Using colour exhibited by venous leg ulcers to develop a range of hues that represent the clinical manifestations of erythema and wet necrotic tissue.

Submitted by

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Dedication

I dedicate this thesis to my late father who passed away as the thesis was being written. The standards he set and his undying love provided me with the commitment and resourcefulness required to undertake the study and complete the thesis. The pride he derived from my achievements will remain with me always.

Acknowledgments

Whilst this thesis has one author listed on the title page it is a culmination of work that has involved the support of several other people.

I would like to publicly thank my supervisors, Associate Professor Tim Neild, Professor Sandra Dunn and Dr Merrill Jones for their mentorship, perseverance and encouragement as the ideas that initiated this project were transformed into a thesis.

I would like to further thank Dr Michael Bailey whose statistical support was much appreciated during the design of this project and the analysis of the findings.

To my wife Wendy McGuiness and daughter Christine McGuiness I would like to acknowledge the support they have provided. If I needed encouragement, time to work, or relief from my family duties Wendy and Christine were able to accommodate my needs without complaint. This thesis is as much a testament to their patience as it is to the research undertaken.

Finally, I would like to thank the patients and clinicians who agreed to participate in this study; the project would not have been possible without their willingness to provide time and support.

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SUMMARY

This project sought to develop a system that facilitated the visual inspection of venous leg ulcers by establishing a selection of reliable parameters. The project had three principal aims: to develop a reliable method for capturing the colours exhibited by a venous leg ulcer; to establish a colour range that experienced clinicians believed represented wet necrotic tissue and erythema; and to develop software that highlighted the two manifestations in digital photographs.

The project method was divided into three phases. The first phase examined images taken from twenty-two patients over forty-seven episodes of care. During each episode three sequential images were captured using a frame to control for orientation, magnification and lighting resulting in a bank of 141 images. The reliability of the system to accurately capture colour was then determined by examining the amount of colour variation recorded across the set of three images taken at each episode. The second phase asked eight experienced clinicians to examine a set of twenty photographs taken from the bank established in phase one. On each photograph the clinicians were asked to identify areas of wet necrotic tissue or erythema and outline the areas with a colour pen supplied for each manifestation. A colour range was then constructed to represent each manifestation by measuring the range, mean and standard deviation of pixels that were located within the outlined areas. The third phase developed a computerised system that used the colour range established in phase two to highlight areas of a digital image that represented either erythema or wet necrotic tissue. The validity of the

highlighted areas was then tested by asking experienced clinicians to identify their level of agreement with the areas selected by the computer system.

Analysis of the results from phase one indicated that the system used to record images at each episode of care provided a reliable method for maintaining consistent orientation, magnification and replication of colour. Results from phase two yielded a two distinct colour representation of erythema and wet necrotic tissue. Erythema ranged from 360^0 to 378^0 of hue with a mean of 369.21^0, and wet necrotic tissue ranged from 367^0 to 390^0 of hue with a mean of 387.73^0. Results from phase three indicated that whilst clearly delineated areas of erythema and wet necrotic tissue were visible, the validity of the representations was varied. 50 per cent of experienced clinicians agreed with the areas selected as erythema and 60 per cent agreed with the areas selected by the computer system as wet necrotic tissue.

The system developed during this study for recording images of venous leg ulcers provides a reliable method for further research into the visual progression of this disease. However, the colour range identified as being representative of erythema or wet necrotic tissue and the computer system developed to highlight such areas in a digital image, requires further investigation before it is applicable to the clinical setting. The findings do however provide further insights into the varied nature of expert opinion when judging the colour of venous leg ulceration.

STATEMENT OF AUTHORSHIP

Except where reference is made in the text of the thesis, this thesis contains no material published elsewhere or extracted in whole or in part from a thesis presented by me for another degree or diploma.

No other person's work has been used without due acknowledgment in the main text of the thesis.

This thesis has not been submitted for the award of any other degree or diploma in any other tertiary institution.

Appreciation is extended to Dr Tim Neild, Professor Sandra Dunn and Dr Merrill Jones who provided valuable assistance and encouragement in the preparation of this thesis.

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William McGuiness
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1. Chapter One: Background

Chronic Venous Insufficiency (CVI) and the resulting clinical manifestations of varicose veins and venous ulceration pose a significant health problem. The condition is associated with long-term, high cost care, with a frequent incidence of recurrence and a number of negative patient outcomes[1-9].

Knowledge of clinical manifestations and associated venous pressure dates back several centuries. Hippocrates, when discussing the treatment of ulcers stated:

> "In the case of an ulcer, it is not expedient to stand; more especially if the ulcer be situated in the leg; but neither, also, is it proper to sit or walk. But quiet and rest are particularly expedient." [10]

Whilst the existence of CVI has been known for some time, the underlying aetiology and predisposing risk factors are yet to be accurately identified.[5, 11-17] Some argue that because CVI doesn't threaten life or limb, research in this area is given a low priority.[18] The result has been an underestimation of the extent of the health problem and an absence of evidence based management protocols.[1-9]

As the average age of the world population increases and the incidence of obesity in all age groups continue to rise, it is estimated that the personal and societal burden of this disease will be high. Armed with such forecasts researchers and clinicians have been exploring methods for accurately

estimating the extent of the disease, determining the aetiology and risk factors, and testing management strategies.

The following is a review of relevant research in the area and is presented as a foundation for subsequent chapters and as background for the study undertaken. The review will examine contemporary definitions of CVI; estimates of the prevalence of the condition; theories of the underlying aetiology; and the impact of CVI and its manifestations on both the health care sector and patients suffering from the condition.

1.1. Chronic Venous Insufficiency (CVI) defined

The International Classification of Disease, version 10 (produced by the World Health Organisation) lists disease states related to venous insufficiency as *ICD No.187.2 Venous insufficiency (chronic) (peripheral)*. Despite this listing, there is currently no agreed definition for CVI. Ruckley et al.[18] stated that the term 'chronic venous insufficiency' was used indiscriminately in the literature leading to confusion for clinicians and the introduction of methodological flaws for researchers. Whilst the majority of authors use the term 'chronic venous insufficiency', other terms such as 'chronic venous disorders', 'venous incompetence', 'chronic venous disease' and 'chronic venous disorders of the leg' are used interchangeably.[3, 5, 12-15, 19-30] The definitions cited for each often use aspects from other definitions cited for one of the other terms.

Attempts to define CVI usually make reference to the clinical manifestations of the disease; the underlying pathophysiology; associated risk factors; or a combination of each. Initial references to clinical manifestations were confined to the most obvious signs: varicose veins and venous ulceration.[20] More recent definitions expanded the list to include the various skin and subcutaneous changes associated with CVI. The definition used by Carpentier et al.[12] in a project aimed at determining the prevalence of CVI in France is an example:

> "Chronic venous disorders include several signs and symptoms assumed to be related to venous dysfunction in the lower limbs. Clinical manifestations include varicose veins of any type; vein related skin trophic changes, ranging from pigmented dermatitis to lipodermatosclerosis, white atrophy, and leg ulcers; pitting ankle oedema; and symptoms attributed to venous dysfunction, such as aching, pain, congestion, skin irritation, and muscle cramps, heaviness, tension, feelings of swelling and itching." (p. 650)

It is generally agreed that patients may suffer from some or all of the above signs and symptoms and that there is a hierarchy of severity. Heaviness of the legs, itchiness and telangiectasias (small superficial vein dilations – spider veins) are often cited as early signs of the condition, with trunk varicose veins (tortuous varicose veins of the great and small saphenous veins) and venous ulceration often described as signs of advanced venous disease.[3, 12, 19, 20, 22, 24, 26, 27, 29]

Others have expanded on the 'venous dysfunction' described by Carpentier et al.[12] to incorporate an underlying aetiology in the definition. An example is provided by Schmid-Schonbein et al.[30] who state that:

> "The clinical hallmark of chronic venous insufficiency is distal venous hypertension, which follows the development of valvular incompetence, reflux, and/or the venous obstruction." (p. 27)

Cesarone et al.[22] defined valvular incompetence as:

> "The presence of duplex venous reflux less than three seconds with compression-release (patient standing) at the major junctions (i.e., the sapheno-femoral junction) and/or at varicose segments or perforating veins (any vein considered as a perforating vein at any level) or at the main venous (saphenous) trunks." (p. 120)

In 1995, the American Venous Forum presented the CEAP classification system. This classified patients according to their: clinical signs (C); aetiology (E); anatomic distribution (A); and pathophysiology (P).[3, 27, 31-33] Clinical signs were divided into seven classes (C_0 to C_6) with 0 being no signs and 6 being the most severe (see Table 4). Aetiology was divided into: congenital (E_c); primary (E_p); or secondary (E_s). Anatomical distribution was divided into: superficial (A_s); deep (A_d); or perforator (A_p); alone or in combination. Pathophysiology was divided into: reflux (P_r); or obstruction (P_o), alone or in combination.[3, 5, 31-33]

Valvular incompetence is thought by a number of authors to be associated with identified risk factors including the development of a deep vein

thrombosis, age, obesity, occupation and pregnancies.[9, 12-14, 19, 25-27, 34-38] Whilst the evidence for these assertions will be discussed later in this chapter, the inclusion of risk factors into a definition of CVI has been considered. In 1997 an ad hoc meeting of the American Venous Forum, including representatives from the Cardiovascular Disease Educational and Research Trust, the European Society of Vascular Surgery, the International Angiology Scientific Activity Congress Organisation, the International Union of Angiology and the Union Internationale de Phlebologie laid the foundation for the formulation of a consensus document regarding CVI.[3] This was subsequently reviewed in 1998 and 1999 and provided the following definition:

> "Chronic venous insufficiency of the leg (CVI) is characterised by symptoms or signs produced by venous hypertension as a result of structural or functional abnormalities of veins. Symptoms may include heaviness, leg tiredness, cramps, itching, sensation of being, swelling, the restless leg syndrome, dilation or prominence of superficial veins, and skin changes. Signs may include telangiectasia, reticular or varicose veins, oedema, and skin changes such as pigmentation, lipodermatosclerosis, eczema, and ulceration. The most frequent causes of CVI are primary abnormalities of the venous wall and the valves and secondary changes due to previous venous thrombosis that can lead to reflux, obstruction, or both." (p. 1)

In 2008 The American Venous Forum convened a VIEN-TERM meeting that finalised some 3 years of work to reach a consensus on the terminology used for reporting the management of chronic venous disorders (CVD)[39]. Participants of the meeting concluded that chronic venous insufficiency was

> "A term reserved for advanced CVD, which is applied to functional abnormalities of the venous system producing edema, skin changes, or venous ulceration." (p499)

The above definitions incorporate the critical elements of clinical manifestations, aetiology and contributing factors such as deep vein thrombosis. However, they do not incorporate recent research findings arising from molecular studies and quality of life surveys in this area. For example, it is now believed that the resulting skin and vascular changes evident in CVD are associated with an inflammatory process. There is also some evidence that, contra to popular opinion, patients with CVD suffer from leg pain. Equally, quality of life research has demonstrated that patients with CVD, in particular leg ulceration, endure a number of physical handicaps, poor self-esteem and social isolation.

Therefore, the above definition could be modified to include these findings. For the purposes of this thesis, CVI will be defined as:

> Chronic venous insufficiency of the leg (CVI) is characterised by symptoms or signs of advanced chronic venous disease produced by venous hypertension as a result of structural or functional abnormalities of veins. Symptoms may include *pain*, heaviness, leg tiredness, cramps, itching, sensation of being, swelling, the restless leg syndrome, dilation or prominence of superficial veins, and skin changes. Signs may include oedema, and skin changes such as pigmentation, lipodermatosclerosis, eczema, and ulceration. The most frequent causes of CVI are primary abnormalities of the venous wall and the valves *arising from changes in the inflammatory cascade,* and secondary changes due to previous venous thrombosis that can lead to reflux, obstruction, or both. *The condition is often accompanied by a*

lowered quality of life exacerbated by the physical manifestations of exudate and odour leading to social isolation and loneliness.

1.2. The prevalence of the condition

Reporting the prevalence of CVD, associated manifestations and patient factors must be done with some caution. Whilst the majority of authors agreed that CVD and the associated clinical manifestations is a common and significant health problem, attempts to quantify the prevalence of this condition have proven difficult. The absence of an agreed definition and established diagnostic criteria has prevented aggregation of data across populations surveyed.[4, 6, 19, 20, 40]

An example is the prevalence data for venous ulceration. The terms 'gravitational ulcer', 'hydro-static ulcer' and 'status ulcer' have all been used to describe venous ulcers[41] and must be considered when searching for relevant literature. Once such studies are obtained, the reader is often forced to sift through data to exclude other aetiologies such as arterial and pressure ulcers that have been included in the findings to determine venous ulcer prevalence.

Similar problems are encountered when methods for diagnosing CVI are examined. Prior to the introduction of duplex scanning (an ultrasound that enables examination of the blood flow within arteries and veins, usually of the legs) researchers were forced to rely on clinical examination and clinical history as an indicator of CVI. Whilst a number of investigators included

symptoms such as tired legs, itchiness and restless leg syndrome, the majority of studies relied on the presence of varicose veins and/or venous ulcers to identify patients suffering from CVI. The reliance on clinical manifestations to determine the prevalence of CVI introduces a degree of subjectivity which some authors argue results in an underestimation of the prevalence of the condition.[4]

Such methodological approaches prevent aggregation across studies necessitating the need to report a range (often large) of frequencies in preference to an established prevalence of CVI and associated manifestations. It further limits comparison of patient variables such as age, gender, occupation and pregnancies across the study groups; which in turn prevents the identification of associated risk factors that contribute to the development of CVI.

The following summarises the findings to date, in order to highlight what is often an underestimated community health problem, whilst being cognisant of the methodological problems described above.

1.2.1. Overall prevalence

Within the studies identified, prevalence was usually reported as either *point prevalence* (the number of people, who currently had chronic venous insufficiency or its clinical manifestations that developed prior to the study period) and *period prevalence* (the number of cases that were present at the

start of the study, plus the number of new cases developed during the study period) [42].

The majority of prevalence studies, reported *point* prevalence findings. An example is a study undertaken by Moffatt et al.[9] when examining the prevalence of leg ulceration is in a London population. Health professionals were asked to identify patients they were currently treating at that time for chronic venous leg ulceration in the Wandsworth community.

The time period used for period prevalence varied from 2 months to 16 years. The Framingham study[43] is a commonly cited *period* prevalence study with subjects were examined over a 16 year period. Subjects found to be free of varicose veins in 1966 undertook bi-annual examinations until 1988 in an effort to determine the number of people who develop varicose veins over that period.

In an effort to establish overall trends, a number of authors have aggregated findings from various prevalence studies. This has provided estimates for chronic venous insufficiency, varicose veins and venous ulceration. The variation of findings reported in the literature necessitates a large range for each.

It is estimated that chronic venous insufficiency affects between 10 to 40% of the general population[21]. The prevalence of varicose veins, in various forms (telangiectasias, reticular, or trunk) has been estimated at < 1%, up to 60.5%

of the population. When confined to validated population studies the range is reduced to between 25 to 32% of the population[6, 27]. Venous ulceration prevalence has been estimated to affect 0.06% to 1.97% of the population. When the figures for both open ulcers and healed ulcers are considered the prevalence increases,1.3% to 3.6%[40]. The figure differs between countries, gender, age and occupation[4-6, 20, 21, 27, 40].

1.2.2. Prevalence across geographic locations and associated life style

Table one provides a summary of the geographic locations in which prevalence studies have been conducted. The majority of studies have examined populations from industrialised countries, with an emphasis on Caucasian populations. The populations varied from 4000 to 1.6 million and included total populations and cross-sectional studies[40]. Although any conclusions drawn are limited by the methodological problems highlighted earlier, it would appear that the prevalence rate in industrialised, or developed countries is higher than in developing countries[27, 40]. This in turn suggests that chronic venous insufficiency is in part influenced by environment and/or life style.

This assertion is best illustrated by a study undertaken by Baeglehole et al.[44] in which the prevalence of New Zealand Maoris were compared with Polynesian subjects living on atolls in the Cook islands. Although of similar race, subjects living on the atoll of Pupuka had a lower prevalence than those

living in Rarotonga, who in turn had a lower prevalence than those living in New Zealand (see table one).

The argument is further strengthened when the prevalence of varicose veins amongst people who have moved from developing countries to developed countries is examined. For example prevalence of varicose veins amongst black and white Americans is equal[4]. Studies examining populations in Africa report a very low prevalence (<1.0%) for varicose veins. When subjects from Africa immigrate to the United States the prevalence of this condition increases to that of their adopted population [45, 46].

The trend also emerges for immigrants moving from Asia to the United Kingdom. In a recent study, Sam et al.[47] examined the prevalence of chronic venous disease amongst a group of men that had been born on the Indian subcontinent and immigrated to the United Kingdom. They found that 50% of subjects had clinical evidence of lower leg venous disease with 8% having skin changes associated with chronic venous insufficiency. These findings contrast with earlier studies conducted in India (see table 1), in which the prevalence of varicose veins was between 6.8% and 25.08%[48]. Sam et al. concluded that their findings were similar to those of predominantly white populations.

Country	Year and	Sample	Prevalence of CVI VV or VU
Australia-Perth[2]	1989	Patients referred from health professionals including general practitioners, medical specialists, nursing	VU: 0.62%

		homes, and silver chain (district) nurses, or by self referral. Aged 20 to 99 years.	
Brazil - SanPaulo	1985	Patients attending the university health centre in Botcuatu	VV: 37.9% Men 50.9% Women VU: 2.3% Men 5.5% Women
Cook Islands[44]	1975	Convenience sample of Polynesian subjects living on the Rarotonga and Pupuka atoll islands.	VV: Rarotonga 16% Men 15% Women Pupuka 2% Men 4% Women
France – National[12]	1988-1992	Cross-sectional sample of the general population from four locations in France.	CVI: 30.1% Men 50.5%Women
Greece - Rural[29]	1997	Convenience Sample of patients attending primary health care providers in rural Greece	CVI: 18.25% 4.91% Men 15.3% Women VV: 7.5% 1.9% Men 5.67% Women
Hong Kong_ Kowloon district[49]	2003	Retrospective review of nursing records of older people receiving community nursing services in the Kowloon East district	VU: 128/1000
India- Madras and Ajmer	1972	Sample of male Indian rail sweepers	VV: 6.8% North 25.08% South
Ireland-National[7]	1984	National random Sample of households derived from the 1984 quarterly consumer survey carried out by the economic and social research Institute	VU: 1.5% of adult population

		and An Foras Taluntais	
Israel – Jerusalem[50]	1969-1971	A survey of residents in a community neighbourhood of Western Jerusalem aged 20 or over.	VV: 10% Men 29% Women
Italy- National[23]	2003	Cross sectional, non random Sample of women and men, selected by means of advertising in television, newspapers, and leaflets supported by press agencies. Respondents were aged 18 to 89 years	Not reported
Italy- San Valentino[22]	1994	Sample of residence of eight different villages in central Italy aged 8 to 94 years.	CVI: 0.86% Of those VV: 7.0% VU: 0.48%
New Guinea- Low Land, Ramu[51]	1972	Population enrolled in the mission medical services database of villages on the Ramu flood plain	VV: 5.1% Men 0.1% Women
New Zealand-North Auckland and central Auckland[42]	1997-1998	Convenience sample of patients referred by health professionals and self referral via a toll-free number	VU: 39 per 100,000
Portugal - National[52]	1996	An epidemiological survey of consecutive attendances to the Portuguese national health service	CVI: 20% Men 40% Women VU: 3.2%Men 3.9% Women
Portugual – Unit B2 of Sub-Regiao Saude, Lisbon[52]	2001	Case identification by health professionals of patients suffering from chronic leg ulcer from the third to the 17th of December 2001	VU: 1.30/1000 Men 1.46/1000 Women
Saudi Arabia[14]	2001	Patients attending 16 primary health care centres randomly selected from the district in three major cities of the Kingdom of Saudi Arabia.	CVI 45.6% 10-20% Men 25-40% Women
Scotland - Edinburgh[18, 24]	1995-1996	An age stratified cross-sectional random sample of men and women, aged 18 to	CVI: 9.4% Men 6.6% Women

		64 years, derived from computerised registers of 12 general practices geographically and socio-economically evenly distributed across Edinburgh.	Of those VV : 39.7% Men 32.2%Women
Scotland – Lothian and Forth Valley[53]	1981	Convenience Sample of patients identified by general practitioners, district and occupational nurses, and wardens of old people's homes.	VU: 1.48/1000
Spain - National[16]	2002	An intentional sample of patients older than 14 years, being managed by primary health care professionals, hospital health care professionals, and residential care professionals, throughout Spain.	VU: 0.09% Of those 32.8% Men 67.8% Women
Sweden-Skaraborg[54]	1988	Patients identified by district nurses, general practitioners, outpatients department, long-term hospitals, and private long-term care facilities.	VU: 1.8%
United Kingdom - National[8]	1988-1996	Retrospective cohort study of data obtained from the General Practice Research Database derived from 1562 GP practices throughout the UK. Participants were aged between 65 and 95 years of age.	VU: 1.69% 0.76% Men 1.42% Women
United Kingdom London[9]	2004	Case ascertainment by health professionals used to identify patients suffering from chronic leg ulcer within the Borough of Wandsworth.	VU: 0.45/1000
United Kingdom – Middlesex health district[34]	1986	All patients with limb ulceration identified by general practitioners and district nurses in the health district.	VU:1.8%
USA - Framingham[43]	1966-1988	Longitudinal data collected via a bi-annual examination from subjects who	VV: 39/1000 Men 52/1000 Women

		were free of varicose veins in 1966	
USA – Olmsted County, Minnesota[55]	1966-1990	Patients with a first lifetime diagnosis of venous stasis syndrome and venous ulcers were identified using the data resources of the Rochester Epidemiological project	CVI: 76.1/100,000 person years VU: 18.0/100,000person years
USA – Tecumseh, Michigan[56]	1959-1960 1962-1965 1967-1969	Data derived from a longitudinal study of the total community of the city of Tecumseh.	VV: 12.9% Men 25.9%Women VU: 0.1%Men 0.3%Women

Table 1 A summary of year, location and prevalence of studies examining chronic venous insufficiency.
(CVI = chronic venous insufficiency, V V = varicose veins, VU = venous ulcer)

Several possible reasons for a higher prevalence of chronic venous insufficiency in developed countries have been cited in the literature[5]. Dietary habits, percentage of obesity levels and type of occupation have been examined in an effort to determine any associations between life style and the prevalence of chronic venous insufficiency.

