the reactions were from study participants with respect to LILT, the clinic visits, and study participation.

1. LILT gives an impression of being a sophisticated treatment leading participants to expect it to be effective.
2. Comments from clients to WMCNCs as to the perceived efficacy of LILT varied; one wanted LILT for the non-study leg, others were sceptical of its efficacy, another experienced pain and withdrew from the trial.
3. Treatment was described as relaxing (some participants slept), provided an opportunity for conversation, although the LILT and the data collection could be repetitive, time-consuming and laborious.
4. Attending the clinic encouraged client mobility that provided health benefits.
5. Regular visits with the same clinicians produced social engagement and attention that contributed to client wellbeing.

6. Free transportation, free dressings, and willingness to trial anything to reduce the pain were incentives to participate in the study.
7. Completion of the trial was sad for some who wish to continue attending the clinic but could not fund the visits, and unexpected for others who thought the same nurse would continue to provide care after the study.

It would appear most (but not all) study participants had few problems with LILT even if the actual treatment (and data collection) might have been a bit tedious for some or they were sceptical regarding LILT's efficacy. There were a number of other benefits from their study participation. These included increased mobility to attend the clinic as well as the benefits of continuity of care. There were a number of incentives to participate in the study, not the least of which was a willingness to try anything to reduce the pain. For this reason as well as the socio-demographic circumstance of these participants, this population should be considered highly vulnerable and the commitment to safeguard the wellbeing of potential participants maintained when designing future trial protocols. Expectations regarding care following the trial would benefit from more and continuous management.

4.2.5 Research Protocols

A number of comments were made which have significance for the study's research and treatment protocols.

1. LILT was thought unable to generate improvements for people with arterial disease and this group should have been excluded from the study.
2. The two weeks of standard best practice prior to study recruitment should have been delivered by WMCNCs. Clinicians felt their expertise was able to achieve improvements in client wound pain and healing beyond that possible by generalist nurses despite the training these nurses received prior to the commencement of the study.
3. Some clients were described as poor historians and struggled with data collection. Some needed to be led through the questions each time, asked the same questions, and some did not change their pain score, making the WMCNCs question the accuracy of these data.
4. Protocol changes outside of the guidelines established for the study were recommended to clinicians during treatment by external consultants. Though perhaps consistent with practice, these changes could not and were not pursued in the study.

Some important considerations when developing future trials were raised by WMCNCs including refinements to the exclusion criteria, the value of WMCNCs coordinating best practice care prior to commencing the study, as well as establishing a shared understanding by all project contributors that treatment guidelines in a research project should not be adapted unless shown to be detrimental. Comments pertaining to data collection reaffirm the importance of utilising appropriate and validated data collection instruments and ensuring data collection is as brief as possible to avoid excessive burden for participants and data collectors alike.

4.3 Research method review

A review of the research method was conducted by three project contributors (CM, RN, SK) with comments circulated for subsequent critique by remaining project collaborators. The comments identified areas for further refinement or consideration when planning future clinical trials examining the effectiveness of LILT in the community as well as clinical trials in general. A number of the issues pertaining to structure and processes by the lead organisation were in the process of being addressed concurrently with the implementation of the LILT proof of concept study and have resulted in the development of comprehensive research governance and policy and procedures.

4.3.1 Design

The trial was conducted in a clinic setting for safety reasons. This approach, however, limited capacity to test the feasibility and efficacy of the hand held laser in the home and constrained the control group to clinic care which differed to the normal care setting. A three-phase study could have addressed the study aims more effectively. Phase one would have involved clinic based use of LILT for a few clients to establish safe use of LILT by nurses for whom this was a novel technology. Phase two would have further assessed the safe use of the hand-held laser in the home environment with another small group of clients. In phase three, the proof of concept study could have been conducted, obtaining effect sizes from the desired treatment settings which could then have informed the development of future trials. Understandably, this approach would have had considerable cost and timeline ramifications.

The trial could have been simplified by including only the hand held laser which aligned best with the in-home service delivery model of the lead organisation. The inclusion of the scanning laser for its additional functionality was undermined as this functionality was not incorporated extensively in the trial treatment protocols.

Given the impact of LILT on the frequency of dressing changes, wound products were provided for free during the study. However, in the present funding environment in Victoria, Australia, most clients are required to purchase their own wound dressings with the cost of products sometimes acting as a constraint to best choice of wound dressing. The funding of wound care products in the trial impacts on the generalisation of results, and future trials might consider only reimbursing clients for the additional dressing changes resulting from their trial participation. This, although still different to the usual practice setting, balances the cost ramifications and potential disadvantage of participating in the trial with the need to extrapolate the results beyond the clinical trial setting.

4.3.2 Eligibility

A heterogenous small sample prohibited examination of the effectiveness of LILT across sub-groups such as wound types and potentially masked the benefits of LILT for some sub-groups. Increasing the sample homogeneity by targeting groups either identified by the literature or perhaps by clinical need—focusing upon those wounds with greater pain or that are the most resistant to pain management strategies—could have enabled more confident conclusions regarding the efficacy of LILT for certain groups.