Cleave[57] initially proposed that a relationship existed between diet, specifically insufficient dietary fibre ('western diet') and the prevalence of varicose veins. He asserted that insufficient fibre led to constipation, which in turn increased intra-abdominal pressures. Burkitt et al.[45, 46] supported this position citing the propensity of people from developing countries to developed similar prevalence rates of those of their adopted country. The Edinburgh study (see table one) demonstrated an opposing view. Fowkes et al.[25] recorded subjects' effort to open their bowels, their dietary fibre intake

and transit times of faecal material within their bowel. Whilst they found an increased prevalence of trunk varices in men reporting that they had strained when opening their bowels, the findings did not demonstrate any significant association between fibre intake, faecal transit time, and venous reflux.

In keeping with the influence of dietary habits on chronic venous insufficiency additional studies have examined associations between basal metabolic index and the prevalence of the disease. A number of authors argue that obesity is associated with chronic venous insufficiency[4, 5, 12, 26, 45, 50, 58]. Danielsson et al.[58], using a convenience sample, attending a Hawaiian hospital, investigated the impact being overweight had on the severity of chronic venous insufficiency. Subjects were classified as overweight (BMI>25 kg/m^2) or obese (BMI>30 kg/m^2) and examined for clinical signs of chronic venous insufficiency and the degree of venous reflux. They concluded that overweight patients were more likely to have skin changes and ulceration than patients with a body mass index of less than 25 kg/ m^2. This was regardless of the amount of venous reflux present.

It would appear that the relationship between obesity and chronic venous insufficiency affects women, more so than men. Siedell et al.[59] undertook a retrospective cohort study to examine the influence that being overweight had on chronic illness amongst patients attending four general practices in the Netherlands. They found that moderately overweight women were more likely to have varicose veins than normal weight women, and that obese women were three times more likely to have varicose veins. The same

relationship was not found for male subjects in the study. Abramson et al. examined a community in Western Jerusalem (see table one), in an effort to identify factors associated with chronic venous insufficiency. They found that the prevalence of varicose veins was 1.4 times higher amongst women than men, and attributed this finding to the number of women in the study that were classified as overweight.

Further investigations have focused on the impact of physical activity and occupation on the prevalence of chronic venous insufficiency. Principally, the relationship between long periods of standing and the prevalence and severity of the disease has been examined[36, 43, 60-66]. The findings are varied, some authors finding a positive correlation between periods of standing and chronic venous insufficiency, while others have not found significant associations.

Large population studies have demonstrated an association between standing and the prevalence of varicose veins. Tuchsen et al.[66] followed 1.6 million Danish workers for a period of three year after their first hospital admission due to varicose veins of the lower extremities. They concluded that working in a standing position was associated with subsequent hospitalisation for varicose veins. Abramson et al.[50], mentioned above (see table one) also found that prolonged standing contributed to the development of varicose veins, as did the Framingham and Edinburgh studies (see table one).

In contrast the study undertaken by Maffei et al[67] in Brazil (see table one) found that working posture was not correlated with the incidence of varicose vein is or venous ulceration. Likewise, Scott et al.[63] who performed a multivariate analysis of patients with venous ulcers and a control group in the Boston area, found no significant association between occupation and periods of standing on the prevalence of venous ulceration.

1.2.3. The influence of age and gender on prevalence

The majority of studies report a linear relationship between the prevalence of chronic venous insufficiency and age[2, 5, 12, 20, 22, 43, 46, 50, 56, 68, 69]. Generally, the older the subjects, the higher the prevalence of chronic venous insufficiency, varicose veins, and venous ulceration. For example, Brand et al.[43] (see table one) when examining the prevalence of varicose veins in the Framingham area found that for subjects less than 30 years old it was <1% for men and <10% for women. This increased to 57% for men and 77% for women once they were 70 years of age or older. Nelzen et al.[54] when determining the prevalence of venous leg ulcers in Skaraborg (see table one), reported a prevalence of 1.5% for subjects aged 60 to 79 and 3.2% to subjects aged 80 to 89.

Although the prevalence of clinical manifestations associated with chronic venous insufficiency increases with age, it seems that this condition gradually progresses from early life. School children of the same age (10-12 years) in eleven secondary schools of Bochum, Germany, were examined for the presence of varicose veins and venous reflux[70, 71] using Doppler

ultrasonography. The subjects were examined on four separate occasions, 1982-1983 (10-12 years old),1986-1987(14-16 years old),1991(18-20 years old) and 2001-2002 (29-31years old). On initial assessment 2.9% of students were found to have reflux of the saphenous vein, and no signs of varicose veins. By aged 14 to 16 years, 12.3% showed saphenous reflux and 1.7% of the children had trunk varices. This figure increased to 19.8% for saphenous reflux and 3.3% for trunk varices by age 18 to 20 years. Although the same measures have not been published for the fourth assessment, Stocker et al. reported that the median venous refilling times for the subjects has increased over time from 24 seconds in the initial study to >45 seconds in the fourth examination.

When gender is examined the majority of authors describe a higher incidence of chronic venous insufficiency, varicose veins, and venous ulceration in women, even when standardised for age. For example, Abramson et al.[50] when examining the prevalence of varicose veins in a population in Western Jerusalem, found 10% of men affected, as opposed to 29% of women. Coon et al.[56] when examining the prevalence of chronic venous insufficiency in the Tecumseh community (see table one) found the prevalence of varicose veins to be 12.9% for men and 25.9% for women. This study also found a prevalence of 0.1% for males and 0.3% of females for venous leg ulcers.

In contrast, the Edinburgh study (see table one) conducted by Evans et al.[24] found a higher prevalence of chronic venous insufficiency and varicose veins in male subjects. The prevalence of varicose veins was 39.7% in men, as

opposed to 32.2% in women. In Australia, Baker et al[2] (see table one) found the prevalence for venous leg ulcers to be the same for both male and females subjects. Therefore, while there seems that a higher prevalence of chronic venous insufficiency and the associated clinical manifestations exists amongst females, the evidence is not fully conclusive.

Some authors argue that the prevalence for women is artificially high[3, 20]. The majority of studies have used self reporting, or reporting by health professional to determine the prevalence of chronic venous insufficiency (see table one). It is argued that because women are often more concerned with conditions that affect their cosmetic appearance than men, they will seek medical help earlier and in larger numbers than men. Thus women will be over represented in the studies.

Others believe that the higher prevalence in women is related to pregnancy[5, 6, 20, 27, 36, 40, 43, 72]. Whilst not being supported by all studies, there is general agreement that a relationship exists between pregnancy and the development of at least varicose veins. For example, the Edinburgh study (see table one) found a higher prevalence of reticular varices amongst parous women than childless women. Henry et al.[7] reported that the prevalence of women with leg ulcers in Ireland increased with the number of pregnancies. Maffei et al.[67] also reported a higher frequency of both open ulcers and ulcers scars in Brazilian women with a higher number of pregnancies. In contrast, the West Jerusalem, and Tecumseh studies (see table one) were unable to demonstrate similar associations.

There is some reference in the literature to an association between the prevalence of chronic venous insufficiency and the wearing of tight garments, particularly amongst women. Such assertions are not supported by the literature. Abramson et al[50] as part of the West Jerusalem study (see table one) asked women if they wore stockings, garters, corsets, or elastic belts. When compared with the prevalence of varicose veins or ulceration the researchers were unable to demonstrate an association between this data and the prevalence of varicose veins or venous ulceration.

In summary, whilst the evidence is inconclusive, it would appear that the prevalence of chronic venous insufficiency is between 10 to 40% of 'western' or 'developed' societies. Varicose veins are found in 25-32% of the same populations and venous ulceration in 0.06 to 1.97%. The prevalence is higher amongst the elderly, particular above the age of 70 years. Women have a higher prevalence than men, particularly women who have had one or more pregnancies.

In tandem with the prevalence studies, research has been conducted to understating the physiological and pathological processes that lead to chronic venous insufficiency. The following is summary of this work.

1.3. Chronic Venous Insufficiency (CVI) aetiology

1.3.1. Normal venous function

The veins of the leg are divided into the superficial and deep venous systems, connected by a series of perforating veins. The superficial system begins in the arterio-venous capillaries located in the cutaneous tissue of the leg and continues on to form a network of small veins, which in turn are joined to form larger veins known as 'truncal' veins. The latter are referred to as the small saphenous vein, which runs from the ankle to the popliteal vein, and the great saphenous vein, which runs from the ankle to the common femoral vein. The veins of the superficial system are located above the muscular fascial layer.[73-75]

The deep venous system, as the name implies, is located below the muscular fascial layer. It is comprised of intramuscular veins and larger axial veins that follow the major arteries of the leg. Intramuscular veins of the calf join to form the popliteal vein which continues as the femoral vein as it passes through the abductor canal at the knee. Intramuscular veins of the thigh join to form the profunda femoris, which in turn joins the femoral vein, to form the common femoral and eventually external iliac vein. The superficial and deep venous systems are connected by veins and are known as 'perforating veins' that pass through anatomical spaces in the muscle fascia.[73, 74, 76] Both systems are in closest proximity at the ankle and veins in this area have the least amount of supportive connective tissue surrounding them.[13]

There has been some disagreement about the anatomical division between deep and superficial venous systems. Caggiati,[77] having studied the lower extremity hypodermis using a variety of techniques including dissection and ultrasonography, concluded that the saphenous vein could no longer be considered a truly superficial vein. He demonstrated that the saphenous vein ran deeply in the hypodermis and was covered by a 'fibroelastic sleeve' that in turn was connected to the muscle fascia. He further demonstrated that the adventitia of the saphenous vein was anchored to the fibroelastic sleeve, which may assist the vein to empty as the calf muscle is contracted.

In an effort to establish a common nomenclature for the veins of the lower leg, the International Interdisciplinary Committee was formed in 2001 to provide a consensus.[78] This was published in 2002 citing the anatomical structures that should be referred to as superficial, deep and perforator venous systems. This was revised in 2004 to expand the structures of the superficial venous system to include not only the greater and lesser saphenous vein, but the sapheno-femoral junction and the sapheno-popliteal junction as part of the superficial system.

Bicuspid valves are located throughout the deep and superficial veins and ensure the blood moves towards the heart by preventing blood returning to the lower extremities when the person is standing. The frequency of the valves increases from the proximal to the distal end of the leg in order to reduce the pressure in the distal veins, resulting from gravity. The bicuspid

valves are also found within the perforating veins ensuring that blood moves from the superficial to the deep venous system.[73]

It was commonly believed that the bicuspid valves were forced closed by the flow of the blood reversing through the valve as the muscles of the leg relax. Lurie et al.,[79] using duplex ultrasound scanning, examined the time between flow and venous valve movements in the saphenous veins of twelve volunteers with no history of venous disease. They identified that all but one subject showed zero reverse flow prior to valve closure and concluded that reverse flow was not necessary for the closure of healthy venous valves. These findings lead White et al.[13] to assert that the normal resting state of venous valves is the coapted position.

Valvular function is enhanced by the contraction of skeletal muscles within the leg, particularly the calf muscle. Contraction of the muscle forces blood from the superficial veins into the deep venous system and is known as the 'calf pump'. Immediately following contraction of the calf muscle the pressure within the deep venous system of the leg is 80 to 90 mmHg in the standing position. The pressure decreases to 15 to 30 mmHg following contraction of the calf muscle.[19, 76, 80] Pressure in the deep veins is approximately three times higher than the pressure in the superficial system. The fall in pressure in the deep venous system immediately following muscle contraction is greater than the superficial pressure drop, forcing blood to flow from the superficial to the deep systems.[74, 76]

1.3.2. Venous insufficiency

When venous outflow from the leg is impaired the patient is said to have 'venous insufficiency'. Reduced venous outflow results in an increased ambulatory pressure, often affecting the deep venous system first and in time the superficial venous system or vice versa. Although the extent and severity of the effects will vary, the ambulatory venous pressure often increases to levels in excess of 150 mmHg. This is known as a 'venous hypertension'.[13, 76, 81] Studies have shown that the increase in pressure is often not significantly different in each leg.[82]

Venous hypertension can be either primary or secondary. Primary venous hypertension results from valvular incompetence of the deep, perforator and/or superficial veins known as 'primary valvular incompetence'. Incompetent valves can no longer prevent blood from moving back into the distal areas of the leg. Blood is forced back into the venous capillaries when the calf muscle contracts, or drains into the distal area under the force of gravity when the muscle is relaxed. This is known as 'venous reflux'.

Secondary venous hypertension is also related to valvular incompetence. However, damage to the valves is as a result of an obstruction to the outflow of venous blood, usually associated with the development of deep vein thrombosis. The association between a deep vein thrombosis (DVT) and venous insufficiency has been identified in a number of studies.[3, 75] For example, Scott et al.[63] found that 45 per cent of patients with CVI had a

history of DVT compared to 4 per cent in the control group. Damage created to the valves by a DVT and subsequent re-cannulisation results in the incompetence.

The effects of both primary and secondary venous hypertension are exacerbated by failure of the calf pump and obesity. Immobile patients, or patients with reduced activity, have reduced calf muscle action which in turn increases the hydrostatic pressure within the venous system. Equally, immobile patients are predisposed to the development of deep vein thrombosis and the subsequent valvular damage.[3, 12, 27, 37, 41] Obesity increases pressure on the iliac veins, thus reducing venous outflow and increasing ambulatory pressures. Studies have also demonstrated that obesity is common amongst patients with CVI that develop skin changes associated with this condition.[58]

Venous hypertension resulting from valvular incompetence and the associated venous reflux increases pressure within the microcirculation (capillaries of the venous and arterial systems) of the leg. When this increased pressure is exerted on a continual or chronic basis, alterations to the microcirculation result in a number of clinical manifestations.

1.3.3. Clinical manifestations and associated pathophysiology

Patients afflicted with CVI routinely manifest a number of signs and symptoms. They frequently complain of aching, throbbing, heaviness of the legs and at times stinging leg pain. Others report a restlessness of their leg

often called ‘restless syndrome’. Pruritus or itchiness is often reported as the patient’s skin is usually dry. Duque et al.[83] examined the prevalence of each symptom amongst 100 subjects suffering from CVI. Itchiness was the most common symptom identified by the subjects (66 per cent); leg fatigue (63 per cent); leg pain (62 per cent); cramps (53 per cent); muscle ache (48 per cent); and heaviness in the legs (47 per cent). Dry skin was present in 74 per cent of the subjects examined.

Signs observed in this patient cohort included the presence of varicose veins, varying degrees of leg and foot oedema, a darkening of the peri-malleolar skin, dry scaly skin of the leg and foot, lipodermatosclerosis and, in some patients, venous ulcers near the malleoli[13, 75, 84, 85] (see Figure 1). Varicose veins can range from dilation of small superficial veins known as reticular varicose veins, to large dilations of sections of the saphenous veins known as truncal varicoses.

Oedema results from an increased permeability of the micro-vessels, allowing fluid to move from the intravascular to the interstitial spaces. Lipodermatosclerosis is fibrosis of the dermis and subcutaneous tissue.[73] The replacement of dermal and subcutaneous tissue with fibrin reduces the normal elasticity properties of the skin resulting in firm, rigid areas on the distal leg. Darkening of the peri-malleolar skin is a result of hemosiderin, or iron deposits left in situ when erythrocytes break down in the subcutaneous tissues.[86]

Ulceration that occurs as a result of CVI is typically located in the gaiter area, shallow in depth, variable in extent, accompanied with moderate to heavy amounts of exudate, odour and pain. The ulcers are often large, slow to heal and have a high reoccurrence rate.[1, 34, 37, 41, 49, 54, 73-75, 87-105] A review conducted by Persoon et al.[90] of leg ulcer studies revealed that the mean surface area of a venous leg ulcer was 6 cm^2 with between 18 per cent to 48 per cent of the patients surveyed having an ulcer of greater than 10 cm^2. The duration for the ulcers examined varied from one week to 63 years with 40 per cent of ulcers existing for more than one year and 10 per cent for more than five years. Only 21 per cent to 45 per cent of patients examined were experiencing an ulcer for the first time. Other studies have demonstrated that between 26 per cent to 69 per cent of patients suffer from recurring venous ulceration.[1, 38, 106-108]

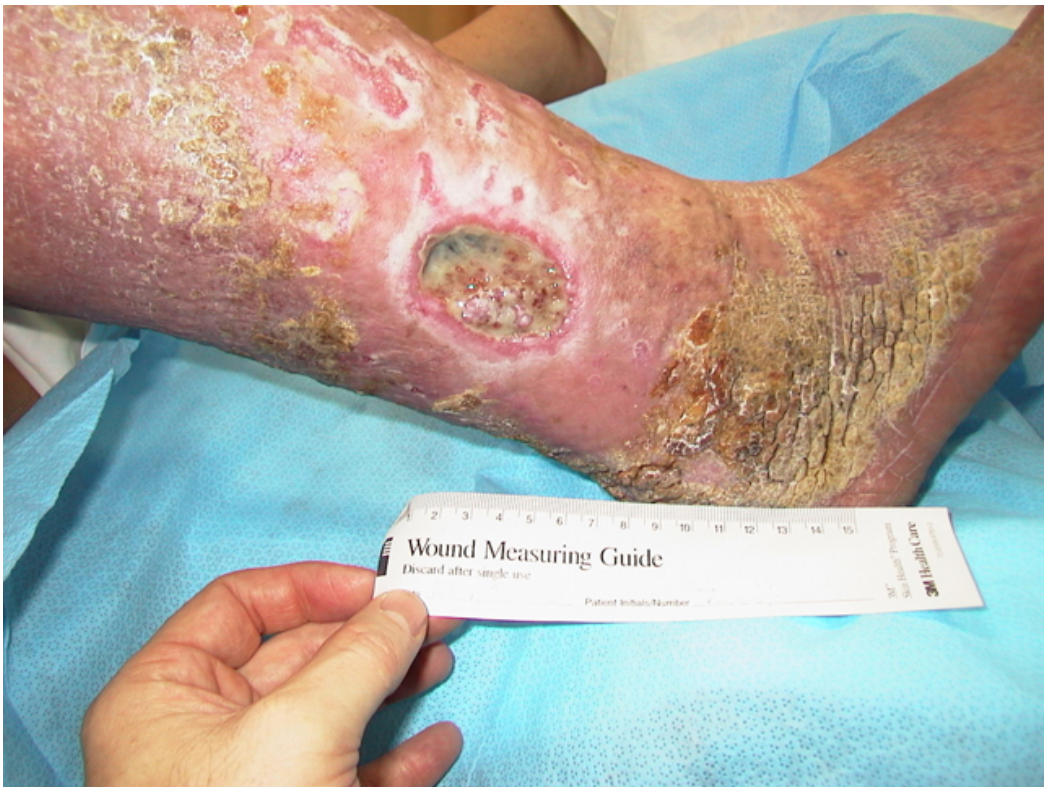


Figure 1. ***Signs exhibited by chronic venous insufficiency: Oedema, dry skin, hemosiderine deposits and ulceration*****.**

Although an association has been demonstrated between valvular incompetence and the above signs and symptoms,[2, 4, 5, 19, 21, 109, 110] the exact mechanism by which these changes occur is not fully understood.

Examinations of surgical specimens removed from patients with chronic venous disease, or via angioscopy, have revealed a number of common characteristics.[111] Bulging, stretching, tearing and perforation of the valve leaflets are often observed and, in some instances, complete destruction of the valve. The lesions are not found along the entire length of the vein but tend to 'skip' some areas resulting in areas of normal vein wall and valves.[73] Histopathological studies of varicose veins have revealed that the vein wall has increased collagen content and a disruption to the normal arrangement of smooth muscle cells and elastin.[112-116] Surrounding the capilliaries are peri-capillary cuffs of fibrin that are believed to have developed from fibrinogen that escaped into the extracellular fluid as the permeability of the vein wall increases with an increase in venous pressure.[92]

Thomas et al.[117] observed that fewer leukocytes (24 per cent less) returned from venous circulation of patients with CVI. They concluded that the leukocytes were being sequestered in the micro-circulation due to venous hypertension. Further studies have identified that leukocytes are adhered to, and in some instances have migrated into the wall of affected veins.[118, 119]

In addition, high levels of proteinases have been found in patients with varicose veins. Proteinases are used to break down tissue as part of the normal repair process. A study by Badier-Commander et al.[120] identified that matrix metalloproteinases (MMPs) and their inhibitors (tissue inhibitors of MMPs, TIMPS) were found to be 3.6 (MMPs) and 2.1 (TIMPs) times higher in patients with varicose veins than in control patients.

A number of theories have been put forward to explain the above observations. The first was proposed by John Homans (cited by Pappas[15]) in 1917. He believed that the skin changes associated with CVI were related to venous stasis and hypoxia. This theory was expanded by Pratt (cited by Pappas[15]) who postulated that skin changes, in particular venous ulceration, were a result of nutrients and oxygen being shunted away from the dermal plexus thus leading to hypoxia.