The inclusion of people with ≥ 1 on an 11 point scale, though acknowledging that any pain should be the subject of clinical attention to alleviate its presence, does create a statistical 'floor effect'. As such, inclusion of clients with a higher pain rating is recommended.

4.3.3 Data collection

The collection of cost data, most specifically relating to product costs, and records of treatment such as types of dressings used or whether sharp debridement was attended, were not gathered in a readily accessible manner for data analysis. A vision to garner product costs from invoice statements in an attempt to minimise the demand on data collectors, was unwieldy during analysis and prohibited reporting. Treatment information (other than LILT) was not specified in the data collection forms and this prohibited a comparison of the study groups to ensure the care they received more generally for their wound was comparable.

Data collection was extensive, gathered to provide both primary and secondary outcome measures as well as to ensure client safety. Some increases in pain, however, were possible following LILT, dressing changes, and debridement, and thus these data could not effectively distinguish adverse events resulting from LILT. The value of these data, and thus the efforts of data collectors and study participants, was undermined. Safety could have been established in an early phase of the initiative with follow-up of a small group of participants at several intervals post treatment. This would have reduced the data collection burden in the proof of concept study proper.

Variation in how questions were interpreted suggests the initial training and supervision of data collectors was inadequate.

Given the difficulty research studies experience recruiting participants, it was commendable that this study achieved 57 recruits of the original 60 targets. With two clients lost to follow-up due to hospitalisation and one client withdrawing from the study, data from 54 participants were included in the primary analysis representing a high follow-up of participants (95%). More information about the population from which these participants were recruited would have been highly valuable for planning future studies as well as providing an indication of the representativeness of these findings.

4.3.4 Data entry & analysis

Data entry was undertaken by a number of people with varying understandings of either data entry or the proof of concept study. As a consequence, despite the database being established by the project manager, differences in how data were coded and entered resulted and were not identified until checks occurred during analysis. Considerable resource was subsequently wasted in progressing analysis on an incorrect database and all data were subsequently double checked, creating substantial delays for the study timeline. The process of data entry would have been more rigorous if undertaken by a single person skilled in data entry and with knowledge of the project.

Delays in attending to data entry meant that variations in how questions were being interpreted by data collectors and errors in question format of standardised instruments were identified too late to rectify. This resulted in some data that could not be used.

A strength of the project was its approach to data analysis. Data analysis was conducted by a team but with central coordination, with the results subsequently confirmed through consultancy with the Melbourne University Statistical Consulting Centre. This enabled vigorous discussion of data cleaning and recoding and internal and external checks.

4.3.5 Management

Feedback was obtained from clinicians and clients involved in this project. Positive elements of project implementation as well as recognition of any burden incurred needs to be considered at length as their participation and interest in research is essential to maintain goodwill towards future research endeavours.

The process of identifying and recording adverse events as established by the project team during its implementation, as well as what 'events' are recorded and investigated, would benefit from review and extended focus during training. One adverse event, identified from clinician feedback after the trial, was subsequently linked to client withdrawal. While the client's withdrawal was noted in Data and Safety Monitoring Board reviews, it was noted as being unrelated to the trial intervention. There were no instances of adverse events noted at any of the scheduled Data and Safety Monitoring Board's reviews of trial safety.

The project infrastructure was a strength of the study, drawing upon expertise in pain management, wound management, LILT, and community nursing clinical and research skills. The project received approval from a Human Research Ethics Committee, received direction from a Research Study Steering Group, support from a Data and Safety Monitoring Group, was registered on the Australian and New Zealand Clinical Trial Registry, and the approach to statistical analysis was endorsed in consultation with the Melbourne University Statistical Consulting Centre. However, staff turnover and a lack of supervision by line management with specific academic experience in the conduct of clinical trials involving wound pain compromised the project outcomes and timelines. Errors could have been avoided by more timely review of project milestones such as data entry. Clarity around validated measures and their translation to the data collection instruments in the project required inspection as mistakes were made which rendered some data unfit for analysis.

5.0 Discussion

5.1 Efficacy of LILT

This study sought to appraise the feasibility of conducting a RCT examining the effects of LILT on unresolved chronic wound pain. The generation of more accurate effect sizes upon which power analyses could be based would indicate first, the clinical significance of the effect of LILT, and second, the viability of conducting clinical trials given the sample size required. The fact that none of the analyses—pain, wound healing, psychological distress or quality of life—generated meaningful significant differences between the treatment groups was not unexpected given the intent was to conduct a proof of concept study which involved a small sample.

The sample was comparable at baseline with the exception of pain duration which was statistically controlled for during analysis. More than a third of wounds in this study progressed to healing within the 12 weeks of monitoring, and pain interference and severity declined in all groups. Thus, although eligibility to participate in the trial was unresolved pain and that pain duration prior to the study was in excess of seven months on average, pain appeared to resolve during the study regardless of the randomised treatment.