Browse and Burnard[121, 122] further supported the notion that cell hypoxia was the underlying aetiology when postulating the 'fibrin cuff' theory. They were the first to identify fibrin deposits in the extracellular matrix (mentioned above), and used the term 'fibrin cuffs' to describe the structure. They hypothesised that the increased venous pressure distended the local capillary bed, allowing fibrinogen to escape into the interstitial fluid. The resulting fibrin deposits formed cuffs that acted as a barrier to oxygen and nutrients, resulting in cell hypoxia and death.

The theories of hypoxia have not been supported in more recent research. Coleridge Smith[123, 124] demonstrated that the oxygen levels of the skin and varicose veins of patients suffering from CVI is not decreased, but increased. It has also been demonstrated that complete cell layers offer little resistance to oxygen diffusion and therefore thinner fibrin layers are less likely to block oxygen diffusion.[125] In addition, Falanga and Eaglstein[126] observed that the fibrin cuffs did not completely surround the capillaries and that venous ulcers had healed despite the presence of fibrin cuffs on the ulcer edge.

Based on the work of Thomas et al.[117] (see above), Coleridge Smith et al.[123, 124] proposed an alternative theory suggesting that changes in capillary flow lead to a *trapping* of leukocytes. Trapped leukocytes in turn release oxygen free radicals and proteolytic enzymes which damage the capillary walls. This increases the wall permeability leading to further trapping of leukocytes. Claudy et al.[127, 128] proposed that the capillary wall damage described by Coleridge Smith resulted from an increased elastase activity and the release of tumour necrosis factor alpha by the trapped leucocytes. These factors decreased fibrinolytic activity resulting in the fibrin cuff formation seen by Browse and Burnard.[129]

Pascarella et al. [80, 111, 125, 130] built on this work when they went on to describe valvular incompetence and subsequent skin changes as a process of *inflammation*. A process they described as the activation of leukocytes resulting from an elevation of blood pressure, mechanical stretching of the venous wall, or an alteration to fluid shear stress within the vein.[111]

Fluid shear stress refers to the sliding forces applied to the wall of the vein by blood passing over that wall. This is a normal physiological process that assists the transfer of nutrients and gases and is believed to promote the release of factors that reduce inflammation and the formation of free radicals,[19] principally nitric oxide.[11] In patients suffering from CVI the force may be lower, have a turbulent flow, and flow in the reverse direction.[131] Changes to fluid shear reduce the release of nitric oxide which in turn increases the release of factors that initiate inflammation.

Leukocyte activation is characterised by the release of many inflammatory molecules. A group of these molecules known as cytokines act to regulate the inflammatory reaction. The activity of two predominant inflammatory cytokines has been found to be higher in patients suffering from CVI. The first is tumour necrosis factor, which Claudy et al.[128] found to be present in the skin of patients suffering from CVI (see above). Tumour necrosis factor stimulates the expression of inflammatory adhesion molecules. These in turn result in leucocytes adhering to the vessel wall. Once adhered, the leucocytes release free oxygen radicals and proteolytic enzymes. Specific proteolytic enzymes known as matrix metalloproteinases had been shown to degrade extracellular matrix components leading to the vessel wall and skin changes seen in patients suffering from CVI.

The second cytokine is vascular endothelial growth factor, which is known to enhance vascular permeability and proliferation of the endothelium, plus the

expression of adhesion molecules. The activity of this cytokine is increased under changes in blood shear stress and during inflammation. High levels of vascular endothelial growth factor had been found in patients with CVI and associated skin changes.[128]

The resulting inflammation and infiltration of leukocytes changes the structure of the bicuspid valve and the extracellular matrix, leading to valvular incompetence and skin changes.[132] Takase et al.[80, 118] created venous hypertension in rats by creating a femoral arterial-venous fistula. They observed the inflammatory process described above, with associated changes to the vein wall and bicuspid valves resulting from leukocyte infiltration and remodelling of extracellular matrix.

In addition to the various attempts to describe the underlying aetiology of CVI, a number of researchers have attempted to provide an explanation for the slow healing properties associated with venous ulceration. Falanga et al.[126, 133] suggested that a possible explanation could be the *binding* actions of 'macromolecules' and fibrin that escape into the interstitial fluid as suggested by Browse and Burnard.[121] They proposed that fibrin and other macromolecules that leak into the dermis trap growth factors and other stimulatory or homeostatic substances, rendering them unavailable for the maintenance of tissue integrity and the repair process.

Wound infections are cited as possible inhibitors of venous leg ulcer healing.[134, 135] Schultz[135] has proposed that ulcers fail to heal because of the

presence of a biofilm. A biofilm is a colony of bacteria adhered to the surface of the wound, surrounded by a polysaccharide capsule. The structure makes them resistant to topical and systemic antibiotics. It is argued that the presence of these bacteria hinder ulcer healing by stimulating the release of inflammatory mediators. Seidman et al. [136] and others[137-139] have examined the action of fibroblasts in chronic leg ulcers. They concluded that venous ulcer fibroblasts show similarities to senescent cells. Senescent cells are slow growing cells with altered morphology. It is argued that the functions of such fibroblast inhibit wound healing.

A number of researchers[140-143] have explored the peripheral nerve function of patients suffering from chronic venous ulceration. The findings suggest that patients suffer from a degree of peripheral neuropathy which increases with the severity of the disease. Padberg et al.[144] found that the most common site of sensory loss was just proximal to the medial malleolus, a common area for venous ulceration. Andron et al.[142] measured the axon reflex vasodilation in the skin over the arms and feet of fifteen elderly patients with chronic venous ulcers. They found that the reduced axon reflex affected the feet, but not the arms of the subjects. Cheatle et al.[140] found that even when heated the vasodilation of patients with lipodermatosclerotic skin was significantly less than control patients. Shami et al.[143] suggested that the increased capillary pressure resulting from venous hypertension resulted in axon hypoxia and neuropathy.

1.3.4. Associated factors

In the previous section reference was made to the prevalence of CVI being influenced by a number of associated factors such as gender, age and lifestyle (see Section 2.1). Some research has been done to identify possible aetiologies that account for this association.

Prevalence studies have shown a familial aggregation of varicose veins and venous ulceration.[6, 8, 11, 24, 29, 48, 54, 63, 67] This would suggest a possible genetic aetiology for CVI. A limited number of studies have been done in this area[145-150] and, although possible genes have been suggested, specific genetic aetiologies have yet to be identified. Ng et al.,[148] after examining 2060 female twin pairs, identified that the FOXC2 gene was implicated in the development of varicose veins but suggested further research was needed to confirm this finding. Zamboni et al.[146] suggested that mutation of the hemochromatosis gene C282Y, leading to an iron overload in the tissues, significantly increased the risk of developing a leg ulcer when compared with a control group. However, once again they suggested further research was needed to confirm this finding.

It has been identified that the prevalence of CVI increases with age (see Section 2.1). Some authors suggest that this results from changes attributable to the ageing process. Caggiati et al.[151] examined the varicosed legs of people < 30 years and > 60 years of age. They found that varicoses of the saphenous vein were more common in the older age group. The

younger group's varices were more common in the tributaries of the saphenous vein or veins not connected to the saphenous veins. They concluded that this was in part due to ageing. Wali et al.[114] compared the microscopic structures of vein walls extracted from young trauma patients and patients with primary varicose veins. The younger trauma patients had no signs of varicose veins.

The prevalence figures also indicate a gender difference with females being affected more than males (see Section 2.1). Pregnancy and the resulting physiological changes has been suggested at the most likely cause of this difference. Significant increase in blood volume; increases in abdominal pressure due to weight gain and foetal growth; and the effects of relaxin have been cited as contributing to CVI.[5] The latter is a hormone that has been shown to be a powerful vasodilator that puts pressure on the venous system.[152]

The prevalence of CVI has also been associated with the patient's body mass index (BMI). Higher prevalence is seen in patients with high BMI, particularly in the overweight or obese category. This has been attributed to the increased intra-abdominal pressures created by obesity. Dannielsson et al. [58] found that patients with a mean BMI of 50.2 kg/m^2 had a mean femoral venous pressure of 19.7 cm H_2O. This was significantly different from the control group (BMI 24.8 kg/m^2) who had a mean femoral venous pressure of 7.5 cm H_2O. They went on to suggest that other factors such as lack of physical activity in overweight people may also contribute to the disease by restricting emptying of the venous system.

As mentioned previously, venous hypertension can occur as a result of obstruction to venous outflow. The most common form of obstruction is a deep vein thrombosis. The development of deep vein thrombosis has been linked to the formation of valvular incompetence and the development of leg ulceration.[3, 17, 41, 55, 107, 153-157] A propensity for patients suffering from CVI to have underlying thrombophilia has been suggested by Bradbury[155]. He supported this assertion by citing evidence that demonstrates the existence of chronic thrombin and fibrin formation long after the acute inflammatory phase of a deep vein thrombosis has passed. Prandoni et al.[108, 158, 159] examined 355 patients with a confirmed deep vein thrombosis. Seventy-eight patients (22 per cent) had one or more documented recurrence of a deep vein thrombosis. Based on these findings they asserted that one in three patients with a deep vein thrombosis will go on to develop post-thrombotic syndrome. This syndrome is characterised by leg cramping, pruritius, leg oedema, pain during calf compression, and ulceration. This would account for the high prevalence of leg ulceration following a deep vein thrombosis. In addition, Kahn et al.[31] identified that patients who had a history of deep vein thrombosis often had a significantly worse level of CVI and a poorer quality of life than patients without prior deep vein thrombosis.

Figure 2 provides a summary of the various aspects identified in the above research. It would appear that the underlying aetiology of CVI is probably one of an inflammatory nature followed by mechanical changes to the vein wall, bicuspid valves and surrounding subcutaneous tissues and skin. Any genetic

influence on this process has yet to be determined[160] as does the influence of predisposing factors such as age, gender and lifestyle.

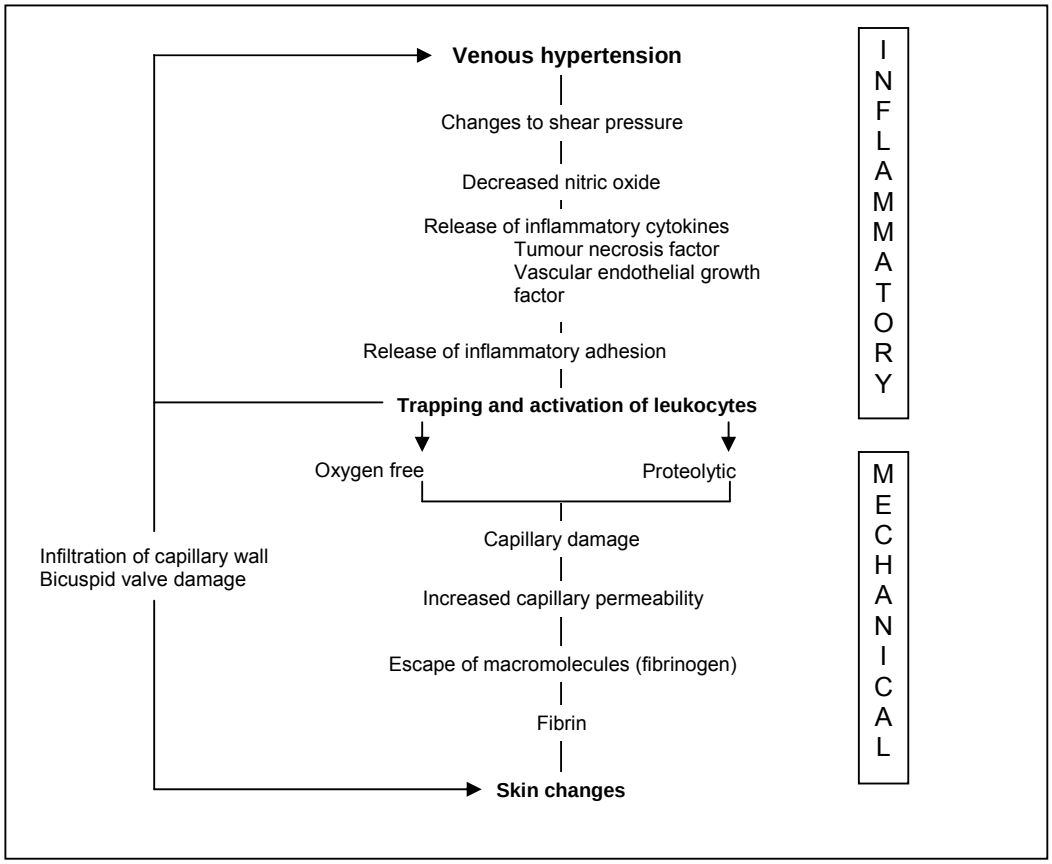


Figure 2: Representation of processes of aetiology for skin changes and ulceration (Modified from Abbade et al.[41])

1.4. The effect on the patient and their society

1.4.1. The financial costs

As with the previous sections, research exploring the impact of CVI on the patient and the community is often varied and inconclusive. Although venous ulcers affect a much smaller percentage of the population, the majority of studies have focused on this manifestation as it is associated with a marked

degradation of the patient's quality of life, and a heavy imposition on health care budgets.[31, 75, 90, 161-165]

It has been estimated that venous leg ulcers cost between $775 million to $1 billion a year in the United States of America (US).[166] This has increased annually with at least 150,000 new cases resulting in an additional $500 million cost.[167] In the United Kingdom (UK) estimates range from £294 million to £949 million annually.[168, 169] The estimates are based on direct costs only (medical and nursing staff and hospital admissions).

A number of studies have examined the actual costs per patient over time and per episode of care. Ragnarson Tennvall et al.[170] compared the costs of treating patients in the United Kingdom, with a cohort of patients in Sweden from 1993 to 1997. Costs were calculated from time of diagnosis until the ulcer was healed. The average cost of treating an initial ulcer varied between €814 to €1994 in the United Kingdom, and from €1332 to €2585 in Sweden. Average cost for preventing new ulcers during the ulcer-free period was €127 in Sweden and €45 in the United Kingdom.

Kumar et al.[168] examine the average annual cost per patient in New Mexico over a five-year cycle (1994–1998). Using Medicaid data they were able to demonstrate that over this period costs were reduced. The average total cost per patient of $2757 in 1996, dropped to $2617 in 1998. They concluded that these findings were a result of a change to Medicaid classifications rather than improvements in service.

A study undertaken by Olin et al.[166] demonstrated much higher figures when examining the costs of 78 patients in 1995. They reported an average total cost per patient of $9685. The study separated hospital costs from outpatient costs revealing an average hospital cost per patient of $2445, and an average outpatient cost per patient of $5736. The outpatient cost per patient reduced from $5736 during the 0 to 90 day period to $5108 during the 181 to 270 day interval. The costs were not significantly related to ulcer size but, as expected, strongly related to the duration of follow-up.

Morrell et al.[169] examined the difference in costs between patients attending a hospital clinic and those being managed in their home by community nurses. The average cost per episode was £29.90 for patients attending the clinic and £10.60 for those being managed at home.

Within Australia, the cost of inpatient care was referred to by Grindlay et al.[171] who estimated hospital costs for an average stay of 23.9 days to be approximately $8734 per admission. Using extrapolated figures from research conducted in the United Kingdom and France, Baker et al.[2] identified Australia's national health expenditure on leg ulcers to be in the vicinity of A$365 million to A$431 million. Santamaria, Austin and Clayton in 2002[172] estimated an increase in expenditure, placing national costs between A$553 million to A$654 million.

The majority of the above research has arisen because of concern about the increasing amount of resources being devoted to the treatment of leg ulcers and the resultant expenses incurred by national health departments. More recently, it has been recognised that the costs associated with this condition go beyond that incurred by the national health budgets.

When exploring the quality of life experienced by patients suffering from chronic leg ulcers, Phillips et al.[173] found that 67 per cent of participants stated that the presence of their leg ulcer impacted negatively on their financial situation. The main sources of expense identified were the cost of medical care, dressings and transportation. In over 30 per cent of cases, these expenses were estimated to be between $101 and $1000 per annum. A further 8 per cent of participants estimated out-of-pocket expenses to be greater than $1000 per annum.

A study conducted by Smith and McGuiness[174] in Australia in 2006 identified that participants spent on average a total of $114 per month on the treatment and management of their ulcer, resulting in a personal cost of $1368 per annum. 60 per cent of the costs incurred were for primary dressing products, with secondary dressing products (bandages, tapes), medications and transport accounting for the reminder of the expenditure. As the average age of participants in this study was 73.4 years it could be assumed that the majority of participants in this study were financially supported by government pensions. Considering the average weekly income from aged pensions at the time of printing was $206 (Australian Bureau of Statistics) the

researchers concluded that it was likely that approximately 14 per cent ($28) of participants' total weekly income was being spent on the treatment and management of their leg ulcer.

1.4.2. The impact on Quality of Life

Personal costs go beyond the financial imposts. A number of studies have examined the impact of CVI on the patient's quality of life. Pain, social isolation, immobility, interference with sleep, and a lack of self-esteem feature as common problems encountered by this patient cohort.

Reviews undertaken by Persoon et al.[90] and Herber et al.[175] provide insights into the quality of life experienced by patients with chronic venous leg ulcers. An examination of qualitative studies revealed four themes: "pain, impaired mobility, sleep disturbance and problems related to wound characteristics" (p. 343). Pain was cited as the most negative aspect of living with a venous leg ulcer. Patients reported that the pain varied in intensity from irritating to intense, with the most intense pain being felt at night. Others reported that the weather and seasonal aspects influenced the intensity of their pain.

Limitations in mobility were linked to swollen legs, the bulk of wound dressings, exudate leakage, and the need to wear large shoes. Patients also reported that they had difficulties maintaining normal hygiene, because of the requirements to keep the bandages dry and the associated limited mobility.[90]

Patients also reported social isolation because of the exudate from their ulcer. Wet shoes and stockings, and the accompanying odour, often interfered with normal social or family interactions. To cover and accommodate for their bandages, women often resorted to wearing slacks and larger shoes. They reported reduced feelings of femininity and a reluctance to mix socially.[90, 175]

A lack of control over their ulcer and its management was a common feeling amongst this patient cohort. Whilst grateful for the support provided by health professionals, most patients felt that the practitioners did not always explain the treatments, listen attentively, or provide consistent messages and advice.[90, 175] Associated with a lack of control was feelings of regret, depression and hopelessness.

Qualitative studies confirm similar results, with pain being the most often cited negative influence on the life of patients with chronic venous ulcers. Hyland et al.[176] found the majority of patients within their study had a degree of pain with 20 per cent having very painful ulcers and 4 per cent reporting excruciating pain. Similar findings were found by other researchers with pain during dressing change being frequently mentioned.[161, 177-180]

Time off work was commonly explored by researchers. Although higher prevalence of ulceration is found in patients over the age of retirement significant correlations were found between time lost from work, unemployment and impost on financial resources, and having a venous

ulcer.[162, 173, 177] Inability to work or retain employment was associated with feelings of anger, resentment and associated depression.

A number of studies demonstrated an association between social class and the duration and recurrence of leg ulcers.[161, 162, 173, 177, 181] Many patients lived alone and had limited fiscal resources for purchasing care and the required nutrition to facilitate healing. Equally, they were unable to purchase preventative equipment such as compression hosiery, to reduce the risk of recurrence.

Dissatisfaction with health care workers was also evident in qualitative studies. Hareendran et al. [181] reported that 50 per cent of the patients surveyed in their research indicated a disappointment with treatment. Ruckley[162] suggested that this was related to the number of different health professionals patients with venous leg ulcers encounter throughout the treatment. Because this condition threatens neither life nor limb, patients with venous leg ulcers are given less attention by busy professionals who 'shunt' them to other carers. The majority of their care is provided in the community by nurses and significant others.[161, 182]

As expected, the quality of life reported by patients deteriorates with the severity of the condition.[31] Surprisingly, improvements in the quality of life are not reported even when the ulcer has healed. When comparing the performance of four instruments measuring quality of life, Walters et al. [183] reported that the 233 patients in the sample appeared to show an overall

deterioration of health status over time, and no improvement was associated with the leg ulcer healing.

1.5. Chapter summary

In summary, whilst the evidence is inconclusive, it would appear that the prevalence of CVI is found in 10 per cent to 40 per cent of 'western' or 'developed' societies. Varicose veins are found in 25 per cent to 32 per cent of the same populations and venous ulceration in 0.06 per cent to 1.97 per cent. The prevalence is higher amongst the elderly, particularly those above the age of 70 years. Women have a higher prevalence than men, particularly women who have had one or more pregnancies. The prevalence of CVI may be influenced by lifestyle practices; specifically those that increase the basal metabolic index of societal members, increase the periods of standing and reduce the amount of faecal fibre.

The aetiology of the condition appears to be a complex interconnection of several physiological and pathological processes. It would appear that the underlying aetiology of CVI is probably one of an inflammatory nature followed by mechanical changes to the vein wall, bicuspid valves, micro circulation and surrounding subcutaneous tissues and skin.

The cost of managing CVI for both the patient and the health care provider are high. Figures approaching the $1 billion mark in the US and UK place a large impost on a national health care budget. Equally, patients who are often

elderly and who have a reduced income struggle to secure the personal fiscal resources required to manage their leg ulcer and prevent recurrence.

Whilst the evidence is inconclusive about the quality of life experienced by patients with CVI, the nature of documented clinical manifestations and social contexts that have been associated with this disease indicate that this patient cohort suffer a number of negative experiences. Excessive exudate, wearing bandages, accompanying odour and pain result in the sufferer becoming a social recluse. This is often accompanied by feelings of helplessness and loss of self worth, which are further heightened with the inability to maintain activities of daily living and gainful employment. It is obvious that the lives of people with venous leg ulceration would benefit from effective and timely treatments aimed at eliminating such manifestations and associated outcomes.

The majority of authors agree that early an accurate assessment of this condition and its associated manifestations is a critical component to more effective management of this condition into the future. The next chapter will examine the techniques and tools that are available to health care clinicians when assessing the patient with CVI with a view to highlighting the significance of the study undertaken.

2. Chapter Two: The significance of objective assessment

In Chapter One it was established that CVI can affect almost half of the Western population over the age of 60, and generate health care costs close to $1 billion annually[21, 27, 34, 41, 156]. It is therefore imperative that accurate and reliable methods for diagnosing the condition and determining ongoing progress are available to health care practitioners. Such techniques provide early recognition of the condition and assessment of ongoing progress. Accurate diagnostics and assessment tools also provide valuable data for the evaluation of interventions undertaken to correct the condition or manage its manifestations.

This chapter explores diagnostic and assessment techniques described within the literature as a foundation for the study undertaken. To help clarify the intent of each assessment the methods have been classified into three categories: diagnosing the condition; classifying clinical manifestations; and judging the progression of outcomes. The chapter describes both objective and subjective assessments. The former techniques measure changes to defined physiological parameters. The latter evaluate the clinical manifestations produced by the physiological changes.

The discussion will demonstrate that whilst clearly defined parameters are available for diagnosing the presence of CVI clinicians are often forced to rely on subjective assessments such as colour when judging the progression of

clinical manifestations. It is argued that as the management of these manifestations form the bulk of health care cost attributed to CVI, it is logical to explore methods of refining such assessment techniques. In particular the need to develop objective measures for determining the healing progression of venous leg ulcers is discussed. The benefits of colour as an assessment parameter for venous ulceration is presented and the need for research in this area described as justification for undertaking the project described in this thesis.

2.1. Diagnosing the condition

Diagnostic investigations for patients with suspected CVI are focused on three principal areas. The initial intent is to detect the presence of reflux and/or obstruction within the venous system and to exclude arterial disease. Once venous reflux has been confirmed the focus changes to identifying the specific location of the reflux and/or obstruction. Data from these investigations is often used to determine if surgical intervention will succeed over more conservative methods. The third focus is to quantify the degree of reflux and/or obstruction. This data is principally used for research examining the efficacy of certain treatments, with clinical applications being reserved for organisations where the equipment is readily available[3].

In 2000 a consensus statement was published by Nicolaides et al.[3] detailing investigations undertaken for CVI. As described in Chapter One, the document arose from a meeting held in 1997, with representatives from the

Cardiovascular Disease Educational and Research trust, the European Society of Vascular Surgery, the International Angiology Scientific Activity Congress Organisation, the International Union of Angiology and the Union Internationale de Phlebologie. The panel concluded that:

> "Because the history and clinical examination will not always indicate the nature and extent of the underlying abnormality (anatomic extent, pathology, and cause), a number of diagnostic investigations have been developed." (p. 4)

The following is a summary of the investigations identified by this group and other authors.

2.2. Identification and localisation of reflux

2.2.1. Phlebography

Phlebography is an x-ray image of the leg veins following the injection of contrast dye. This investigation is seen as the 'gold standard' for diagnosing saphenous reflux, but more recently has been superseded by non-invasive tests such as duplex ultrasounds. The procedure can be performed as either an ascending or descending phlebography. In an ascending phlebography contrast medium is injected into a foot vein and directed into the deep veins by applying a tourniquet at the ankle. It is used to diagnose deep vein thrombosis and the resulting chronic obstruction.[3]

In a descending phlebography contrast medium is introduced into a cannula inserted into the femoral popliteal vein with a patient in a standing position.

The patient is asked to initiate a Valsalva manoeuvre which increases abdominal pressure resulting in closure of valves within the veins. During this procedure any reflux of contrast medium distal to the injection site is recorded on the x-ray. The level of reflux is then allocated one of five grades: grade 0 indicates no reflux; grade 1 indicates reflux in the superficial femoral vein, but not below the middle of the thigh; grade 2 indicates reflux of the superficial femoral vein down to the popliteal vein; grade 3 indicates reflux to a level just below the knee, indicating competent popliteal veins; and grade 4 indicates reflux of the femoral popliteal and calf veins to the level of the ankle.[184-187]

2.2.2. Doppler ultrasound

Continuous wave Doppler ultrasound is used to detect reflux at the saphenofemoral and saphenopopliteal junction.[3] For the former the patient is asked to stand facing the examiner. A 5 MHz to 10 MHz probe is used to locate the femoral vein by asking the patient to conduct repeated valsalva manoeuvres or by repeated compression of the calf by the examiner. Both activities increase blood flow to the heart by the femoral vein, thus increasing the signal detected by the ultrasound. Once a femoral vein has been located, the calf is compressed manually and the pressure suddenly released. The absence of a signal during the sudden release indicates that reflux is not present. A signal lasting > 0.5 seconds indicates the presence of reflux.[188, 189]

To examine the saphenopopliteal junction the patient is asked to stand facing away from the examiner with their weight on the opposite leg and the knee

slightly flexed. The popliteal vein is located using the same techniques described above. The calf muscle is compressed forcing blood through the popliteal vein, and is then suddenly released. As with the femoral vein, any signal following the sudden release indicates reflux (> 0.5 seconds)[3].

This examination can only detect the presence of reflux, not localise the vessels affected. Duplex scanning is used to provide this additional information.

2.2.3. Duplex scanning

Duplex scanning uses ultrasound technology to diagnose a deep vein thrombosis, examine the shape of veins and the degree of reflux within veins. It is a combination of B-scan (picture) and Doppler (flow) [33]. A 4 to 7 MHz multi-frequency transducer is used to examine different areas (femoral, small and long saphenous and popliteal veins) within the venous system of the leg. Examinations are usually made with a patient in a standing position to increase venous pressure, or in a 15° reverse Trendelenburg position using a valsalva manoeuvre to increase venous pressure.[33, 190-192]

The cross-section provided by the scan enables identification of the contents such as aggregates of red cells, the movement of the venous valve, the lining of the vein wall, and the approximation of the anterior and posterior walls with compression.[193, 194] Any obstruction to flow, irregularities of the vein wall, or failure to compress is indicative of a deep vein thrombosis.

With the addition of colour (colour duplex scanning) information about blood flow and reflux can be determined. In normal veins, blood flows towards the heart in a rhythmic motion that reflects changes in thoracic pressure with inspiration and expiration. This blood flow, known as 'cephalic flow' is indicated by a blue colour within the lumen of the vein. During a scan cephalic flow is increased by applying pressure distal to the probe (e.g. a pressure cuff around the calf). Once the pressure is released, any blood that moves towards the foot (reflux) is represented by the colour red. In normal veins the red colour, or reflux, will last until the valve closes (usually < 0.5 seconds).[192, 195, 196] If red is seen within the lumen of the vein lasting longer than 0.5 seconds reflux is considered to be present.[197-201] In the absence of reflux the lumen is black.[3]

2.2.4. Thermography

Thermography has been used to identify incompetent perforator veins. The patient's leg is first raised to an angle of 45° thus emptying the superficial veins and any obvious varices. Tourniquets are applied above the medial malleolus and below the knee and inflated to 80 mmHg. The leg is lowered and the area to be examined cooled by gently rubbing the skin with ice cubes until a uniformly dark colour is seen on the scanner. The patient then plantar flexes the foot for 60 seconds and the thermal image is examined for white circular areas of 0.5 to 2 cm in diameter. Known as 'hotspots' these areas of increased temperature suggest possible sites of incompetent perforator veins.[202.] When compared with other investigations, thermography has been

found to have a sensitivity of 98 per cent when compared with phlebography and 91 per cent when compared with duplex scan.[202-205]

2.2.5. Ankle Brachial Index

Whilst confirmation of the disease using one or more of the above investigations is preferable, often in the clinical setting diagnosis of venous disease is based upon clinical presentation. However, prior to the implementation of treatment (principally compression) an ankle brachial index is calculated to exclude possible arterial disease that would be compromised by the application of compression[206].

This is performed by recording the patient's blood pressure at the ankle and arm. With the patient in the supine position, the ankle blood pressure is measured by inflating a sphygmomanometer cuff around the patient's ankle and using a Doppler ultrasound (fitted with a vascular probe) to detect the post tibial pulse as the cuff has deflated. The blood pressure at the arm is taken using the same technique. The systolic blood pressure from the ankle (A) is then divided by the systolic blood pressure from the arm, or brachial plexus (B) providing an index from zero to one (ABI = A/B).[207]

Significance of the index achieved is provided in Table 2. However, patients with diabetes or advanced arterial calcification may provide readings higher than 1.0 (> 1.2) but actually have advanced arterial disease. To help eliminate false positives resulting from this condition, a toe/brachial index is

calculated using a similar technique as described above but substituting an ankle blood pressure for one recorded at the great toe.[192, 208]

Index	Arterial status
0.9 – 1.0	Normal
0.75 – 0.9	Moderate disease
0.5 – 0.75	Severe disease
< 0.5	Limb threatening disease

Table 2. Relationship of Ankle Brachial Index to arterial status [192, 208]

2.3. Quantifying the degree of reflux

2.3.1. Ambulatory venous pressure

For patients with CVI, measuring the ambulatory venous pressure enables the degree of venous hypertension to be assessed. The examination originates from observations made by Pollack in 1949 (cited by Nicolaides et al.[3]) when he discovered that venous pressure of the foot decreased when walking.

A needle is inserted into the vein on the dorsum of the foot and is connected to a pressure transducer, which in turn is connected to a potentiometric pen recorder or computer. The patient then supports him or herself in a standing position by holding onto a frame. Using a frame to support the patient prevents contraction of the calf muscle resulting in inaccurate pressure measurements. A baseline or resting venous pressure is then recorded.

The patient is asked to plantar flex their foot ten times at a rate of one per second, and then remain still, while the time taken for the pressure to return to the baseline is measured in seconds. A pressure cuff is then inflated at the ankle to occlude superficial veins, and the above procedure is repeated. The procedure is repeated with the cuff position just below the knee, the lower thigh and upper thigh. The difference between the resting pressure (P_0) and the pressure recorded towards the end of the foot exercises (P_{10}) is calculated to give the ambulatory venous pressure ($P_0 - P_{10}$).[3] Different ambulatory venous pressures have been associated with differing underlying pathologies. Table 3 provides an example of the changes to P_{10} ambulatory venous pressure associated with underlying valvular incompetence (see Table 3).

Type of limbs	No ankle cuff	Ankle cuff inflated
Normal	15–30mm Hg	15–30mm Hg
Primary varicose vein and competent perforators	25–40mm Hg	13–30mm Hg
Varicose veins and incompetent perforators	40–70mm Hg	25–60mm Hg
Deep venous valve incompetence and proximal occlusion	55–85mm Hg	50–80mm Hg
Proximal occlusion and competent popliteal valves	25–60mm Hg	10-60mm Hg

Table 3 Values of ambulatory venous pressure at P_{10} (Adapted from Nicolaides et al.[209])

Although this examination remains the standard for validation of non-invasive tests, the invasive nature of direct venous pressure recording prevents its use in clinical settings. To compensate, a number of non-invasive methods have been developed.

2.3.2. Plethysmography

Plethysmography is the measurement of changes in blood volume. For patients with CVI it is used to examine blood flow and volume changes of the leg in an effort to quantify the degree of venous reflux.

2.3.2.1. Water plethysmography

Water plethysmography measures volume changes of the foot during exercise. Measurements are made using a box filled with water to a level of 14 cm, containing a photoelectric float sensor connected to a strip chart recorder or computer. The volume of blood within the patient's foot is decreased by asking the patient to undertake a series of knee bends, performed at a rate of one every two seconds. Once the exercise stops, blood volume within the foot increases to the pre-exercise state. The refilling displaces water within the box thus providing a measure of foot volume.[3]

When compared to studies undertaken in control groups the readings obtained can be used to calculate the volume expelled from the foot (EV), the rate at which it is expelled (EVR), and the refilling flow rate (Q). Dividing the refilling flow rate by the rate at which it is expelled (Q/EVR) provides a ratio that can be used to discriminate patients with normal venous return from those with CVI. The normal ratio has been reported as 1.5 to 2.8.[210-213]

Determining the location of any venous reflux can be achieved by using a tourniquet, at the knee and just above the ankle, to compress the superficial venous system and then repeating the exercise. Deep venous disease will provide the same Q/EVR ratio when the superficial venous system is compressed whereas superficial venous disease will show a change in its ratio when compressed.[3]

2.3.2.2. Air plethysmography

Air plethysmography measures the venous volume of the leg by recording the amount of air displaced in a specially designed chamber as the venous system refills. A 35 cm polyurethane tubular air chamber is placed around the leg, inflated to 6 mm Hg and connected to a pressure transducer, which is in turn connected to a computer[3].

The patient is placed in the supine position and the venous system is drained by elevating the leg to 45°. The patient is then asked to take their weight on the opposite leg. As blood drains back into the venous system it displaces air in the chamber surrounding the leg, increasing the pressures in the chamber, which is recorded by the pressure transducer and computer. Patients with venous incompetence have an increase in the volume of blood returning to the leg[3].

The volume recorded is known as 'functional venous volume'. In normal limbs this volume is 80 mls to 150 mls and can increase up to 400 mls in limbs with CVI.[214] The refill time after leg elevation taken for the leg to reach

90 per cent of its filling capacity is also recorded. This is known as a 'venous filling index' and is a measure of the average filling rate of the veins expressed in milliseconds. In normal limbs this is < 2 milliseconds which may increase up to 30 milliseconds in limbs with severe venous reflux.[214]

During the investigation the patient is also asked to plantar flex both feet (stand on tiptoes). The volume decrease during this activity is known as the 'expelled volume'. When the expelled volume (EV) is divided by the functional venous volume (VV) and multiplied by 100, the 'ejection fraction' (EF) of the calf muscle pump can be calculated: EF = (EV/VV) x 100). A normal ejection fraction is > 60 per cent;, 30 per cent to 70 per cent in limbs with primary varicose veins and 10 per cent in limbs with the venous disease.[214]

The remaining volume in the leg after the tiptoe exercises is also recorded. This is known as the 'residual volume' (RV) and, when divided by the functional venous volume and multiplied by 100, enables calculation of a residual volume fraction: RVF = (RV/VV x 100). In normal limbs, the residual volume fraction ranges from 5 per cent to 35 per cent; in limbs with primary varicose veins it ranges from 20 per cent to 70 per cent; and up to 100 per cent for sever venous disease.[214]

The calculation of the functional venous volume, ejection fraction and residual volume fraction enables performance of both the vein valves and calf pump to be evaluated. However, as this investigation requires specialised

equipment and operators, it is often confined to vascular laboratories and research projects.

2.3.2.3. Photoplethysmography

Photoplethysmography uses a light source, placed on the leg to transmit light through the tissue of the skin. A light sensitive diode records the amount of light present in the area of skin being examined. The number of red blood cells in the skin affects the amount of light passing through the tissue.

The patient is placed in a sitting or standing position and a baseline measurement (the amount of red blood cells in the peripheral circulation at rest) is recorded.[215] The venous system is then emptied by either raising the leg or by plantar flex of the foot as described above. The time taken for the reading to return to the baseline measurement is recorded. This is known as the 'venous refilling time'. Refilling times shorter than normal (< 20 seconds in the sitting position or 18 seconds in the standing position) indicate venous reflux as the vein is not emptied as efficiently as veins with normal valves.[216-218]

An inflatable cuff can be placed at the ankle or below the knee to occlude superficial veins. If the refilling time returns to normal after the application of the cuff, the veins affected are likely to be superficial. If the refilling time does not return to normal then the affected veins are likely to be part of the deep or perforator systems.

Establishing initial reliability for this technique proved difficult. Obtaining an accurate calibration and returning the reading to the baseline were difficult to achieve consistently. Further refinements of the system (in the 1990s) has improved the reliability of this technique.[219-222]

The ability of the above non-invasive investigations (photoplethysmography. air plethysmography and duplex ultrasonography) to accurately predict the severity of chronic venous disease has been examined. Using the Society for Vascular Surgery / International Society for Cardiovascular Surgery classification system (CEAP), Iafrati et al.[221] found that these investigations were unable to differentiate between CVI with ulceration and without ulceration. They concluded that the above investigations were appropriate for large vessel disease but insufficient for assessing changes to microcirculation thought to result in skin ulceration (see Chapter One).

2.4. Assessment of venous microcirculation

A number of investigations had been undertaken to examine the pathophysiology of skin lesions and CVI. These were principally used for research with little evidence of clinical application within the literature. They included skin biopsies, laser Doppler fluxmetry, transcutaneous oxygen tension and investigation of the microlymphatics.[3]

Traditionally, skin biopsies have been used to exclude malignant lesions in patients with non-healing leg ulcers. When assessing microcirculation,

biopsies are used to examine structural changes in the capillaries, lymphatic, and dermal tissue (see Chapter One).

Laser Doppler fluxmetry uses a light source in the red to near infrared range to measure the number and velocity of cells moving within the area under examination. The technique examines changes to micro blood flow, in response to a stimulus, or over time. Findings are reported as a 'red cell flux'. Patients with lipodermatosclerosis resulting from CVI have been found to have an increased flux.[223]

Transcutaneous oxygen tension is measured using an electrode which is heated to 45°C to induce hyperaemia. This method measures surplus oxygen molecules available for diffusion to the skin surface from the capillaries under hyperaemia conditions.[3] Patients with CVI exhibit a significant decrease in transcutaneous oxygen tension associated with changes to the blood capillaries (see Chapter One). The decrease in transcutaneous oxygen tension is linearly related to a reduction in capillary density.[224, 225] The method is principally used in research investigating skin changes leading to ulceration.

Fluorescence microlymphography is used to examine the structure and function of the lymphatics of the skin. Fluorescein isothiocyanate is injected below the epidermis using a micro needle. The dye is cleared via the lymphatics within the area injected. The spread of the dye is visualised using an incident light fluorescence microscope.[3] Structural changes to the micro

lymphatic system have been demonstrated in patients with skin areas of induration and hyper pigmentation using this technique.[226, 227]

Lymphoscintigraphy is also used to examine the lymphatic system, principally in patients with lymphoedema. Radioactive plasma proteins are injected into the web space between the second and third toe, and a gamma-camera used track their progress. The time taken for radioactivity to become evident in the major lymphatic regional nodes is recorded, with fifteen minutes indicating rapid lymphatic transport and the absence of activity after an hour suggesting delayed transport.[3] Patients with CVI have been shown to exhibit a delayed lymphatic transport using this technique.[228] Once again this method is used principally for research with the limited clinical application.

Whilst the major application for techniques used to assess the microcirculation have been limited to research, assessment of clinical manifestations associated with CVI is principally performed in the clinical setting. Recording the patient's history, performing visual inspections, classifying the severity of varicose veins or skin changes, and assessing a patient's progress are common techniques used in the clinical environment.

2.5. Assessment of clinical manifestations

Problems associated with the absence of a clear definition for CVI were described in Chapter One. Similar problems plague the terminology used to describe the clinical manifestations of the condition. In an effort to provide

consistency for the communication of a patient's status, and comparison of interventions, a number of efforts have been made to reach consensus on terminology. Equally, a number of researchers have attempted to devise methods for quantifying signs and symptoms of the condition. The following describes the outcomes of these activities.

2.5.1. Classifying chronic venous insufficiency

There have been a number of classification systems proposed, and to detail each is beyond the scope of this chapter. The following provides a summary of key systems consistently identified in the literature.

In 1978, Widmer proposed a classification system based mainly on clinical signs documented by photographs taken by over 4000 health employees.[27, 229] The system provided two main categories: one for varicose veins; and one for CVI. Varicose veins were classified as telangietases, reticular veins or trunk varicoses.[230] CVI was categorised into three grades based on the clinical signs presented. Patients were classified as: *Grade I* if dilated subcutaneous veins were present; *Grade II* if there were skin changes evident; and *Grade III* if the patient had a venous ulcer.

In 1988, Porter et al.[230, 231] created a classification for CVI intended as a reporting standard for publications. It consisted of four classes:

Class 0 was asymptomatic.

Class 1 had mild signs and symptoms including mild to moderate ankle swelling and local or generalised dilation of subcutaneous veins.

Class 2 had moderate signs and symptoms including hyper pigmentation of the skin, moderate oedema, subcutaneous fibrosis, and prominent local or regional dilation of subcutaneous veins.

Class 3 had signs and symptoms of severe CVI, including ulceration and severe oedema. This class was usually associated with deep venous system disease and widespread loss of valvular function.

In 1995, the American Venous Forum presented the CEAP classification system. This classified patients according to their: clinical signs (C); aetiology (E); anatomic distribution (A); and pathophysiology (P).[3, 27, 31-33] Clinical signs were divided into seven classes (C_0 to C_6) with 0 being no signs and 6 being the most severe (see Table 4). Aetiology was divided into: congenital (E_c); primary (E_p); or secondary (E_s). Anatomical distribution was divided into: superficial (A_s); deep (A_d); or perforator (A_p); alone or in combination. Pathophysiology was divided into: reflux (P_r); or obstruction (P_o), alone or in combination.[3, 5, 31-33]

Class	Clinical indication
C_0	No visible signs of venous disease
C_1	Telangietases or reticular veins
C_2	Varicose veins
C_3	Oedema
C_4	Skin changes, including pigmentation, venous eczema, and lipodermatosclerosis
C_5	Skin changes as above, with healed ulceration
C_6	Skin changes as above, with active ulceration

Table 4. C classes of the CEAP classification system
(Adapted from Nicolaides[3])

The classification has received a number of criticisms.[232] The requirement for exhaustive investigations and detailed clinical examination makes it difficult to use in everyday practice. A lack of precision for the subcategories makes it difficult to use the classification system consistently. For example, classes $C_{4, 5, 6}$ are cumulative in that the criteria of the lower classes validate the higher class (e.g. oedema is present prior to ulcer formation). The same is not true for classes $C_{1, 2}$. If the patient has varicose veins will they also have telangietases or reticular clinical signs? The patient's venous history is also not included in the classification. A patient with varicose veins (C_2) who receives successful treatment would revert to class (C_0). Any epidemiological surveys examining the prevalence of venous leg ulcers based on this classification would therefore be inaccurate.[232]

Questions about the inter-rater reliability of the system have also been asked. Antignani et al.[233] surveyed 3681 plebologists to compare terms used in everyday language with the seven classes used in the C category of the CEAP. Although the response rate was low (n = 206, 5.6 per cent) they demonstrated a wide variety of opinions about basic descriptions of conditions used in venous dysfunction. In addition, only 60 per cent of the physicians who responded actually used the CEAP classification in their practice.