Quite possibly, this finding could be explained by a Hawthorne Effect; an effect on the dependent variable resulting from subject's awareness that they are participants under study, a concept which can be extended to a double Hawthorne Effect if the clinicians in a study also adjust their clinical practice given their involvement with participants in a clinical trial (Polit, Beck, & Hungler, 2001; Polit & Tatano Beck, 2012).

Another plausible explanation for a reduction in wound pain is that greater access and regular treatment by a WMCNC during the study resulted in enhanced care and client outcomes. This perspective is consistent with feedback received from WMCNCs who assigned the improvements they saw in wounds to consistency in care, improved access to best practice care through staffing expertise and product funding, improved communication with the healthcare team and specifically the client's general practitioner regarding pain management medication.

While there might also have been an ongoing effect from the Best Practice Wound Pain Education improving the practice of generalist nurses, WMCNCs suggested that a longer lead in following this education and increased involvement of senior clinicians would facilitate the inclusion of participants in future trials with genuine unremitting, unresolved wound pain. If the clinical changes observed in this study were sufficient to generate these improvements in client's wound pain, there would also appear to be scope to monitor and enhance wound pain management in clinical practice more generally to minimise client experiences of pain.

The provision of wound dressings at no cost might be another reason that pain reduced during the study if cost had been a barrier to the use of best practice wound treatments.

This study examined the effect sizes across the trial groups during the LILT Treatment Phase (0-6 weeks) and the combined Treatment / Monitoring Phases (0-12 weeks). Given a notable difference in the first fortnight of treatment, an effect size was calculated at this point also. A medium effect in the initial fortnight was observed favouring a pain reduction for the hand held laser group. The effect is sufficiently large to suggest some clinical significance for this treatment compared to the control or scanning laser group, and a small sample per group ($n < 30$) would be required to find a significant difference based on this effect size.

A smaller effect was observed during the LILT Treatment Phase (0-6 weeks). Pursuing a clinical trial comparing a control group with the hand held laser would require a sample of 48 or 93 per group for the pain severity and interference measures respectively. These represent larger but not excessive sample sizes in contrast to that required for the first fortnight.

The only pain measure for which there was a 12 week follow-up was the pain interference score for which a small effect was observed and an impractical sample size requirement of 484 per group estimated.

5.2 Trial feasibility & methodological considerations

The threshold for pain for the trial was ≥ 1 on an 11 point scale. This level recognises the clinical imperative of alleviating all pain, that older age is associated with greater acceptance of pain (Arnold, Roberts, & Gibson, 2010), and age-related changes in the nervous system which alters the experience of pain. The average level of pain experienced in this study was low, possibly reflecting these age-related factors, and increased the risk of a statistical 'floor effect'. The inclusion of clients with a higher level of unresolved pain for future trials is recommended.

Feedback from clients indicated high satisfaction with nursing care, clinic attendance, and for those receiving LILT, with this treatment also as the vast majority of participants were willing to receive LILT again. Although some differences between the groups emerged, there was no related theme linking these dimensions to a particular aspect of care. These findings broadly suggest that the experience of receiving the LILT treatment was acceptable to clients.

Pain resolution and healing was observed in all groups and there were no meaningful significant differences detected between groups. Nonetheless, participants randomised to the scanning laser had the least impressive results in this trial compared to the control and hand held laser groups. The treatment protocol was standardised in this study for transparency regarding the treatment intervention. This approach, however, limited the extent to which the full functionality of the scanning laser could be employed. The scanning laser also presents perhaps the lowest applicability to a mobile community healthcare workforce because it is clinic bound. While it would be possible, in the event of a clear demonstrated benefit of the scanning laser to reduce wound pain, to transfer clients to a clinic setting for treatment, the provision of in-home care more closely aligns with the client's demonstrated need for home care.

In contrast, the hand held laser is a portable device that could be taken into a client's home. The results of this study provide some provisional support for the short term effectiveness (up to 6 weeks) of the hand held laser in providing pain relief compared to the control and scanning laser groups. Set-up and operating procedures of the hand held laser in the home require development.

This study was conducted in a clinic setting for the safety of clients and clinicians because LILT was a novel technology for use by nurses in the community and for the organisation in which the study was conducted. As such, the effect sizes generated may differ to those that would have been found if the participants had been treated at home. It is recommended that the effect sizes determined in this study are confirmed comparing a hand held laser to control in the home setting to further refine the safety, feasibility, merit and sample size targets as a preamble to a large randomised controlled trial.

With one exception, LILT was used without adverse incident. For one participant the length of time the wound was exposed to the air while the LILT was being administered resulted in increased pain. While clinicians deferred to the study findings to ultimately indicate whether LILT was clinically effective, they did share some consternation regarding the length of time the wound was exposed during the LILT treatment and the potential the wound bed would dry out and could cause pain. Irrigation of the wound with saline was specified in the pre-treatment protocol and facilitated the maintenance of a moist wound bed as well as aiding energy conduction. In addition to re-iterating in the treatment protocol and clinician training the need for continual assessment and application of room temperature saline to stop the wound bed from drying out, the development and evaluation of other strategies and techniques that would promote a moist wound bed environment is encouraged. More generally, however, this study would suggest that LILT can be used safely by nurses in a clinic to treat chronic wounds.

A number of considerations for future trials regarding training in LILT, other trial education, the useability of the two lasers, and the research protocol were identified. These comments are specific and can be readily incorporated into protocol refinements and planning for trial implementation (see Chapter 2).

5.3 Study Limitations

Several limitations apply to this study. As participants were recruited from one Australian community nursing service, the generalisability of the results to people with chronic wound pain more broadly is limited. As discussed, the conduct of the study in a clinic environment may have influenced the treatment effect compared to what might have been found if participants had received their care in-home. A small, heterogeneous sample was included in this proof of concept study, limiting the potential to examine the effectiveness of LILT for subgroups, for instance by wound aetiology. This also limited the capacity to run statistical tests that would detect significant differences in wound aetiology between the study groups and identify a potentially confounding variable. The exclusion of participants with arterial disease or ensuring sufficient and equivalent presence of individuals with Diabetes Mellitus in the study groups given the effect of Diabetes Mellitus on the effectiveness of LILT (Brown, 1992; Hartmann, 1983) is recommended for future studies.

Details regarding the size of the population, eligibility of participants, and willingness to participate in the study were not gathered and would have been helpful information for researchers planning subsequent LILT trials. Further streamlined measures monitoring the care provided to the groups would have enabled greater comparison of the groups to eliminate differences in wound management as a potential confounding variable. Finally, this study was conducted as an open label trial. Future studies might explore the viability of utilising a placebo 'laser' treatment to enhance the design rigour and mitigate potential placebo effects.

LILT has been effective in the treatment of nerve pain (Conti, 1997), pain associated with arteriosclerosis (El-Kasef & Attia, 1999), rheumatoid arthritis (Palmgren et al., 1989), neck pain (Chow et al., 2004), and pain associated with acute injuries or surgical wounds. (Bjordal et al., 2006) This study provides initial evidence using a RCT design considering the effect of LILT on chronic wound pain. A specific protocol for the use of LILT was developed and reported as a key strategy to improve the transparency of research findings regarding LILT and to facilitate the planning of future clinical trials.

5.4 Conclusion

This study sought to appraise the clinical significance and viability of future clinical trials examining the use of LILT to resolve chronic wound pain in the community. A small short-term benefit of the hand held laser treatment to resolve wound pain was found. In preparation for a large randomised controlled trial, it is suggested that the safe use of the hand held laser in-home is assessed whilst simultaneously confirming the effect size resulting from when the hand held laser is compared to a blinded control group. The prospect that LILT can offer older people a non-pharmacological means of reducing wound pain requires further large clinical trials to substantiate.

6.0 Recommendations for research & practice

Small to moderate effect sizes provide provisional support of a short term clinical benefit from the use of the hand held laser compared to the scanning laser and control groups. This finding requires substantiation. The following steps are recommended:

1. As a precursor to a large clinical trial, an in-home evaluation of the hand held laser is conducted to:
 - a. Establish the safe use of the hand held laser in the home setting and to develop guidelines supporting this implementation
 - b. Confirm/refine effect sizes based on information arising from the in-home application of the hand held laser with comparison to a home-based care control group.
2. The study protocol is revised for future clinical trials in light of the specific comments outlined throughout the report and specifically noted in Chapter Two, with respect to participant eligibility, data collection, and project management.
3. Methods of managing prolonged wound bed exposure are established to promote the best environment for wound healing.
4. A homogenous sample with respect to wound aetiology is sought by:
 - a. Excluding clients with arterial disease
 - b. Either adopting a focus on participants with Diabetes Mellitus or excluding this group
 - c. Targeting wound aetiologies that are associated with the most chronic and unresolved pain and/or highly prevalent wound types that are also painful.
5. Large clinical trials are conducted comparing pain reduction associated with the hand held laser and a control group for home based nursing clients. Given less evidence of efficacy associated with the scanning laser and the obvious logistic difficulty using this laser in a homecare setting, further testing of the scanning laser is optional for this population.

In light of the improvements observed in enduring chronic wound pain as a result of study participation that are not necessarily attributable to the intervention, it is recommended that:

6. Pain management is reviewed within the lead organisation commencing with an audit of pain assessment and management to inform future approaches to pain management including staff education; staffing skill mix and utilisation; systems and procedures; and new pain management initiatives (e.g. models of inter-disciplinary pain management, psychosocial education with clients).

Appendices

Appendix 1: Plain Language Statement



PLAIN LANGUAGE STATEMENT

A New Light on Wound Pain: A Proof of Concept Study of the Effect of Low Intensity Laser Therapy (LILT) in the Management of Wound Pain

Royal District Nursing Service is seeking people to participate in a research project that will evaluate the effect of using Low Intensity Laser Therapy (LILT) to manage chronic wound pain. This project will investigate the viability and effectiveness of LILT to reduce wound pain.