In response, the CEAP classification system was revised in 2004 to incorporate more precise definitions.[234] C_4 was divided into two subgroups: C_{4a} for pigmentation and eczema; and C_{4b} for lipodermatosclerosis or

atrophie blanche. In addition, a designation was added to identify if symptoms were present ($_S$) or absent ($_A$). For example, a patient with varicose veins, lipodermatosclerosis and reporting symptoms (e.g. pain, itchiness, heaviness) would be classified as $C_{2,4b,S}$. A new descriptor was added to the E, A and P classification to identify that no venous abnormality had been identified ($_n$). For example, E_n depicted no venous cause identified, A_n depicted no venous location identified, and P_n indicated that no venous pathophysiology had been identified.

Ekolf et al.[234] further recommended that documentation of any of the CEAP classification system be followed by the date, for example $C_{2,4b,S,}$ $E_{p,}A_{s,p}$ P_r (2007-08-01). In addition, a *level of testing* should be indicated:
Level I (LI): office visit, with history and clinical examination, which may include use of a handheld Doppler scanner.
Level II (LII): non-invasive vascular laboratory testing, which includes duplex colour scanning, with some plethysmography method added as desired.
Level III (LIII): invasive investigations or more complex imaging studies, including venous pressure measurements, computerised tomography, or magnetic resonance imagery.[234]
Thus, using this classification for a patient with the same clinical scenario described above, who had undergone duplex scanning, the documented classification would be $C_{2,4b,S,}$ $E_{p,}A_{s,p}$ P_r (2007-08-01, LII).

Such changes addressed many of the criticisms concerning precise definitions. However, the patient's venous history is still not captured and the

obvious complexity increases the likelihood of it not being implemented by busy clinicians. Full implementation will probably have to wait until automated systems are developed that collect various parameters from the patient's assessment and investigations, then assigns the relevant CEAP classification.

In parallel with the development of the CEAP system Rutherford et al.[235] developed the Venous Clinical Severity Score. Using the seven classes of the C classification they assigned a 0 to 3 grading scheme to certain clinical manifestations (see Table 5). This provided a severity score, which Rutherford et al.[235] argue allowed practical assessments of changes in response to treatment or adverse events.

Attribute	Absent = 0	Mild = 1	Moderate = 2	Severe = 3
Pain	None	Occasional: not restricting activity or requiring analgesics	Daily: moderate activity limitations, occasional analgesics	Daily: severely limiting activities or requiring regular use of analgesics
Varicose veins	None	Few: scattered: branch varicose veins	Multiple: GS varicose veins can find the calf or thigh	Extensive: thigh and calf or GS and LS distribution
Venus oedema	None	Evening: ankle oedema only	Afternoon: oedema above ankle	Morning: oedema above the ankle requiring activity change and elevation
Skin pigmentation	None or focal, low intensity	Diffuse, but limited in the area and old (brown)	Diffuse over most of gaiter distribution or recent pigmentation (purple)	Wider distribution (above the lower 1/3), and recent pigmentation
Information	None	Mild cellulite: limited to marginal area around ulcer	Moderate cellulite: involving most of the gaiter area	Entire lower leg and more
No. of active ulcers	0	1	2	>2
Active ulceration duration	None	< 3 months	> 3 months, < 1 year	Not healed > 1 year
Active ulcers' size	None	< 2 cm diameter	2 cm to 6 cm diameter	> 6 cm diameter
Compressive therapy	Not used or not compliant	Intermittent use of stockings	Wears elastic stockings most days	For compliance: stockings plus elevation

Table 5. Venous Clinical Severity Score
(Adapted from Rutherford[235])

Rutherford et al.[235] further added a Venous Segmental Disease Score, which was calculated by assigning venous segments with reflux or obstruction a numerical score (see Table 6). Disease segments of the venous system were identified using a duplex scanner. They recommended that the Venous Clinical Severity Score and Venous Segmental Disease Score both be used rather than one or the other.

Reflux	**Obstruction**
1/2 Lesser saphenous	
1 Greater saphenous	1 Greater saphenous (only if thrombosed from groin to below knee)
1/2 Perforators, thigh	
1 Perforators, calf	
2 Calf veins, multiple	1 Calf veins, multiple
2 Popliteal veins	2 Popliteal veins
1 Superficial femoral vein	1 Superficial femoral vein
1 Profunda femoris	1 Profunda femoris
1 Common femoral vein and above	2 Common femoral
	1 Iliac vein
	1 IVC
10 Maximum reflux score	**10 Maximum obstruction score**

Table 6. Venous Segmental Disease Score
(Adapted from Rutherford[235])

Once again, the clinical application of the system is limited by the complex nature of the classifications and the requirement for comprehensive investigations and detailed clinical assessments.

2.5.2. Measuring leg oedema

Whilst plethysmography enables a venous volume of the leg to be determined additional tests are required to determine the volume of fluid within the interstitial space, or oedema. These investigations are either direct or indirect measurements of leg volume; the former using water displacement or leg measurement techniques, and the latter using mathematical equations.

2.5.2.1. Direct methods

Water displacement volumetry uses a similar technique to that of water plethysmography. The patient places their leg in a water tank, equipped with two overflow tubes or a photoelectric float sensor connected to a strip chart recorder or computer. The water is heated to 29°C because the skin of the lower leg and ankle are approximately this value. The amount of water displacement when the patient places their leg in the tank indicates the volume of their leg. This can be compared to known figures from control

groups or compared at subsequent clinical reviews to establish that oedema is reducing.[236]

Another direct method is to measure the leg circumference at the calf. An instrument known as the Leg-O-Meter[237, 238] has been used to ensure consistent measurements across clinical visits. This instrument consists of a tape measure fixed to a stand which is in turn attached to a small board that the patient stands on. Having the tape fixed to a stand means the measurement of the patient's calf is always taken in the same location, facilitating comparison across clinical examinations.

Berard et al. [237-239] have undertaken a number of studies to examine the validity of the Leg-O-Meter. In 2002, they compared measurements taken with the Leg-O-Meter with the observations of experienced physicians. The Sample included 1521 patients and 243 physicians from France, Belgium, Italy, and Quebec. Clinical variation in oedema was assessed as: improved if that oedema was present at baseline and absent at final visit; unchanged, if that oedema was present at both visits; and worse, if oedema was absent at baseline and present at final visit. This assessment was compared with those made by the physicians and the researchers concluded that the Leg-O-Meter correlated with the physician's opinion in 84 per cent of cases. Although limited by the subjective opinion of the physicians, the results seem to indicate physicians perceive an increase in calf diameter as an increase in oedema.

2.5.2.2. Indirect methods

Indirect methods of measuring leg oedema use mathematical formulas. One method assumes that a swollen limb can be visualised as a cone that is reduced to its 'frustum' (a slice taken between the base and a plane parallel to the base).[236] It requires a measurement from the lower and upper circumferences of the lower leg, and the distance between them.

Another method divides the leg into discs. The total volume is equal to the sum of the individual disc volumes. The circumference of the leg is measured every 3 cms and the volumes are added to come up with a total leg volume.[236]

Kaulesar et al.[236] compared the truncated cone and disc methods with water displacement volumetry. They measured the lower leg volume of twenty healthy male amateur soccer players. The results indicated that there was considerable discrepancy between the truncated cone method and the results received by water displacement volumetry, but a high correlation (r = + 0.99) with the disc method. They concluded that the water displacement volumetry and disc model methods were interchangeable with the latter providing a technique that could be used in clinical settings more easily. Further research using patients with CVI was not identified.

Magnetic resonance imagery has also been explored as a potential tool for diagnosing leg oedema.[240, 241] Haaverstad et al.[240, 241] used an MRI to

investigate the oedema of twenty-eight patients following reconstructive surgery, or with chronic lymphoedema. They were able to illustrate different compartments of oedema within the different groups of patients (surgical and lymphoedema) and concluded that the magnetic resonance imagery may be a useful diagnostic tool for diagnosing oedema but requires further investigation.

2.6. Assessment of venous leg ulcers

Four principal themes are evident in the literature pertaining to the assessment of venous leg ulcers: clinical history; observation of the surrounding skin; examination of the ulcer bed; and the measurement of ulcer dimensions.

2.6.1. Clinical history

In conjunction with a normal medical examination, a number of authors recommend the collection of specific ulcer related data: the patient's age at the onset of ulceration; the number and duration of any previous leg ulceration; previous history of deep vein thrombosis; duration of the current ulcer; family history of venous ulceration and site of the current ulcer were frequently identified.[84, 110, 178, 242-245] The proponents argue that the above data set provides the clinician with insights into the severity of the underlying CVI and the healing properties of the patient.[84, 110, 178, 242-245]

2.6.2. Measuring ulcer dimensions

Measuring ulcer dimensions is recommended by a number of authors as it provides objective criteria for assessing ulcer healing outcomes.[246-253] Traditionally three dimensions are assessed: linear measurements; area measurements; and volume measurements.

2.6.2.1. Linear measurements

Linear measurements are based on the assumption that a wound is a simple shape represented by two dimensions. Conjecture over the type of shape is evident within the literature. Commonly a rectangle is used, but some authors argue that a wound is circular or elliptical in shape. The former is measured using length and width, whereas the latter requires the measurement of wound diameter(s).[248, 254]

Most clinicians measure a wound as if it is rectangle, recording the length and width of the wound. Length is measured by recording the distance of the longest section of the wound, and width by measuring the widest section of the wound, perpendicular to the length (see Figure 3).[246, 250, 253, 255] A disposable ruler is used to measure the length and width to prevent contamination of the wound. Although a simple technique, it fails to accommodate for wound shape and suffers from poor inter-rater reliability as

the length and width axis varies from clinician to clinician. To help maintain a similar axis a 'clock face' has been suggested.[256] The length measurement is always taken between the patient's head and feet and the width measurement between the left and right arm. Regardless of the wound's location the axis remains similar (see Figure 3).

If a circle is used as the basic shape (e.g. an arterial ulcer) the diameter of the wound is measured.[248] The technique is similar to length and width, using a disposable ruler and taking two measurements of the diameter of the wound at right angles to each other providing length and width. If an ellipse is used as the basic wound shape, then the major and minor diameter are measured.[257] The major diameter is the maximum diameter of the wound and the minor diameter is a measurement of the maximum diameter perpendicular to the major diameter (see Figure 4).

2.6.2.2. Surface area measurements

The area of an ulcer is calculated by multiplying two perpendicular linear measurements. The product is represented as square centimetres (cm^2). If the rectangular shape is used, length is multiplied by width (e.g. 2.1 cm x 3.5 cm = 7.35 cm^2). The surface area is often captured by tracing the wound onto a clear plastic sheet. The technique was pioneered by Lecomte du Noüy (cited by Copper[258]) in 1937 using cellophane sheets to build a library of sequential tracings in an effort to evaluate healing. Using this data, he

defined the ‘index of cicatrisation’ or scar tissue formation calling it a constant property of a wound.

Since then a number of commercial products have been made available to facilitate the tracing of wounds. They commonly contain two sheets of plastic; one which is placed against the wound and a second on which the tracing is recorded. The sheet against the wound is then discarded to prevent contamination and the sheet containing the tracing is placed in the patient's documentation or is used to calculate the surface area and is then discarded. Commercial tracing sheets generally have a 1 cm by 1 cm grid printed on the first sheet to facilitate calculation of the surface area (see Figure 5).

Bohannon and Pfaller[259] termed this technique ‘graph paper counting’ as clinicians had to count the number of complete squares within the wound margin and estimate the remaining area covered by partial squares of the graph. They suggested that this was time consuming and subjective. An alternative and more accurate method was to cut out the tracing of a wound and weigh it to determine surface area. The heavier the cut out section of tracing, the larger the wound surface area. Unfortunately, gaining access to precision scales required for this technique has prevented its adoption in the clinical setting.

As with linear measurement, the ulcer surface area has a potential for inaccurate findings related to the underlying assumptions of wound shape and inter-rater reliability. For example, using the product of length x width

(rectangular shape) is said to overestimate the surface area of a circular wound by approximately 25 per cent.[248]

In an effort to improve the reliability of surface area measurements digital planimetry techniques have been introduced.[3, 248, 259-262] Initially wound tracings were scanned to produce a digital image and computer algorithms used to calculate the surface area. As the technology has developed digital photographs have replaced the scanned images. Reliability of digital planimetry techniques have been established by comparing measurements made of latex moulds with the known surface area of the moulds.[263, 264]

Until recently the technology required for digital planimetry was expensive and often too cumbersome for the clinical context. However, the recent introduction of portable devices such as Visitrak® has provided clinicians with robust and inexpensive technology utilising this technique. This system uses a tracing of the wound which is placed on a pressure sensitive tablet. The clinician then retraces the outline of the wound using a stylus. Based on the area outlined by the clinician the width, length and surface area is calculated and displayed on a liquid crystal display on the device. Studies comparing the accuracy of Visitrak® with previous validated digital planimetry systems have demonstrated high correlation and inter-rater reliability.[265-267]

Recent developments in robotic vision have provided some additional, non invasive tools for measuring wound diameters. The use of ‘structure light’ and computer image analysis has provided systems that can measure the area of a wound. Structure light uses parallel lines or dots of light to provide

reference points in a digital image. Light reflected from the base of an ulcer will distort the lines or dots of light. Computer algorithms are then used to detect this change and outline the area of distortion. The area outlined is then measured, giving the area of the wound.[268] Proponents argue that such systems provide a detailed topographical map of the wound which enables more precise measurements of wound healing. The disadvantage of such system is that a darkened room and specialised equipment is required.[269]

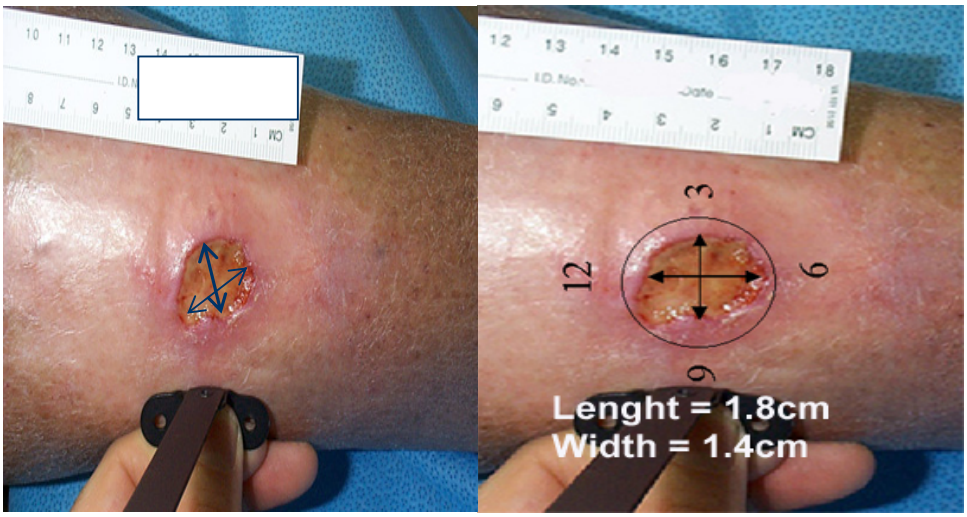


Figure 3. Alternative measurement techniques for length and width

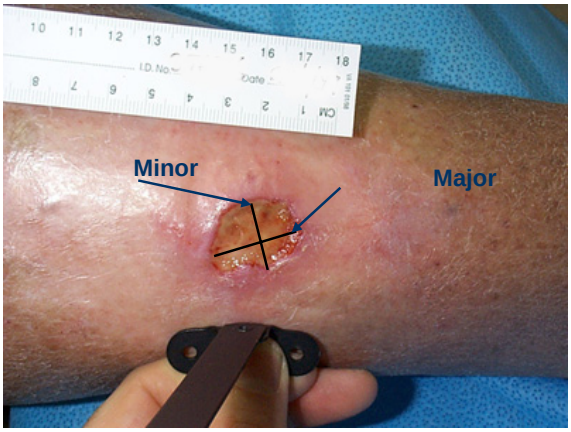


Figure 4. Dimensions measured for an elliptical shape

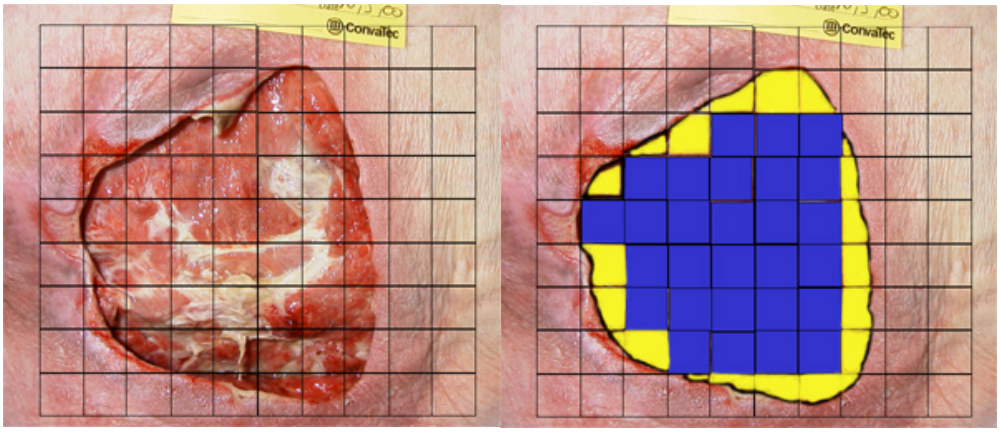


Figure 5. Graph paper counting technique

2.6.2.3. Depth and volume measurements

A common method for measuring the depth of a wound is to insert a sterile probe, tipped with cotton wool into the deepest part of the wound. The probe is pinched between thumb and finger level with the skin, the probe removed and the distance between the end of the probe and the thumb and finger measured using a ruler.[256]

This method is most successful for deep wounds, or wounds with a sinus track such as pressure ulcers. Measuring depth in shallow wounds such as venous leg ulcers is difficult to achieve using this method.[248] Stereophotogrammetry has been suggested as an alternative for shallow wounds. A stereocamera connected to a computer was used by Bulstrode et al.[270] to capture the dimensions of chronic venous leg ulcers. They compared the system with direct tracing and simple photography and concluded that Stereophotogrammetry was between five and ten times more accurate than the other methods. Although portable, the user sophistication and technology required to capture and analyse the image has prevented mainstream use.

A user-friendly and cost-effective method was suggested by Kundin[271, 272] when he developed the *wound gauge*. This disposable device consisted of cardboard rulers arranged to represent the Cartesian coordinate system of X, Y and Z axes. The X and Y axes formed the horizontal crossarms of the device while the Z axis formed a sliding vertical ruler. The X axis was labelled N (North) and S (South). The Y axis was labelled E (East) and W (West). The

patient was placed in a position that enabled ready access to the wound, the vertical Z axis placed into the deepest section of the wound and the crossarms moved down the Z axis until they touched the skin. The following procedure was used to calculate the surface area:

1. N + S = value A
2. E + W = value B
3. Multiply (A x B) by .785

To calculate the wound volume the following procedure was recommended:

1. N + S = value A
2. E + W = value B
3. Depth reading of vertical axis = value C
3. Multiply (A x B x C) by .327

Although no data was cited, Kundin[271, 272] claimed that in clinical trials the instrument proved to be safe, and correlated well with standard methods of measurement such as planimetry or fluid measurements. Once again, this instrument would be hard to use in shallow wounds such as venous leg ulcers.

Johnson[273] proposed a further simplification stating that wound volume could be calculated by multiplying the surface area by the maximum depth. He proposed several mathematical formulae that used the measurements of length, width and depth to calculate the surface area and wound volume. Johnson[273] believed that as the formulae could be calculated using a hand-held calculator they were suitable for clinical environments.

Two additional methods for measuring wound volume have been used; saline fills and casting. Filling a wound with sterile saline provides a safe method of calculating wound volume. However, it only provides volume not the surface

area, and it is difficult to perform on shallow wounds or in wounds where the top of the wound cannot be positioned horizontally.

Casting of wounds to determine volume has been used since the 1960s. A variety of materials have been used, including those used for dental impressions,[274, 275] silastic foam dressings,[276] and foam elastomer.[277] Once the materials solidified within the wound the mould was removed and placed in a graduated cylinder partly filled with water. The volume of the wound was determined by the amount of water displaced, similar to the leg oedema measurements described above. The introduction of a foreign body into a wound is not without hazard and wounds with several undermined areas would make removal of the mould difficult. Once again, this method is better suited to deep wounds rather than the shallow venous leg ulcer.

2.6.2.4. Wound measurements as a predictor of healing

Several authors argued that in order to accurately access the efficacy of various management methods a valid *rate of healing* needs to be calculated.[192, 251, 278, 279] However, trying to calculate a healing rate requires a number of variables to be considered. For example, large deep wounds have a larger surface area and can create greater amounts of new tissue in a given time than superficial wounds. This creates a deceptively faster healing rate in larger or deeper wounds than superficial wounds, even if both wound types are contracting at the same linear rate (length and width).[280, 281] Therefore, any models used to calculate healing rate should be independent

of the area and/or volume of a wound.[281] Equally, the rate of change of wound area progressively decreases as the residual wound area approaches total closure.[282] Thus, any models used to calculate healing rate also need to account for this progression curve.