RDNS clients who participate in the study will be randomly placed into two groups: one group will receive best practice wound management from RDNS and LILT treatment, and the second group will receive best practice wound management from RDNS and no LILT. People in both groups will receive free wound dressings for the study wound for up to 12 weeks, or less if their wound heals earlier. If dressings are required after 12 weeks (when the study time is completed), the usual process for obtaining them will apply.

What is LILT?

- LILT is compressed laser light that is beamed over a specific area of the body, in this case over a wound and the full leg
- The laser light makes its way through the surface of the skin with no heating effect or damage to the skin
- Laser light directs the light energy to help promote natural healing and pain relief.

It is important to note that some studies have shown LILT to cause some inflammation immediately after treatment, however, this has been shown to be part of the 'normal healing process' and usually disappears quite quickly.

If you are to receive LILT:

- You will receive up to six weeks of LILT therapy three times per week. The treatment will last for approximately 10-30 minutes over the full leg and wound. The attending nurse who is a Wound Care Specialist will also do your dressing at that time
- After the first six weeks of clinic visits you will receive your care at home as usual, but we will want to obtain extra information about you at 8, 10 and 12 weeks so this may mean again attending the RDNS Box Hill or Rosebud Care and Assessment Centres at those times
- The days that you will receive LILT are Monday, Wednesday and Friday by appointment
- All treatments will be done at the RDNS Care and Assessment Centres, and your transport options to and from there will be negotiated if this is needed.

If you are to receive best practice wound management:

- You will receive up to 12 weeks of care to your study wound plus dressing and bandages at no cost for up to 12 weeks or less if wound heals earlier
- The nurse will assess your wound and determine how often wound dressings will be changed
- Some treatments will be done at the RDNS Care and Assessment Centre (twice a week), and your transport options to and from there will be negotiated if this is needed.

Some additional information about you and any wound pain will be collected when you start the project and at various times during or at the end of the project. Information about your wound progress will be recorded at the scheduled dressing change. The nurse will also take a digital picture of your wound so that we can measure its healing rate and keep a record of the wound appearance. This information may help us to understand the wound pain you are experiencing and also how this affects your ability to undertake your daily activities. These questions will not take any more than 10-15 minutes of your time.

All information you provide during the study will remain strictly confidential. Your name and any other identifying details will not be disclosed in any report of this research. Also, your participation in the study is completely voluntary, and you are free to withdraw at any time.

The Team undertaking this research includes experts in this field of LILT and in wound and pain management, plus experienced researchers based at the RDNS Helen Macpherson Smith Institute of Community Health. The team includes:

RDNS Staff:

- Ms Terry Gliddon, Manager, Research and Development, Helen Macpherson Smith Institute of Community Health
- Dr Leila Karimi and Ms Charne Miller , Researchers, Research and Development Department, Helen Macpherson Smith Institute of Community Health
- Ms Suzanne Kapp, Clinical Nurse Consultant Wound Management, Clinical Research Coordinator, Helen Macpherson Smith Institute of Community Health
- Ms Janine Sunderland, Clinical Nurse Consultant Wound Management, Clinical Research Officer Helen Macpherson Smith Institute of Community Health

External Experts:

- Ms Tina H. E. Czech, Director of the Australian Institute of Laser Therapy
- Mr Bill McGuiness, Deputy Head, Division of Nursing & Midwifery, La Trobe University

Pain Consultant:

- Dr Carolyn Arnold, Clinical Director, Caulfield Pain Management and Research Centre

If you have, any questions about this project or would like to participate please contact:

Ms Terry Gliddon

Manager, Research & Development

RDNS Helen Macpherson Smith Institute of Community Health,

31 Alma Road, St. Kilda, VIC, 3182

Phone (03) 9536 5360, Fax (03) 9536 5300

Email: tgliddon@rdns.com.au

If you have any concerns or complaints about the conduct of this research project please contact:

Dr Lisa Donohue

Chair, RDNS Research Ethics Committee

RDNS Helen Macpherson Smith Institute of Community Health,
31 Alma Road, St. Kilda, VIC, 3182
Phone (03) 9536 5382, Fax (03) 9536 5300
Email: ldonohue@rdns.com.au

Appendix 2: Consent Form



INFORMED CONSENT FORM

Name of research project: A New Light on Wound Pain: A Proof of Concept Study of the Effect of Low Intensity Laser Therapy (LILT) in the Management of Wound Pain

Participant’s details:

Name:
(in block letters)

Address:

I hereby consent to participate in the above research project.

- The details of this research project have been explained to me verbally, and
- I have received a copy of the Plain Language Statement, and
- Any questions I have asked in regard to this project have been answered to my satisfaction.

I agree to participate in this research project and understand that I may withdraw at any time without my care being affected in any way. If I withdraw from the project I know that any information previously collected about me will be destroyed if I request this. I consent to the nurse taking a digital picture of my wound and give permission for these images to be used for research purposes. The images would not have any information on them which would enable me to be identified in any way. I agree that research data provided by me will be analysed and reported in aggregate and presented at conferences or published in journals on the condition that neither my name nor any other identifying information is used. I understand that any information I provide will be treated with the strictest confidence.

Signature of participant
(Print name) (Signature) (Date)

OR

On Participant’s behalf
(Print name) (Signature) (Date)

Relationship to participant

Witnessed by
(Print name) (Signature) (Date))

Appendix 3: LILT Protocols

HAND HELD LASER (Polylaser)			
Pre treatment protocol	APPLICATION 1 &	APPLICATION 2	Post treatment Protocol
	Laser treatment for lymph drainage and circulation Approx. time 10-13min	Laser treatment for wound surface and minimum of 3cm beyond wound edge	
<ul style="list-style-type: none"> Review Study Care Guide Measure thinnest ankle and widest calf Complete pre treatment pain assessment tool Irrigate wound with saline 	<p>CONTINUOUS (no pulse) Part (a) : Contact Treat sole of foot, and continue up posterior calf including popliteal fossa and wound surface 1min = 1.2Jcm²</p> <p>Part (b): Treat anterior foot then anterior thigh including gluteal fold and wound surface (if applicable). 1min +1.2Jcm²</p>	<p>PULSED MODE (10hz) Non-contact: laser to be positioned 2cm above wound. Treatment time= 4 min. per area = 2.4Jcm²</p> <p>Necrotic 6 min. =3.6Jcm² Infected 2min. = 1.2Jcm²</p> <p>Fixed spot size 20cm</p>	<ul style="list-style-type: none"> Complete post treatment pain assessment tool Measure thinnest ankle and widest calf Complete study care guide and wound progress record Assess wound appearance and note on progress record

SCANNING LASER (Photonic 500)						
Application 1: Universal Program						
Select: SKIN Indication: Circulation						
Pre treatment protocol	Treatment Protocol	Beam length per area	Treatment energy dose per beam area	Energy density per cm ²	Treatment Time per beam area	Total time per lower leg
<ul style="list-style-type: none"> Review Study Care Guide Measure thinnest ankle and widest calf Complete pre treatment pain assessment tool Irrigate wound with saline 	<p>Part 1: lower leg Treat sole of foot and continue up posterior calf, including popliteal fossa and wound surface</p>	10 X 20cm	30J	0.15Jcm ²	1 min. 49sec. per application area	<p>5-8min</p> <p>Total time per upper leg 5 –8 min</p>
	<p>Part 2: upper leg Then treat anterior thigh including groin,commencing just below knee including wound surface if applicable</p>	15 X 20cm	45J	0.15Jcm ²	2min. 44 sec. per application area	

SCANNING LASER (Photonic 500) Application 2: Universal Program Select: Nerve Indication: Pain							
Treatment protocol	Beam length per area	Wound size	Treatment dose per beam area	Wound depth	Energy density per cm ²	Treatment time per beam area	Post Treatment Protocol
Treat entire wound surface and minimum of 3cm beyond wound edge	11 X 11cm	5cm or less	73J	2cm or less	0.6Jcm ²	4min. 25sec.	- Measure pain and note the score on care guide.
	16 X 16cm	6 - 10cm	154J	2cm or less	0.6Jcm ²	9min. 0sec.	
SCANNING LASER (Photonic 500) Application 3: Derma Program Select: Wound Chronic							
Treatment protocol	Beam length per area	Wound size	Treatment dose per beam area	Wound depth	Energy density per cm ²	Treatment time per beam area	Post treatment
• Treat entire wound surface and minimum of 3cm beyond wound edge	11 X 11cm	5cm or less	73J	2cm or less	0.6Jcm ²	4min. 25sec	- Complete post treatment pain assessment tool - Assess wound appearance and note of progress record - Complete study care guide and wound progress record
	16 X 16cm	6 - 10cm	154J	2cm or less	0.6Jcm ²	9min. 20sec	
Necrotic OR no response after 2 sessions	11 X 11cm	5 cm or less	85J	2cm or less	0.7Jcm ²	5min.9sec	
	16 X 16cm	6 – 10cm	179J		0.7Jcm ²	10min.51 sec	
Infected OR increased pain	11 X 11 cm	5 cm or less	24J	2cm or less	0.2Jcm ²	1min. 27sec	
	16 X 16cm	6 – 10cm	51J		0.2Jcm ²	3min. 5 sec	