Denouy (cited by Robson[282]) developed an equation that plotted a curve that he believed was a theoretical representation of wound healing. The equation included the percentage healed over time and made allowance for the reduction in healing towards the end of the healing cycle. Further development of this theory, including validation studies, was not evident in the literature.

The majority of methods cited since Denouy have returned to using linear measurements in preference to exponential curves of healing. Gillman[278, 283] introduced the concept of using wound perimeter to account for distortions in healing rate that result from deep verses shallow wounds. The equation ($d = 2^* (A_2 - A_1) / (P_1 + P_2)$) used the change in wound area (A), and the change in wound perimeter (P) between two consecutive visits. The wound area was calculated using the techniques described above. The wound perimeter was measured by tracing the wound using plastic sheets (see above) or a digital photograph which was then traced on screen and measured using appropriate software.

Gillman[278, 283] argued that linear measurements provided a more reliable method for calculating healing rate and hence wound healing progress. He

asserted that area based parameters such as absolute change in area, or the percentage change in area (used by the majority of wound care studies) were biased by differences in wound size. As mentioned above, deeper wounds can demonstrate a much larger healing rate than superficial wounds. By measuring linear changes between sequential visits Gillman[278, 283] believed that he eliminated this bias. As an example he cited two wounds; one with a surface area of 42.73 cm^2 (A) and another with a surface area of 8.90 cm^2 (B). At the next sequential visit the surface area for wound A was 21.817 cm^2 and wound B was 1.37 cm^2 – a reduction of 20.92 cm^2 and 7.53 cm^2 respectively. This would indicate that wound A has a greater healing rate. When using the linear parameters described in Gilman's formula each wound has advanced 0.96 cm, resulting in the same healing rate.

Using Gillman's equation, Margolis[284] collected data from patients suffering from venous leg ulcers, diabetic ulcers and deep pressure ulcers. They reported a liner healing rate of 1.12 mm / week for venous leg ulcers, 0.64 mm / week for diabetic ulcers and 0.28 mm /week for pressure ulcers. Using these finding they were able to compare a new treatment for the pressure ulcer group (Warm-a-wound®) demonstrating a 0.84mm / week heal rate, three times faster than the controls.

Ramirez[285] used linear measurements to examine the healing rate for acute surgical wounds created on volunteers. They calculated a mean healing rate of 7 mm / week, six to twenty-five times faster than that for chronic wounds cited in the above study. Gillman[278, 283] argued that findings from both studies

demonstrate the validity of liner measurements (e.g. acute wounds heal faster than chronic) and therefore can be used to draw comparisons across patient populations and episodes of care.

Margolis[284] and Gillman[278, 283] both asserted that healing rate calculations could be used to predict *time to total healing*. Using the healing rates established for venous leg ulcer patients (see above), Margolis postulated that it was reasonable to expect that ulcers responding to treatment (principally compression) would reduce by a third in four weeks and be healed by week twelve.

Tallman et al.[260] used Gilman's equation to examine the healing rate of venous ulcers in elderly patients. They found that Gilman's equation was 'inherently unstable' and devised a new method to calculate the rate of healing. Instead of using data from baseline visits only, as in Gilman's equation, Tallman et al.[260] calculated the healing rate at each visit by averaging the healing rate for all previous visits. They called this method a 'mean-adjusted healing rate' and asserted that it provided a more reliable method of predicting final healing status. The study demonstrated a healing rate of approximately 0.7 cm to 0.9 cm per week when calculated from week to week as opposed to 0.2 cm to 0.4 cm per week when calculated from the baseline visit only (Gilman's equation). They concluded that this was a more accurate measurement of week by week progress and, upon further analysis, were of the opinion the new methods were able to accurately predict ulcer healing as early as the third week of observation. However, it is important to

recognise that this data was derived from fifteen patients only and subsequent studies were not evident in the literature.

Hokanson et al.[286] proposed an alternative method using mathematical modelling and endpoint analysis to calculate wound closure estimates. Their method left the wound parameters in their raw form which was believed by the authors to be an advantage over Gillman's equation. Reliability of the method has been tested in large animal studies but not with human wounds. Once again, further studies using this method were not evident.

Despite the reservations postulated by Gilman[278, 283] a number of researchers have continued to examine the use of area based measurements as a predictor of wound healing. Skene et al.[245] attempted to develop a simple scoring system that predicted healing prognosis for venous leg ulcers. A series of parameters were examined with the results suggesting that ulcer area, duration of ulceration, age of the patient, and a history of deep vein thrombosis provided the best predictors for wound healing. Using regression analysis, a score was assigned to each parameter and summed to provide a 'prognostic index'. The index was then compared to the time required to heal by patients in the study. Patients with a prognostic index of 1 to 4 had a median time to heal of 40 days. Patients with an index of 4.5 to 5.5 had a median time to heal of 70 days, and patients with an index of ≥ 6 had a median time to heal of 118 days. The authors concluded that these findings provided significant justification to incorporate the prognostic index into future studies comparing methods of treatment.

Robson et al.[282] examined the usefulness of wound healing trajectories in which the percentage of wound closures versus time of wound treatment was plotted on a graph. They believed the advantage of this method was that it takes into account data from patients who have not completed the entire course of the study and can thus be used across large patient populations. To test the theory they examined the wound healing trajectories of 160 diabetic neuropathic ulcers and found that the trajectory was almost identical in patients achieving complete healing. They concluded that this method provided more information about the entire continuum of the wound healing process and, once replicated across larger samples, may provide a reference against which interventions can be examined.

More recently Margolis et al.[208] have revisited the use of wound parameters to predict healing rate. They used logistic regression analysis to analyse data from 20,793 patients with a venous leg ulcer. The study was built on work undertaken in 2000[287] in which they demonstrated that *wound area* and *wound age* could be used to accurately predict patients who would do well using standard compression therapy. The findings supported this assertion. Using simple prognostic models the researchers concluded that a wound ≤ 10 cm^2 and ≤ 12 months old has a 29 per cent chance of not healing by the 24th week, whereas a wound > 10 cm^2 and > 12 months old had a 78 per cent chance of not healing. Given the size of the sample, it would seem logical that these findings can be generalised at least to patients with venous leg ulcers undergoing compression therapy.

2.6.3. Visual assessment of a venous leg ulcer

Visual assessment of the ulcer bed and the surrounding skin is consistently promoted within the literature describing the assessment of venous leg ulcers.

Recommendations for assessing the skin surrounding a venous ulcer rely heavily on visual examination. It is recommended that clinicians observe for hyper pigmentation, lipodermatosclerosis and eczema.[84, 89, 100, 110, 178, 242-245, 288-290] Comparisons are drawn between the observations made and the presentation of a normal limb, or between the current presentation and previous presentations for that patient. It is assumed that the development of skin changes or an increase in their severity is indicative of increasing CVI or of inadequate treatment.[61, 68]

Johnson[291] recommended the use of indices to help objectify assessment of hyper pigmentation and liposclerosis, ranging from 0 (absent) to 3 (severe). Content validity was assessed by seeking the opinion of nine experts selected from nurses, physicians, surgeons and dermatologists. However, further validation of the proposed indices was not evident in the literature.

Ulcer bed assessment, as with surrounding skin assessment, relies heavily on visual observation. The bed of the ulcer is observed for the type of tissue present (granular, necrotic) and the amount of exudate produced. The ulcer margins are observed for erythema (redness) and maceration (whiteness).[292]

The observations are predicated on a theory that wounds heal by passing through four stages of healing. The first stage is the *inflammatory stage* when tissue damage results in an inflamed response including increased vessel permeability, oedema of surrounding tissues and the presentation of erythema (redness) around the wound. The second stage, known as the *destructive stage*, refers to the removal of necrotic tissue via a phagocytic mechanism making room for the new tissue. The third stage, known as the *proliferative stage*, refers to the rebuilding of the collagen matrix (granular tissue), new blood vessels and filling the deficit created by the initial injury. The fourth and final stage, known as wound contraction, refers to the migration of epithelial cells over the granular bed and completion of the skin barrier.[293-297] It is argued that observations of tissue type present in the ulcer bed and the status of the ulcer margins enable clinicians to determine if the ulcer is following the above healing trajectory.[298]

The subjective nature of the above assessment limits use of the observations to clinical episodes only. Attempts to use data derived from these observations to establish normal distributions of relevant manifestations, or to compare different interventions is limited by the subjective perception of the clinician collecting that data. Lorentzen et al.[299] asked six specialists in wound management to independently assess 120 photographs of non-healing chronic wounds. Participants were asked to diagnose hypergranulation, redness and infection. After examining the frequency with which respondents diagnosed each clinical manifestation (hypergranulation 2 per cent to 36 per cent, redness 15 per cent to 55 per cent, infection 48 per

cent to 85 per cent) they concluded that the reliability of the clinical diagnosis was low.

When describing how clinicians should undertake human wound assessment Cooper[258] stated:

> "Assessing the appearance of the wound, with an overall 'gestalt' is not now, nor ever, 'good enough'. Progression and regression in healing must be measured using theoretically sound, tested, technically practical ways, even if at first these measurements are less than perfect." (p. 553)

In an effort to standardise ulcer bed and margin assessments, a number of systems have been proposed. They include the use of colour, assigning the clinical manifestations a score, and the development of a wound bed preparation framework.

The use of colour as an assessment criterion when evaluating venous leg ulcers is abundant throughout the literature.[96, 255, 258, 300-309] The III Colour Concept® first introduced by Marion Laboratories in 1988 is the most frequently cited. The system, built upon the Red-Yellow-Black classification schemes developed in 1983 by Hellgren (a Swedish dermatologist),[309] asked clinicians to determine the predominant colour being displayed in the ulcer bed. Red represents granular tissue, yellow represents wet necrotic tissue or slough, and black indicates dry necrotic tissue or eschar.

Since its introduction in the US in 1998 by Cuzzell[301] the system has gained in popularity and can be found in articles pertaining to both acute and chronic

wounds. Introduction of the system has been facilitated by manufacturers of dressing products, who have found it a particularly useful model for helping clinicians select wound care products. Clinicians are taught to select products that protect red wounds, clean yellow wounds and debride black wounds. Given the increasing number of products available on the market, a model that simplifies clinicians' choices is often readily accepted, hence the continued support for the Red-Yellow-Black system.

Despite the popularity of the Red-Yellow-Black system, investigation of its reliability has not been exhaustive. In 1998 Lorentzen et al.[310] undertook a study to examine inter-observer agreement of health care personnel using the Red-Yellow-Black system. Twenty-one participants were asked to rate 120 wound photographs. As with their previous study (see above) the inter-observer agreement was only rated as 'moderate'. In contrast, Buntinx et al.,[311] when comparing different wound classification systems, found inter-observer agreement to be good when using a system with three colours; red, yellow and black. Equally, Vermeulen et al.[309] found similar positive results. They presented eighteen photographs of red, yellow and black wounds to 63 nurses and 79 doctors. The responses were compared to an expert panel of two international and four local wound care experts. They also found moderate to good agreement on wound colour, which was similar for both nurses and doctors.

Whilst these results are encouraging it is important to remember that these are one-off assessments and provide little data about the reliability of this

method for episode to episode or ongoing assessments. Equally, correlations between these observations and the physiological processes being observed have yet to be determined.

In 1995, Johnson[291] modified the III Colour Concept® to include *pink* and assigned a score to each tissue type. Black (necrosis) = 1; yellow (exudate / yellow necrosis) = 2; red (revascularisation granulation tissue present) = 3; and pink (new tissue, reepithelialisation) = 4. The lower the score, the lower the wound status index. The system was tested using 156 community patients in Melbourne. Patients were assessed during an initial visit and then again four to five weeks later. They found that the wound status altered substantially over four weeks which was not reflected in the wound status index scores assigned by the clinicians. Johnson concluded that inter-rater reliability was therefore low for this method (r_s = .49).

A major criticism of the colour system is that it is predicated on the healing cycle of acute wounds. Shultz et al.[312] argued that basing assessments of chronic wounds, such as venous leg ulcers, on the healing cycle of acute wounds fails to provide adequate assessment of the complex physiological processes identified in the chronic wound (see Chapter One). They argued that assessment for chronic wounds should use a *wound bed preparation* model. Wound bed preparation was defined as:

> "the global management of the wound to accelerate endogenous healing or to facilitate the effectiveness of other therapeutic measures" (Falanga, cited by Schultz[313] p. 22)

Four assessment parameters were identified as essential: tissue viability; infection and inflammation; moisture balance; and the edge of the wound. With financial support from Smith and Nephew Pty. Ltd. an international Wound Bed Advisory Board was established in 2003 that formulated the key assessment parameters into a TIME mnemonic[312-315] (see Table 7). The system, with accompanying pictures, was published widely in a variety of marketing materials provided by Smith and Nephew. The framework was accepted by member countries of the World Healing Union in Paris in 2005. The system has yet to be validated by research.

Clinical observation	Proposed pathophysiology	WBP clinical actions	Effect of WBP actions	Clinical outcomes
Tissue	Defective matrix and cell debris impair healing	Debridement	Restoration of wound base	Viable wound base
Infection	High bacterial counts or prolonged inflammation	Remove infected foci	Low bacterial count or controlled inflammation	Bacterial balance and reduced inflammation
Moisture	Desiccation slows epithelial cell migration	Apply moisture balancing dressings	Restored epithelial cell migration	Moisture balance
Edge	Non-migrating keratinocytes	Reassess and consider corrective therapies	Migrating keratinocytes	Advancing edge of wound

Table 7. TIME framework
(adapted from Schultz[313])

Ligresti et al.[316] recommended the addition of *healing time* as an additional assessment parameter. They argued that the TIME system failed to take into account the general condition of the patient and the influence such pathologies may have on the healing of the wound. They recommended the addition of a scoring system that correlates with the medical pathologies of

the patient, suggesting a TIME-H mnemonic with H representing the patient's health.

In 2006 Falanga et al.[317] combined colour and the wound bed characteristics described by the TIME system to develop a *Wound Bed Score*. Parameters assessed included: the edges of the wound; wound depth and exudate; oedema; peri-wound dermatitis; peri-wound callus; and fibrosis (see Table 8). Each parameter was assigned a score from 0 (worst) to 2 (best). A wound could be assigned a maximum score of 16 (highest possible) or 0 (worst possible).

Characteristic	0	1	2
Healing edges	None	25% to 75%	> 75%
Black eschar	> 25%	0% to 25%	None
Greatest wound depth / granular tissue	Severely depressed or raised when compared to peri-wound skin	Moderate	Flushed or almost even
Exudate amount	Severe	Moderate	None / mild
Oedema	Severe	Moderate	None / mild
Peri-wound dermatitis	Severe	Moderate	None or minimal
Peri-wound callus / fibrosis	Severe	Moderate	None or minimal
Pink wound bed	None	50% to 75%	> 75%

Table 8. Wound Bed Score criteria
(modified from Falanga et al.[317])

Falanga et al.[317] asserted that the higher the wound bed score, the shorter the healing time. To test their assumption observers (blinded to the patient) were asked to examine 177 venous ulcer photographs and assign a Wound Bed Score to each. The assigned score was compared to the healing

outcomes achieved by patients within a 24 week period. Using an independent sample *t*-test they found that patients who had healed within the 24 week period had a higher initial wound bed score (11.83) than those who did not heal (10.62). They concluded that outcomes appeared promising but would require further research.

2.7. Justification for the study undertaken

When reviewing assessment techniques available from clinicians it is obvious that the established validity for each is variable. When examining the underlying pathology a number of objective and validated methods including ultrasound duplex scanning, ambulatory venous pressure measurement, and air plethysmography are available. Equally, when describing some of the clinical manifestations of CVI similar objective assessment methods exist. These include volume displacement techniques used for measuring oedema, and the precise measurement of venous ulcer dimensions using stereocameras and planimetry. Although the latter rely heavily on consistent clinician to clinician recording of a wound tracing, the use of precision technology to quantify areas within the trace has at least increased the reliability of these techniques.

Methods for classifying the severity of CVI are less objective relying on expert consensus to promote consistency. These methods not only use material from expert opinion to establish content validity, but have also undergone inter-rater reliability testing to demonstrate their reliability. The

CEAP classification system and subsequent modifications provide an example of this approach. Similarly the development of the Venous Clinical Severity Score and Venous Segmental Disease Score.[235]

Visual examination of clinical manifestations of CVI offers the least objectivity. It is interesting that the manifestation of CVI responsible for a disproportionate amount of health care expenditure (venous ulceration[1, 2, 21, 37, 41, 52, 68, 75, 92, 126, 288, 290, 318-320]) is assessed using a subjective approach. As the average age of the population increases and with it the prevalence of venous leg ulcers, it becomes essential to establish methods that enable accurate assessments of the status and progression of this manifestation. The selection of increasingly expensive wound care products, the allocation of community health care resources, and the establishment of management plans to ensure optimal quality of life will rely heavily on data collected from such assessments.

The assessment of colour provides a non-invasive low cost option to assess the progression of venous leg ulceration. It can be examined in a variety of clinical settings including community, aged care and acute care services and be taught to clinicians with differing qualifications and clinical backgrounds. However, the heavy reliance on colour as an indicator of tissue type and wound progression (Red-Yellow-Black or Red-Yellow-Black-Pink system) has been founded on material produced principally as a marketing tool to sell wound care products. Since its introduction little testing for reliability or validity has been undertaken. When examined, the intra-rater reliability of

established colour systems has been found to be variable.[291] The research is mostly centred on single assessments not assessments over time. Little research has been done to connect the subtle colour manifestations exhibited by venous leg ulcers with underlying physiological processes of wound healing.

Equally, limited focus has been given to techniques for accurately recording the colour exhibited by venous leg ulceration. Clinicians faced with an ever increasing array of digital technology have little evidenced based guidance for the selection of appropriate equipment and the establishment of photographic capture techniques.

What is needed is a program of research aimed at establishing reliable parameters and processes for the colour assessment of venous leg ulceration. The parameters should be indicative of underlying physiological changes and describe expected fluctuations throughout the healing cycle. The process should ensure reliable methods for capturing the colours exhibited by venous leg ulcers, be easily implemented in a variety of clinical settings and be robust enough to allow for the differences between clinicians.

The project described in this thesis attempts to contribute to the above endeavours by: establishing a reliable method for capturing colour displayed by venous leg ulceration;, developing a colour range that experts believe represent two clinical manifestations – erythema and wet necrotic tissue (slough); and producing a computer system that can highlight each

manifestation in a digital image of a venous leg ulcer. It builds on the popularity of colour as a tool for wound assessment, but attempts to introduce a degree of objectivity missing in the Red-Yellow-Black colour system by using image analysis technology. The selection of erythema and wet necrotic tissue has been derived from the pathological mechanism thought to impede the healing of venous leg ulcers; principally the processes of inflammation (see Chapter 1). The intent was to develop a venous ulcer assessment system that provided a non-invasive, objective measure that used colour to determine the amount of erythema and wet necrotic tissue being manifested within a venous ulcer. The long-term aim was to provide an assessment tool that when evaluated in subsequent studies could provide more objective indicators of both the current status of a venous leg ulcer and progression of that ulcer through the healing cycle.

Using colour analysis in an effort to assess wound healing is not unique. Chapter Three examines research currently undertaken in this area in order to provide a foundation for the method used in this project. It examines colour perception, image analysis techniques and the relationship of these concepts to the assessment of wound healing.

3. Chapter Three: Literature Review

In the previous chapter it was asserted that there is a growing need to establish objective and reliable assessment techniques for the review of venous leg ulceration. It was further asserted that such techniques should be readily available in clinical settings; be easily used by a variety of clinicians; and should build on the assessment techniques and experiences used by health care practitioners. To this end, it was suggested that attempts be made to objectify the visual interpretations made by clinicians when assessing venous leg ulcers, in particular the colour of the wound bed and surrounding skin.

To determine previous endeavours that had attempted to address the above challenge a review of relevant literature was undertaken. Comprised of a discursive analysis the review examined three discrete areas: the importance of visual assessment in clinical decision making; the perception of colour; and the measurement of wound colour. Literature was identified via a search of Medline®; Cinahl®; Cochrane database of systematic reviews®; manual extraction of relevant vendor research reports; and a Google® search of the worldwide web resources. Keywords used included ‘colour’, ‘color’, ‘wound assessment’, ‘human perception’, ‘visual perception’, ‘colimetry’, ‘image analysis’ and ‘computer analysis’.

3.1. The importance of measurement in clinical assessment

Attempts to objectify the visual interpretation of clinical manifestations are not new. Hippocrates (cited by Warren[321]) described the observation of the patient and the progression of their disease as the science of medicine. It is a science which over the intervening years has systematically attempted to objectify the observations of patients. Central to this work has been the tenet that observations are more scientific if measured.[321] An example is the assessment of cardiac function. Herophilus of Alexandria (cited by Warren[321]) in 300 BC would count a patient's pulse using a water clock. Sanctorius (cited by Warren[321]) in 1620 AD adapted Galileo's pendulum clock to produce a device called the pulsilogium. It was designed to facilitate counting the pulse and had a sweeping hand that moved over a clock face with marks every second for a period of fifteen seconds. In 1707 Sir John Floyer (cited by Warren[321]) adapted the work of Sanctorius and introduced the first pulse watch. The same configuration remains today in a nurse's fob watch. In 1816 Laennec (cited by Warren[321]) described the first stethoscope and auscultation was added to the palpation of pulses described above. This was followed by the measurement of the heart's electrical impulses in 1878 by John Sanderson and Frederick Page (cited by Warren[321]), finally arriving at the array of hemodynamic monitoring available to today's clinicians.