References

- Andrew, G., & Slade, T. (2001). Interpreting scores on the Kessler Psychological Distress Scale. *Australian and New Zealand Journal of Public Health*, 25(6), 494-497.
- Arnold, C., Roberts, B., & Gibson, S. J. (2010). *Age Differences in Pain Attitudes and Psychosocial Adjustment in Patients with Chronic Pain*. Paper presented at the 13th World Congress on Pain.
- Baker, S. R., & Stacey, M. C. (1994). Epidemiology of Chronic Leg Ulcers in Australia. *ANZ Journal of Surgery*, 64(4), 258-261.
- Basford, J. R. (1989). Low-energy laser therapy: controversies and new research findings. *Lasers in Surgery and Medicine*, 9, 1-5.
- Basford, J. R. (1993). Laser Therapy: Scientific Basis and Clinical Role. *Orthopedics*, 16(5), 541-547.
- Bashford, J. R. (1995). Low-intensity laser therapy: still not an established clinical tool. *Lasers Surg. Med.*, 16, 331-342.
- Bihari, I., & Mester, A. R. (1989). The biostimulative effect of low level laser therapy of long-standing crural ulcers using helium neon laser, helium neon plus infrared lasers, and noncoherent light: preliminary report of a randomized double-blind comparative study. *Laser Therapy*, 1(2), 97-98.
- Bjordal, J. M., Johnson, M. I., Iversen, V., Aimbire, F., & Lopes-Martins, R. A. B. (2006). Low-Level Laser Therapy in Acute Pain: A Systematic Review of Possible Mechanisms of Action and Clinical Effects in Randomized Placebo-Controlled Trials. *Photomedicine and Laser Surgery*, 24(2), 158-168.
- Brown, G. C. (1992). Control of respiration and ATP synthesis in mammalian mitochondria and cells. *Biochemical Journal*, 284, 1-13.
- Campara, V. R., Moya, M., Gavotto, A., Soriano, F., Juri, H., Spitale, L., et al. (1999). The relative effects of He Ne laser and Meloxicam on experimentally induced inflammation. *Laser therapy* 11(1), 36-41.
- Carville, K. (2005). *Wound care manual*. Osborne Park, WA: Silver Chain Foundation
- Carville, K., & Lewin, G. (1998). Caring in the community: a wound prevalence survey. *Primary Intention*, 6(2), 54-62.
- Chow, R. T., Barnsley, L., Heller, G. Z., & Siddall, P. J. (2004). A pilot study of low-power laser therapy in the management of chronic neck pain. *Journal of Musculoskeletal Pain*, 12(2), 71-81.
- Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences* (Vol. 2nd edition): Lawrence Erlbaum Associates.
- Conti, P. C. (1997). Low level laser therapy in the treatment of temporomandibular disorders (TMD): a double-blind pilot study. *Cranio*, 15(2), 144-149.
- Cutting, K., & Harding, K. (1994). Criteria for identifying wound infection. *Journal of Wound Care*, 3, 198-201.
- Department of Human Services. (2001). *Identifying and planning assistance for home-based adults who are nutritionally at risk: A resource manual*. Melbourne: Aged, Community and Mental Health Divisiono. Document Number)
- Dereure, O., Vin, F., Lazareth, I., & Bohbot, S. (2005). Compression and peri-ulcer skin in outpatients venous leg ulcers: results of a French survey. *Journal of Wound Care*, 14(6), 265-271.
- Dumville, J. C., Torgerson, D. J., & Hewitt, C. E. (2006). Reporting attrition in randomised controlled trials. *British Medical Journal*, 332(22), 969-971.
- Edwards, L. M. (2003). Why patients do not comply with compression bandaging. *British Journal of Nursing*, 12(11), S5-S16.
- El-Kasef, H., & Attia, M. A. (1999). Low level laser therapy in the treatment of arteriosclerosis for the lower limbs. *Laser Therapy*, 11(1), 26-29.
- Flemming, K., & Cullum, N. A. (2008). *Laser therapy for venous leg ulcers*: Cochrane Database of Systematic Reviews. (L. John Wiley & Sons)
- Gardner, S., Frantz, R., Troia, C., Eastman, S., MacDonald, M., Buresh, K., & Healy, D. (2001). A tool to assess clinical signs and symptoms of localized infection in chronic wounds: Development and reliability. *Ostomy/Wound Management*, 47(1), 40-47.
- Hartmann, K. M. (1983). Action Spectroscopy. In W. Hoppe, W. Lohmann, H. Marke & H. Ziegler (Eds.), *The Biophysics*. Heidelberg: Springer-Verlag.
- Holland, R., Smith, R., Harvey, I., Swift, L., & Lenaghan, E. (2004). Assessing quality of life in the elderly: a direct comparison of the EQ-5D and AqoL. *Health Economics*, 13(8), 793-805.
- Hopkins, J. T., McLoda, T. A., Seegmiller, J. G., & Baxter, G. D. (2004). Low Level Laser Therapy facilitates superficial wound healing in humans: a triple blind, sham controlled study. *Journal of Athletic Training*, 39(3), 223-229.

- Humaz, M. D., & Diamantopoulos, C. (1993). Multi-wavelength low reactive-level laser therapy (LILT) as an adjunct in malignant ulcers: case report. *Laser Therapy*, 5, 149-152.
- James, J. (1994). Laser therapy on trial. *Primary Health Care*, 4(10), 18-20.
- Karu, T., Andreichuk, T., & Ryabykh, T. (1993). Changes in oxidative metabolism of murine spleen following laser and superluminescent diode (660-950 nm) irradiation: effects of cellular composition and radiation parameters. *Lasers in Surgery and Medicine*, 13(4), 453-462.
- Karu, T., Ryabykh, T. B., & Letokhov, V. S. (1997). Different sensitivity of cells from tumour bearing organisms to continuous-wave and pulsed laser irradiation(632nm) evaluated by chemiluminescence test. *Lasers Life Sci*, 7, 141-156.
- Katz, S., Ford, A. B., Moskowitz, R. W., Jackson, B. A., & Jaffe, M. W. (1963). Studies of illness in the aged. The Index of ADL: a standardized measure of biological and psychosocial function. *JAMA*, 185(12), 914-919.
- Lawton, M. P., & Brody, E. M. (1969). Assessment of older people: self-maintaining and instrumental activities of daily living. *The Gerontologist*, 9, 179-186.
- Lievens, P. (1988). Effects of laser treatment of the lymphatic system and wound healing. *Lasers*, 2, 12-15.
- McNulty, F. (1997). Low level laser therapy - trial by district nurses. *Scottish Nurse*, 12, 42-45.
- Mester, E., Szende, B., & Tota, J. G. (1967). Effect of laser on hair growth of mice (in Hungarian). *Kiserl Orvostud*, 19, 628-631.
- Miller, C., Karimi, L., Donohue, L., & Kapp, S. (accepted for publication). Inter- and Intra-Rater Reliability of the Silhouette Wound Imaging Device. *Advances in Skin & Wound Care*.
- Moffatt, C., Kommala, D., Dourdin, N., & Choe, Y. (2009). Venous leg ulcers: patient concordance with compression therapy and its impact on healing and prevention of recurrence. *International Wound Journal*, 6(5), 386-393.
- Palmgren, N., Jensen, G. F., Kaae, K., Windelin, M., & Colov, H. C. (1989). Low power laser therapy and rheumatoid arthritis. *Laser in Medical Science*, 4, 193-196.
- Pasher, T., Ghesick, Y. P., Winkler, J. R., & Gray, H. B. (1996). Protein folding triggered by electron transfer. *Science* 271, 1558-1560.
- Pieper, B., Templin, T., Dohal, M., & Jacobs, A. (1999). Wound prevalence, types and treatments in home care. *Advances in Skin and Wound Care*, 12(3), 117-126.
- Polit, D. F., Beck, C. T., & Hungler, B. P. (2001). *Essential of nursing research: Methods, Appraisal, and Utilization* (Vol. Edition 5). Philadelphia PA: Lippincott Williams & Wilkins.
- Polit, D. F., & Tatano Beck, C. (2012). *Nursing Research: Generating and Assessing Evidence for Nursing Practice* (Ninth ed.). Philadelphia, PA: Wolters Kluwer Health , Lippincott Williams & Wilkins.
- Posten, W., Wrone, D. A., Dover, J. S., Arndt, K. A., Silapunt, S., & Alam, M. (2005). Low-level laser therapy for wound healing: mechanism and efficacy. *Dermatologic Surgery*, 31(3), 334-340.
- Rochkind, S., Ruosso, M., Nissan, M., Villarreal, M., Barr-Nea, L., & D.G., R. (1989). Systemic effects of low-power laser irradiation on the peripheral and central nervous system, cutaneous wounds and burns. *Lasers in Surgery and Medicine*, 9, 174-182.
- Schindl, I., Kainz, A., & Kern, H. (1991). Effect of low level laser irradiation on ondolent ulcers caused by Buerger's disease: literature reiew and preliminary report. *Laser Therapy*, 4, 25-31.
- Surgrue, P. A., Carolan, J., Leen, E. J., Feeley, T. M., Moore, D. J., & Shanik, G. D. (1990). The use of infrared laser therapy in the treatment of venous ulceration. *Annals of Vascular Surgery*, 4, 179-181.
- Takaduma, K. (1993). Possible application of the laser in immunobiology. *KEIO J Med*, 42(4), 180-182.
- Vice, P. A., Walters, J. S., & Robinson, B. J. (1991). *Trial of Low Level Laser Therapy in the out-patient treatment of diabetic ulcers*. Paper presented at the The 5th International Biotherapy Laser Association Meeting.
- Woodruff, L. D., Bounkeo, J. M., Brannon, W. M., Dawes, K. S., Barham, C. D., Waddell, D. L., et al. (2004). The Efficacy of Laser Therapy in Wound Repair: A Meta-Analysis of the Literature. *Photomedicine and Laser Surgery*, 22(3), 241-247.
- World Union of Wound Healing Societies. (2008). *Principles of best practice: Wound infection in clinical practice. An international consensus* London: MEP Ltd.