The assessment of a wound has not experienced a similar degree of measurement. Galen (129 AD, cited by Keast et al.[322]), a surgeon to the Roman gladiators, documented the importance of touch for the diagnosis and assessment of wounds and injuries. Unfortunately he identified pus as an

indicator of wound healing and went as far as introducing foreign bodies into a wound to stimulate the production of pus. The mystery of wound healing experienced by Galen continues to the present day and may account for the lack of an agreed framework for assessing wound healing.[322] Recognition of this lack of understanding of the healing mechanism was best expressed by a French military surgeon called Ambroise Paré (1510–1590, cited by Cohen[323]) when he said "I dressed the wound. God healed it." It was not until the 1970s that attempts were made to measure the characteristics of a wound.

Several elements are cited as necessary considerations when conducting a wound assessment. Identification of systemic diseases or conditions that either create or interfere with wound healing are mentioned frequently.[324] Likewise the need to document physical characteristics of a wound including location, size, colour, wound bed tissue, surrounding skin and wound drainage.[89, 110, 249, 250, 255, 288, 300, 304, 308, 324-331] Objective measures and predictive formulae are available for assessing the dimension changes within wounds[256, 260, 265, 266, 278, 279, 283, 284] (see Chapter Two). However colour, a manifestation often used by clinicians[89, 110, 249, 250, 255, 288, 300, 304, 308, 324-331] to assess wound status and progression, remains subjective. Therefore, this review will focus on attempts to objectify the colour manifested by wounds, and in particular venous leg ulcers. It examines colour perception, image analysis techniques and the relationship of these concepts to the assessment of wound healing.

3.2. Colour perception

The ability to classify objects by their colours is an integral part of the human and animal perception. Colour recognition facilitates the identification of food and water, potential threats and safe shelter. It helps determine spatial relationships between objects and their environment and assists in the detection of movement.

Despite the numerous advantages attributed to colour vision, the physiological and psychological mechanisms of colour perception are still not fully understood. It is beyond the scope of this thesis to provide a detailed account of the extensive research undertaken in this area, but a review of contemporary knowledge is necessary to substantiate the central argument; that the quantification of wound colour using computer technology may provide additional insights into the healing cycle not available to the naked eye.

Object light property, retinal physiology and post retinal psychophysiology research, as it pertains to colour vision, will be explored. The resultant theories of tristimulus reception; spectral opponent process; colour constancy; adaptation; and cortical colour interpretation will be discussed.

3.2.1. The different philosophical views of colour

The term ‘colour’ attracts multiple definitions and interpretations. In everyday language colour can describe the hues of objects, act as a racist taunt, or

describe a current emotional state, i.e. “feeling blue or seeing red”. In the scientific arena the term ‘colour’ is no better defined.

MacAdam[332] states that the term ‘colour’ is used in “three distinctly different senses”. The chemist uses colour as a generic description of dyes and pigments. The physicist views colour as the optical properties of objects. The psychologist defines colour as sensations of the human consciousness.

Byrne and Hilbert[333] continue this notion of a separation between colour as a physical entity and colour as a psychological experience. They describe two types of colour experiences; ‘colour representing’ and ‘colour feeling’. The first is derived from a theoretical framework that states objects have colour representing properties that can be specified without reference to colour perception (e.g. nm of light). The second, a colour feeling experience refers to the affect that we attribute to the colour experience. For example, a particular colour hue of a sunset may help recall a previous event like a holiday. This is often referred to as the ‘phenomenology of colour vision’.[334] Byrne and Hilbert[333] assert that differing theories of colour perception can be classified as either ‘colour representing → colour feeling’ or ‘colour feeling → colour representing’.

Land[335] provides an example of a ‘colour representing → colour feeling’ experience. He defines colour as a complex neural operation that differentiates the wavelength of light reflected from one surface with that reflected from the surrounding surfaces. He represented this complex

operation as a computer algorithm and coined the term 'retinex' to describe the processes between the retina and cerebral cortex. Central to Land's[335, 336] definition is the assertion that colour results from a 'mind-independent' process not influenced by memory or experience.

In contrast, Boghosian[337] argued that colour does not result from the physical properties of an object. He argues that colour perception is a qualitative process that is very much 'mind dependent', or a 'colour feeling → colour representing' experience. Central to this view is the assertion that objects are not coloured. Colour results from humans mistakenly projecting visual experiences onto objects. This philosophical stance is known by different names: eluminativsim; dispositionalism; or primitivism, and originates from an early Greek anatomist called Democritus.

Although proponents of the 'colour feeling → colour representing' experiences pose some interesting philosophical questions, the view of 'colour representing → colour feeling' experience (objects have physical colour properties) is predominant in contemporary science literature. The findings from such research have formed the basis for many technological innovations including the capture techniques made possible by film or digital cameras, and image analysis computer algorithms that replicate human visual perception. For this reason the remainder of this chapter focuses on literature drawn from proponents of the 'colour representing → colour feeling' experience theories.

3.2.2. Colour representing → Colour feeling

A keystone of the 'colour representing → colour feeling' theory is that objects have properties that determine the colour of the object. Proponents believe that human colour perception is derived from a physiological process (response) that interprets the physical properties (stimuli) of objects. This view is often classified as 'Physicalism' or 'colour realism'.[333]

The object property, or stimuli most frequently cited, is the optical ability of objects to reflect incident light. As far back as Isaac Netwon there is documented evidence that daylight passed through a prism will reflect as a spectrum of colour. The physical difference between the hues of that spectrum is attributed to the radiated *wavelength* of the reflected light. The unit of length commonly used to specify the wavelength is the *nanometre*. Therefore, for the physicist the colour red is a wavelength of light ranging from 630–700 nanometres (nm), yellow is 560–590 nm and blue is 400–450 nm etc.

The wavelength of light reflected by an object is a combination of the incidental light reaching the object and the surface reflectance properties of the object. For example, an object can only reflect as much red as the red that is present in the light that reaches it. Equally, an object can only reflect as much red as the optical properties of the microphysical elements that make up its surface will allow. The intensity of the incidental light is called the 'spectral power distribution' (SPD) and the reflected light is known as the 'surface spectral reflectance' (SSR). The amount of light reaching the eye

(product of the SPD and the SSR) can be quantified using a spectrometer.[332] This instrument divides the amount of each spectral component in the reflected light by the amount of each spectral component of the incidental light and converts that figure to a ratio of between 0 and 1. Thus, colour of a surface can be objectified by specifying the amount of each spectral component reflected. For example, the colour characteristics of a wound may be described as the figures represented in Table 8.

Spectral region	Reflectance
Violet	0.06
Blue	0.12
Green	0.17
Yellow	0.11
Orange	0.28
Red	0.33

Table 9. Spectral components of a wound

As different areas of the spectrum have a degree of overlap the above table presents a simplified view. To compensate for this the colour of a surface is quantified as a 'spectral reluctance curve'. This curve is used in industry to quantify a given colour and facilitate reproductions. Figure 6 illustrates the spectral reflectance curve obtained from one wound.

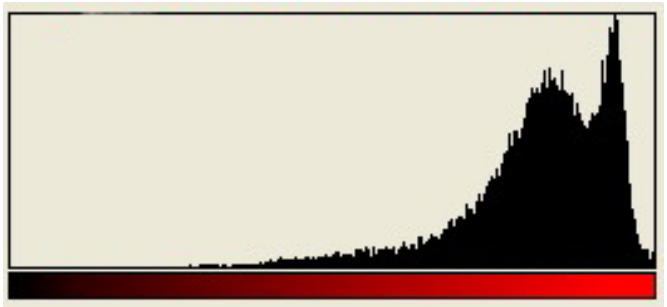


Figure 6. Spectral reflectance curve derived from a photograph of a leg ulcer

The wavelength reflected by an object determines what is called the *Hue* of the object. Hue is what is commonly referred to as the colour, e.g. the 'redness of the wound'. Physics research has revealed two other physical properties that influence the colour of an object; *brightness* and *saturation.* Brightness refers to the intensity (power or amplitude) of a given wavelength. Saturation refers to the purity of the colour or the amount of white light that has been added to a colour.[338] Pure colours are referred to as monochromatic.

The quantification of the colour spectrum in the nineteenth century has allowed researchers to determine the boundaries of light and colour visible to humans. Studies measuring visible colour are known as 'Colorimetry' research. The aim of this area is to develop accurate methods that predict the perceived colour of given objects. A commonly cited method was initially described by Maxwell in 1860 (cited by MacAdam[332]). Participants were asked to look into an instrument that had a two-part field of view. In one field was a coloured light projected onto a neutral background. In the other field participants were allowed to adjust three primary colours (red, green and blue) until the colour matched that in the other field. The amount of each primary colour constituting the match was recorded.

As mentioned previously, the physical colour of an object's surface is a combination of both the illuminating and the reflected light. The International Commission on Illumination adopted a standard for illumination used for this type of research known as *CIE illuminant C*. The standard is used to produce a filter that when used with a tungsten lamp at a given temperature produces

light that is an approximation of average daylight. The composition of daylight used to determine the *CIE illuminant C* is derived from studies that examined the spectral power distribution of daylight in a number of locations around the world and in differing weather conditions.[339]

By repeating the above experiment over a large and representative number of participants, and at differing hues, brightness and saturation, colour scientists claim they can predict the various combinations of primary colours that will lead an observer to perceive a given colour. The primary values are referred to as the tristimulus values. The set of tristimulus values for spectral lights forms the CIE standard observer, again adopted by the International Commission on Illumination in 1931. By plotting these values on a three dimensional graph the limits of the colour spectrum that is visible to humans can be quantified. The area represented on the graph is called the 'colour space'.[338] Figure 7 is a representation of this graph.

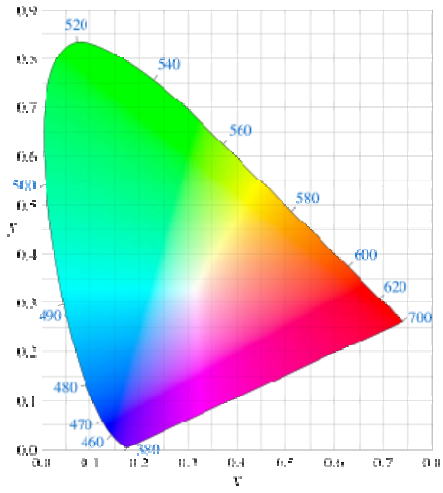


Figure 7. XYZ graph developed by the International Commission on Illumination in 1931
(Retrieved from http://en.wikipedia.org/wiki/CIE_1931_colour_space)

The colour space used by humans to perceive colour is a combination of hue, saturation and brightness, known as the HSB (also know as the HSI, hue-saturation-intensity and HSV hue-saturation-value) colour space. Figure 8 is a graphic representation of this colour space.

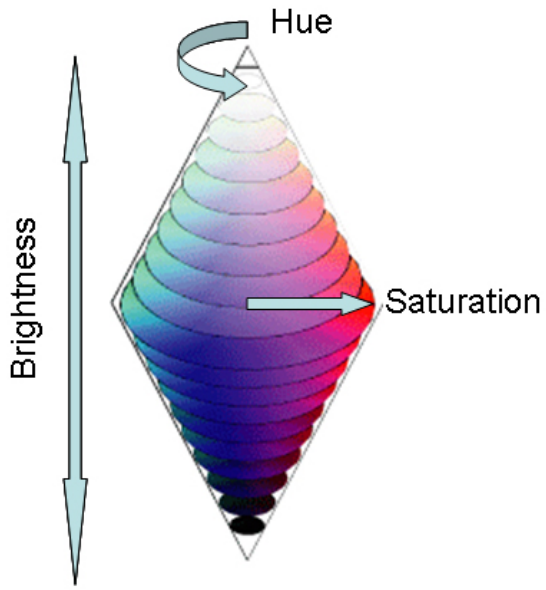


Figure 8. HSB colour space
Adapted from (http://developer.apple.com/documentation/Cocoa/Conceptual/DrawColor/Concepts/AboutColorSpaces.html)

The wavelength determines the hue, brightness and saturation of the colour. Given conditions when the illumination complies with the CIE illumination standard, and access to the CIE observer standard, colour scientists would argue that they are able to predict the colour that would be perceived by an observer.

3.2.3. Colour perception as a physiological process

While the principles of light physics would appear to be well developed, the physiological processes that absorb and convert the light into information is still being explored.

Microscopic examination of the human retinal has revealed that there are two distinct classes of photo receptors. They are distinct both morphologically and physiologically. Their shape has given rise to their names – rods and cones. Based on early colour matching research (mentioned above) Helmholtz (1863) and later Hering (1872) (cited by DeValois[340]), postulated that the human eye needed three types of colour receptors. It was believed that three receptors were needed to differentiate the wavelength of each of the three primary colours.

Support for this assertion was not obtained until the 1960's when a number of studies demonstrated different spectral absorption for specific receptors. Marks et al.[341] were able to demonstrate that when a monochromatic light is passed through primate and human cone receptors (mounted on a microscope slide) the light wavelength that is absorbed by the cone will differ depending on the cone type. They described three cones types: the 'S' cones that absorbed short wavelengths 440–450 nm; the 'M' cones that absorbed medium wavelengths 530–540 nm; and the 'L' cones that absorbed long wavelengths 560–570 nm. The different absorption capabilities were attributed to three types of photopigments found within the cones. They also found that there were significantly more cones containing medium and long-wavelength pigments than short-wavelength pigments.

Helmholtz (1863) (cited by DeValois[340]) theorised that each cone type had an independent pathway to the cortex, where the colour perceived would be

related to the cone receptors that had been activated. DeValois et al.[340] pointed out a number of flaws with this theory. They argued that while the person would be able to discriminate between spectral ranges (red, green and blue) he/she would not be able to differentiate colours within a spectral range such as the different hues of red. Secondly if each receptor was dedicated to a wavelength then it would be expected that visual acuity would be better in white light than in monochromatic light. If the person was in a red light only the red receptors would be activated producing a coarse retinal reception leading to reduced visual acuity. In white light (a combination of all wavelengths) all receptors would fire thus improving visual acuity. They argued that the opposite is true; visual acuity is decreased in white light because the cornea and lens of the human eye are not capable of focusing different wavelengths simultaneously. The result is a slight blurring of the image.

Based on animal research, primarily Macaque monkeys, DeValois et al.[340] put forward the case that cone receptors serve to excite or inhibit ganglion cells in the retina. Recent neurological research has demonstrated that neurons depolarise on a continual basis regardless of the presence or absence of a stimuli. When stimulated the rate of depolarisation either increases (excitation) or decreases (inhibition). By examining the responses of Macaque monkey ganglion cells to various wavelengths they found that different ganglion cells (cells that give rise to the axons of the optic nerve) will excite or inhibit to different wavelengths. They categorised the responses into

two major groupings: the spectrally ‘nonopponent cells’; and spectrally ‘opponent cells’.

Spectrally nonopponent cells are so named because they respond to any incremental changes to a monochromatic light. Some of the cells have been found to excite when exposed to white light and inhibit when exposed to an absence of light (+Wh-Bl). Other cells have shown the reverse characteristics, inhibiting to white and exciting to black (-Wh+Bl).[340] Spectrally opponent cells differ in that they excite to specific wavelengths and inhibit to others. DeValois et al.[340] suggest that these cells can be further subdivided into four types: red excitatory, green inhibitory (+R-G); green excitatory, red inhibitory (-R+G); yellow excitatory, blue inhibitory (+Y-B); and blue excitatory and yellow inhibitory (-Y+B). They are called opponent cells because mixing one with the other would result in a cancellation of both hues.

Using this model the different cone pigments will excite some ganglion cells and inhibit others. Based on the wavelengths established for different areas of the spectrum, S-cones would excite the +B-Y cells and inhibit +Y-B cells. M-cones would excite the +G-R cells and the +Wh-Bl cells and inhibit the +R-G and -Wh+Bl cells. L-cones would excite +Y-B, +R-G and inhibit +G-R, +B-Y and -Wh+Bl cells.[342]

It should be remembered that this research is based on Macaque monkeys and, although some behavioural studies indicate similarities between the

Macaque monkey and human colour perception, definitive research on the response of human ganglion has yet to be done. The same is true when research about neural pathways beyond the ganglion cells is examined.

Research pertaining to cortical neural pathways for colour perception is a compilation of animal (cat and Macaque monkey) and human studies. The latter is limited to case studies of people with pathologies that eliminate a section of the cortex or, more recently, studies that use functional magnetic resonance imagery (fMRI), positron emission tomography (PET) or event related potentials (ERPs) to follow cerebral activity when subjects are exposed to given colour stimuli.

Studies examining primates (Macaque monkeys) have been able to demonstrate that neural pathways associated with changes to light wavelength start at the colour-opponent cells in the retina and reach regions of the primary visual cortex known as area V1.[343] From here the pathway varies with colour information being relayed to areas V2 and V4, then to inferotemporal cortical regions.[344] Figure 9 illustrates the anatomical location of these regions.

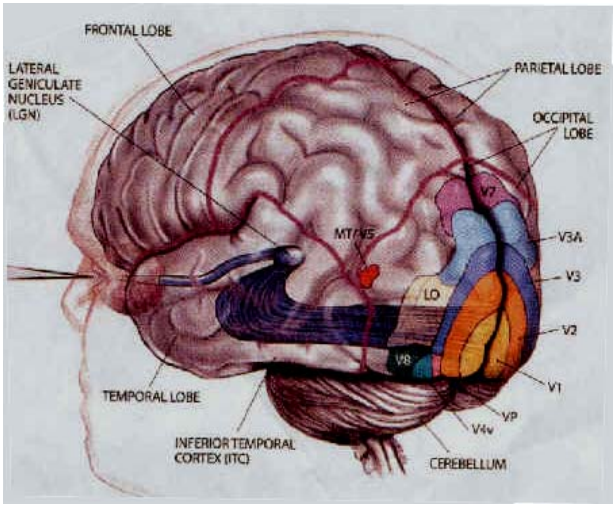


Figure 9. Brain areas identified as being involved in colour perception
(Modified from http://defiant.ssc.uwo.ca/Jody_web/fMRI4Dummies/functional_brain_areas.htm)

Similar pathways have been found in human subjects. A number of studies have asked subjects to observe mondrian stimuli and examined the activity of the human brain using imaging technology (MRI or PET). Mondrian stimuli (named after the Dutch Neo-Plasticist artist Piet Mondrian) are multicoloured or monocoloured abstract scenes with no recognisable objects. They are used to minimise the influence of memory and learning on the perception of colour, and hence the brain areas stimulated. Findings from PET imaging indicate that V1, V2 and V4 are involved in the subject's perception of these abstract images.[345]

Recent work by Zeki and Marini[346] included fauvist images in the examination. These images contain objects with colours not usually associated with them, e.g. green meat. In this study subjects were asked to examine both mondrain and fauvist images while their brain activity was mapped using magnetic resonance imagery. Based on the findings, Zeki and Marini [345, 346] proposed a three staged process for the interpretation of colour.

The first stage determined the wavelength of light from every point in the field of view. They argued that this is accomplished by wavelength selective cells in V1 and V2. The second stage was a comparison of the wavelength of light reflected from one surface with that reflected from surrounding surfaces. They believed that cells located in V4 were responsible for this process. The third stage is to 'invest objects with colours', a process that is yet to be assigned an anatomical area but Zeki and Marini [346]believed this was beyond V4.

Additional studies using event related potentials have found similar cortical areas involved.[347] Annllo-Vento et al.[344] examined the cerebral activity associated with attention to colour. Subjects were asked to observe checker boards on a computer screen. One checker board was composed of red and grey squares on a grey background, the other blue and grey on a grey background. Subjects were asked to *attend* to one colour (red or blue) and asked to press a button if they detected a dimmer presentation of that colour. The brain activity was then measured using 32 scalp electrodes. The findings suggested that attention to colour:

> "Involves successive stages of processing in progressively more anterior regions of the ventral pathways…early attention selection for color takes place in the dorsal occipital cortex….more pronounced selective processing of attended color stimuli in the region of the collateral sulcus." (p. 236).

Pathological evidence appears to lend further support to the above findings. Patients with V1 lesions are blind, supporting the assumption that this area

forms the preliminary reception. People with lesions of the occipito-temporal cortex and V4 are found to be cerebral achromatopsia (inability to perceive the colour of objects). They report an ability to see shape but colour is restricted to greys.[346, 348]

3.2.4. Colour perception as a psychological process

The psychology of colour is frequently reported in the popular press. Research exploring the ability of colour to influence mood, emotions and in some instances our health, form foundations for activities promoting colour selection as an effective commercial or personal tool. Although an interesting area of science, exploration of research pertaining to the psychology of colour is beyond the scope of this literature review. However, colour perception principles, specifically the concept of 'colour constancy' are significant to the argument being mounted.

Although not fully understood, 'colour constancy' refers to a subjective system of human visual perception.[349-359] It was first described by Land[336] as a system that helps ensure that the perceived colours of an object remained constant under varying illumination conditions;[360] this is necessary to function within our environment. If colours changed with the amount of illumination then the ability to make decisions based on colour would be less certain. For example, if the illumination of an ulcer bed was adjusted so that the red normally displayed changed to a colour (i.e. pink) similar to the surrounding skin, the observer would be unable to determine where the ulcer started and

the skin finished. However, being able to accommodate for different illumination of the ulcer bed allows the observer to differentiate the colour from the surrounding skin.

Waltlington[361] described two features that he believed comprised colour constancy; 'spectral normalization' and 'spatial decomposition'. The former was the ability to correct for temporal changes in the spectral content of the area being viewed (e.g. an ulcer bed and surrounding skin going from light to a darker colour as the illumination decreases). The latter was the ability to ignore changes in illumination across the area being viewed (e.g. a memory that the ulcer bed was red and the change to dark red was due to an illumination change not a change in the colour of the ulcer bed).

Van Es et al.[362] demonstrated that colour constancy resulted from a comparative process where humans scan the colour of a scene, comparing colour changes of different surfaces to that of the area under focus, and then making cerebral adjustments to the colour of that area to compensate for illumination changes. Subjects were asked to observe a Mondrian display consisting of "a regular radial coloured checkerboard pattern with twelve wedges and six rings" (p. 143). The innermost ring was replaced with a circular disc (see Figure 10). The illumination of the checkerboard pattern could be altered independently to the grey border surrounding the image. The image was displayed on a computer monitor and subjects observed each image for one second.

Subjects were asked to determine if the colour of the central circle stayed the same (local colour judgements), or if the colour changed to indicate if the changes were consistent with illumination changes over the entire image (relational colour judgements). They found that colour constancy was more accurate when subjects used relational colour judgements than when they used local colour judgements. These findings supported the notion that colour constancy is achieved by comparing changes in the colour of an object in relation to the illumination of the surrounding scene.

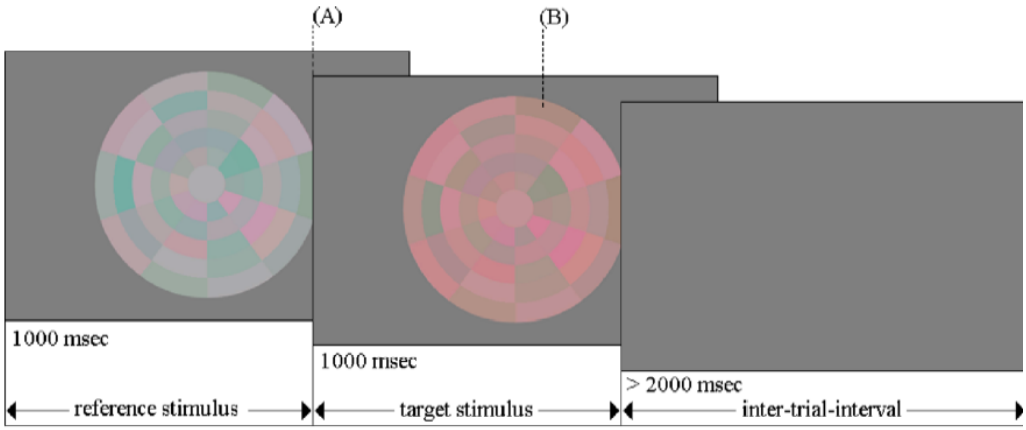


Figure 10. Mondrian display used by Van Es et al.[362] p. 142

Bloj et al.[363] were able to demonstrate that colour constancy was also related to an ability to perceive three dimensional objects. They constructed a "concaved card with trapezoidal sides which appeared rectangular" when viewed (p. 877). The left side of the card was painted magenta and the right side painted white. The card was viewed using a 'pseudoscope' which optically inverted the depths of the surfaces so the observer would either see the card as opening towards them, or away from them (see Figure 11). The illumination and the colour were not altered, only the optical view.

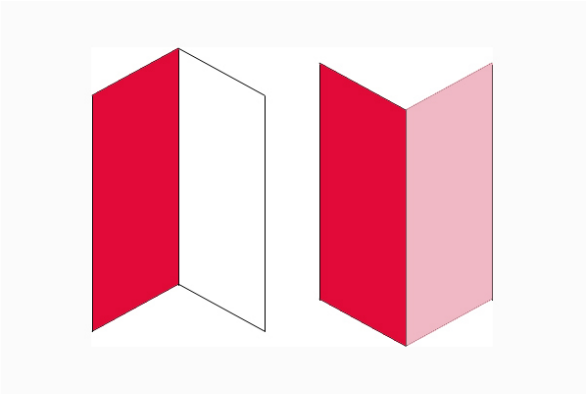


Figure 11. Concave card used and the inverse image by Bloj et al.[363]

When subjects observed the card with the opening facing them they described the right side as white in colour. When the image was inverted (opening away) subjects believed that the colour of the white section changed to a pale pink, although no other change (colour or illumination) had taken place. Bloj et al.[363] concluded that colour perception was influenced by higher cerebral centres where in-built knowledge of light physics and three dimensional structures dictated the colour perceived.

The influence of higher cerebral centres has also been suggested by other researchers. Treisnman et al.[364, 365] found that subjects given verbal descriptors such as “orange carrot or blue lake” made significantly more illusory preconceptions about the colour than subjects given feature descriptions such as “orange triangle or blue ellipse”. They concluded that subjects able to draw on previously learnt shapes and colours (e.g. carrot) were more likely to form preconceptions about the colour of an object.

The notion of memory influencing colour perception is also evident in developmental research. It has been established that accurate and stable

performance in naming different colours occurs between the ages of four and seven years.[366] When examining a group of preschool children, Johnson[367] found that only 38 per cent of children aged 2.6 years could correctly name four basic colours (red, yellow, green and blue). This increased to 50 per cent for 3-year-olds, 56 per cent for children aged 3.3 years, 72 per cent for 4-year-olds and 79 per cent for children aged 4.3 years.

A similar developmental difference was identified by Petzold and Sharp[368] when they tested the hue discrimination and hue memory abilities of preschool children (3–6 years), preadolescent children (9–11 years) and young adults (22–30 years). Hue discrimination was tested by asking the subjects to identify a colour presented on a computer monitor. Hue memory was examined by asking subjects to match a colour that they had viewed previously from a range of similar hues presented five seconds after the initial viewing. They found little difference between the age groups when testing for hue discrimination, but hue memory was found to significantly improve with age.

Colour constancy has been found to be less than prefect by some researchers.[349-351, 354] Surface texture has been found to influence colour constancy. Subjects exposed to dynamically changing colours surrounding a target often predict inaccurate hues.[354] Equally, observation made under unusual illuminations such as sodium vapour lamps can result in a loss of colour constancy.[349]

From the information presented in this section it can be seen that although human colour perception has common physical and physiological mechanisms, the limited understanding of the psychological influences requires that this phenomenon be classified as *subjective*. In an effort to overcome the shortcomings of human colour perception the use of computer technology has been explored.

3.2.5. Using computers to perceive colour

Computers require mathematical formula known as algorithms to function. Using computer technology to perceive colour has required the development of a number of mathematical algorithms that replicate or improve on a human's ability to maintain colour constancy.

Whilst several algorithms are evident within the literature, they tend to fall into one of five methods: Grey world methods; Retinex methods; Gamut mapping methods; Colour by correlation methods; and Neural network methods.[369, 370] Describing the complexity of each method is again beyond the scope of this review, but the underlying assumption of each method is outlined as a foundation for subsequent sections.

Grey world methods assume that the average light reflected from a surface is equal to a pre-specified value which is referred to as 'grey'.[369] A camera using this algorithm assumes that the average light from a scene is equal to the camera's response to grey under the illumination for that scene. The

wavelengths being received by the camera sensors are then adjusted using the algorithm to account for the amount of illumination the algorithm predicts is present.

Retinex methods have been derived from the work of Land et al.,[336] who developed an algorithm that made allowances for different levels of illumination. It is based on the assumption that small spatial (activities that involve visual processing) changes in the scene were related to changes in illumination, whereas large spatial changes originated from surface changes (changes in colour). The amount of change is calculated by examining the colour response of pixel adjacent to the pixel being examined.[336]

Gamut mapping methods were originally introduced by Forsyth[371] in 1990. These algorithms constrain the set of possible maps for a given scene under unknown illumination to an image of the scene under a known illumination.[369] The colour range is restricted to a given gamut (range) of colour. This is best demonstrated by the difference that is often seen between an image on a computer monitor and the printed version. The gamut of colour available for the computer is different from the gamut of colour available for the printer. Thus the colours displayed on the monitor cannot be replicated by the printer or vice versa.

Colour by correlation methods use probability to determine the amount of illumination in a given scene. Initially the probability of seeing a particular colour under each expected illuminant is calculated. The resulting array of

probabilities (contingency table) is used to calculate the probability that each of the potential illuminants is the actual illuminant. The best estimate of the illuminant is then chosen and colours are adjusted accordingly.[369] An example is when a picture is taken outdoors (in sunlight) using the indoor settings on a camera (tungsten lighting). The former uses a different 'probability array' than the latter. The colour balance in the resulting images appears out of balance with the actual image because the incorrect probability table was used.

Neural network methods use algorithms derived from artificial intelligence research. The system is 'trained' using a random selection of synthetic images generated from a database of different colours and illuminates. The colour histogram of a synthetic image is entered into the system together with the correct answer. Using this data the system 'learns' the influences of different illuminates[369, 370] and can then make subsequent adjustments for images in similar conditions of illumination.

Data derived from the above algorithms not only improve the ability of the system to achieve colour constancy but also enable analysis of the image for aspects of interest. Such systems are used to recognise objects in the image.[364] Security systems that capture the face of a person and then compare the captured face with faces contained in a database of 'persons of interest' is an example**.** Evaluation of such systems has revealed high reliability scores, in most instances outperforming human observers.[372-375]

Clinical applications for health care are also evident. For example, clinical neural network systems are increasingly common in the literature. Sammouda and Sammouda[376] used a neural network system to analyse digital images of liver biopsies. They concluded that the results were promising for the development of a Computer Aided Diagnosis system aimed at detecting liver cancers. Usher et al.[377] used a similar system to analyse digital retinal images. They were able to achieve 94.8 per cent sensitivity and concluded that the system could be used for screening of diabetic retinopathy. A number of studies have also explored the use of image analysis to diagnose mMelanoma and other skin lesions.[378-381] Findings suggest that such systems may assist in the recognition of malignant skin lesions. Most however, recommend that further research is required to capture the higher order pattern recognition used by experienced clinicians.[378]

Given the recent exploration of image analysis and object recognition algorithms, it is logical that the use of such systems for assessing wounds is being explored. The following provides a review of that work.

3.3. Measuring wound colour

Technological developments in the 1980s and a desire to move beyond the crude Red-Yellow-Green-Black colour measurement of wounds provided a catalyst for research into systematic wound colour measurements. Technology designed to measure an erythema index following radiation

treatment of the skin, or the application of an irritant (e.g. newly developed cosmetic), provided researchers with the first in a series of tools with which to measure wound colour – the spectrometer. Whilst reliable, the problem was that the spectrometer only measured colour over a very small area. In the 1990s advances in digital technology and computer image analysis derived principally from the measurement of skin lesion colour, specifically melanomas[382-394] provided researchers with the possibilities of measuring colour over a large surface area and being able to digitally manipulate the image and store the data.

However, as attempts were made to apply computer analysis to the images of wounds, a number of confounding variables were discovered. Differing capture devices (cameras); light sources; unwanted reflections; and colours displayed by different types of wounds at different times in the healing cycle, were identified as variables that confounded the results. Once the image was captured, another group of confounding variables were identified including the algorithm used to measure the colour and the difference between computer colour perception and human colour perception. In an attempt to improve the reliability and validity of such systems, researchers have used a number of methods to help eliminate each confounding variable.

3.3.1. Selecting capture devices

The type of capture device has changed as available technology has improved. In earlier studies wound images were recorded using film. Gammal

and Popp[395] used a 35 mm camera and ring flash to record wound images when examining the activity of collagenase in pressure ulcers. Each photograph was assessed by human observers in order to determine the amount of black, yellow or red tissue present. As computer technology became increasingly available, the devices used to capture wound images changed from film to the use of video cameras and frame grabbing cards. The latter enabled computers to capture an image from a video camera and digitise it for digital storage.

Herbin et al.[396] used a colour video camera with binocular lenses, connected to a computer system to record photographs of blisters. Binocular lenses were used to simulate the normal binocular vision of humans. A similar system was used by Mekkes and Westerhof[397] when attempting to measure the healing of a variety of wounds. Their aim was to develop a system for testing wound care products. The video camera and frame grabbing technology enabled digital image capture. More recent studies have captured wound images by using digital cameras. Shai et al.[398] presented digital images of chronic wounds to an expert panel of three dermatologists in an effort to develop a colour range that depicted the 'cleanliness' of a wound. The images were captured using a Canon digital camera and transferred directly into the computer.

3.3.2. Standardising focal length

A number of attempts have been made to standardise the focal length (distance between the camera and the wound) when recording wound

images. Boardman et al.[399] used a camera equipped with a pair of high energy light emitting diodes that provided two beams of light projected in front of the camera. The camera was moved away from, or towards the wound until the light beams converged on a single spot on the wound. This helped to ensure that the camera was the same distance from the wound when each image was captured. Other researchers have used tripods or camera mounting frames that ensure the cameras kept their distance from the patient's wound.[268, 270, 380, 395, 400]

3.3.3. Compensating for different illumination

In an effort to control for different light sources, several researchers have used an in-shot reference. MAVIS (Measurement of Area and Volume Instrument), developed by Jones and Plassmann,[401] is an example. Although developed principally to measure wound volume, Jones and Plassmann[401] attempted to use this system to segment an image into three tissue types: healthy skin, wound tissue and epithelial tissue. To control for the amount of light illuminating the wound Jones and Plassmann[401] used a magnesium oxide chip placed in-shot to act as a white reference. Prior to colours of the wound being measured, the computer system would adjust each colour in the image to accommodate for the amount of light reaching the white in-shot reference and hence the remainder of the image. A similar system was used by Herbin et al.[396] who attempted to develop a colour index of healing by studying blisters. A white disc was placed in-shot, in an effort to provide a colour frame of reference against which colours of the blister could be compared.

In more recent studies, the in-shot references have contained colours that the computer system uses to determine the amount of illumination present in the image. Shai et al.[398] employed an in-shot reference strip that contained a yellow colour (representing the most unclean areas of a wound), a red colour (representing the ideal condition to be achieved), and a green and black colour. The latter colours acted as a reference for the computer to determine the amount of illumination that had been used to take the photograph.

Unwanted glare or reflection created by wound exudate or shiny oedematous skin, has been found to dilute the colour recorded in an image. Attempts to eliminate unwanted reflected light have been to either fix the camera angle or filter the light reaching the camera. Arqvist, Hellgren and Vincent[402] captured a wound image via a camera mounted at thirty degrees to the wound plane; the rationale being that any light reflected from the wound would pass outside of the camera lens. Boardman et al.[399] used a similar technique to examine the different hues exhibited by infected wounds, but not only placed the camera at thirty degrees but employed the use of ring flash. The latter provided a light source from three hundred and sixty degrees thus reducing shadows and reflected glare. Mekkes and Westerhof[397] took an alternative approach by using two polarised filters to reduce unwanted reflections. As with polarised sunglasses, the filters reduced the intensity of specularly reflected light reaching the camera sensors. This enabled a more accurate recording of the wound colour by reducing the influence of glare.

3.3.4. Compensating for different wound types

Different wound types have been found to exhibit different colours. The colours exhibited by Herbin et al.'s [396] study of blisters differed markedly from those exhibited by other wound types such as pressure ulcers or traumatic wounds.[257, 299, 329, 403] When examining pilonidal excision wounds, Boardman et al.[399] reported that the hues displayed fell between yellow and violet. Using the colour standards for printing (CMYK), Shai et al.[398] identified that 'clean' chronic wounds displayed a cyan of 20; magenta of 94; yellow of 87; black of 12; or more red in colour. They found that 'unclean wounds' displayed a cyan of 0; magenta of 0; yellow of 70; black of 5; or more yellow in colour.

In order to control for wound type researchers turned to artificially created wounds. Herbin et al.'s [396] blisters were artificially created on the forearms of eight volunteers using heat. Hansen et al.[404] examined pressure injuries artificially created on the backs of pigs in an attempt to use colour analysis to predict the severity of pressure related injury. By artificially creating wounds the researchers were able to control for wound size, shape, depth and location, all variables that influence the amount of light entering the wound and hence the colour reflected.

3.3.5. Selecting the colour space and associated algorithms

Once the image was captured researchers were faced with selecting the most appropriate method of measuring the colour. Three mathematical equations or 'colour spaces' were available. Red-Green-Blue (RGB), the

colour space used by computer monitors to replicate colour, the Cyan-Magenta-Yellow-Key (CMYK) colour space traditionally used by printers to reproduce colour in clothing or printed material, or the Hue-Saturation-Brightness (HSB) colour space said to be representative of human colour perception, described previously. Whilst CMYK colour space has not been used in wound colour research, both RGB and HSB have been tested.

When using the RGB colour space the majority of researchers concluded that these algorithms were not sensitive enough to detect subtle differences in wound colour. For example, when examining the ability of spectroscopy to differentiate between levels of erythema, Van der Valk and Snater[405] concluded that it could not discriminate grades of erythema any better than the human eye. Jones and Plassmann[401] concluded that the RGB level of measurement was unable to distinguish between the colour of a wound and the colour of skin, or the colour of a wound and the colour of connective tissue. Mekkes and Westerhof[397] came to a similar conclusion when attempting to develop a system that would enhance data derived from comparative studies of wound management products. Unlike Jones and Plassmann[401], Mekkes and Westerhof[397] used a three dimensional RGB histogram to analyse the colour. They found that simple RGB thresholds were not enough to identify a given tissue type. In particular the system was unable to determine the difference between the colour of granulation tissue, surrounding skin and newly formed epithelium.

To date studies that have used the HSB colour space have been limited, but they proffer more encouraging findings. Hansen et al.[404] claimed that they developed a model that provided colour analysis closely representative of the "intuitive notions of human perception" (p. 85). They were able to use colour to differentiate the severity of a pressure injury. Injuries with a blue / grey appearance were more significant than injuries that rapidly assumed a reddish appearance, followed by a gradual reduction in the redness over a period of several hours. Their findings suggest that if the elapsed time was known, colour could be used to distinguish the severity of the pressure injury.

Boardman et al.[399] used HSB to compare colours exhibited by non-infected and infected wounds. They identified that non-infected wounds exhibited a peak of red hue in the mid range of hues, which decreased as healing continued. Infected wounds, on the other hand, exhibited a distinct increase in the peak of red hue range. The red peak was reduced after antibiotic treatment indicating an association between the colour seen and the infected status of a wound. They concluded that the HSB system had advantages over the RGB method because the parameters of hue, saturation and intensity could be measured independently, and that this was beneficial when dealing with the complex colours displayed by healing wounds.

3.3.6. Retention of a human observer

The need to retain human colour perception in the image analysis process was recognised by a number of researchers. Human observers have been

used to either establish colour reference ranges for computerised systems, or to outline the wound within a digital image. Mekkes and Westerhof[397] and Shadi et al.[398] are examples of studies using expert knowledge to establish reference ranges. Mekkes and Westerhof[397] used a clinician's knowledge of colours exhibited by secondary healing ulcers to establish a frame of reference for their system, whilst Shai et al.[398] asked three 'senior dermatologists' to identify photographs that displayed the colour of an 'optimal' wound (red) and an 'unclean' wound (yellow).

Using clinicians to outline the wound helps to eliminate problems incurred by trying to automate the recognition of wound margins (see above). Arqvist, Hellgren and Vincent[402] used an 'operator' to map the base of an ulcer displayed in a digital colour photograph. Once the area of interest had been highlighted, the operator was then required to classify the ulcer by selecting one of sixteen wound classifications. Santamaria et al.[172, 406] used a computer system (Alfred / Medseed Wound Imaging System) to measure the wound and record 'wound characteristics'. The latter included different wound tissue types such as eschar or wet necrotic tissue (slough). To measure the area of different wound tissue clinicians were required to outline the areas on the digital image. The system would then calculate the surface area occupied by the different tissue type.

Broadly speaking, a 'gold standard' for measuring colour represented in digital wound images is yet to be determined. The reliability of any one system has not been fully established. Studies have principally been based

on artificial wounds, using a variety of controls and colour measurement algorithms. Where systems have been tested on real wounds the degree of inbuilt controls are either hard to replicate, or unfit for the practicalities of the clinical setting (e.g. MAVIS). Whilst there is some evidence that systems using a hue, saturation and brightness colour space provide a representation closer to human perception, the majority of systems still require interpretations performed by human observers.

3.4. Conclusion

The human perception of colour is a complex process. From a physical perspective it involves the physics of light; the spectral capabilities of the object being observed; the amount of illumination; and the degree of contrast between objects and their surroundings. From a physiological perspective, the ability of a human to perceive reflected light via the retina of the eye, and engage in cerebral interpretative functions influences their colour perception. Equally, the ability of humans to recognise colours allowing for different lighting conditions (colour constancy) influences colours perceived. Combine the above influences with the influences of a person's psychological development and it is clear that colour perception is a very subjective process.

As the cost of health care grows clinicians will increasingly be required to demonstrate health outcomes achieved. Systems that provide an objective measure of wound colour may help establish parameters against which

clinicians can judge the progress of a wound through the healing cycle. To date attempts to develop such systems have been hindered by limited access to technology for image capture and interpretation; the strict controls needed to reduce the influence of lighting and focal length; and the absence of reliable and valid computer algorithms.

It would appear that the use of a hue, saturation and brightness colour space provides a closer representation of human colour perception, and a degree of flexibility required to examine the subtle hues displayed by a wound. Equally, systems that use an in-shot reference card enable image analysis to be performed under a number of different lighting scenarios. It would also seem that until more reliable algorithms are developed, systems will need to rely on 'experts' to provide a reference range of colour and to help any automated system differentiate the border of a wound.

If colour represents wound status and progress, as suggested by multiple authors (see Chapter Two), and the observations of clinicians are subjective and at times unreliable, then objective measurements of wound colour are required. Systems that reliably record digital images and interpret the colours displayed within the image currently offers the greatest potential for achieving this aim. Chapter Four describes the method used for this project aimed at addressing the above deficit by establishing the foundations of a system for objectifying the colours displayed by a chronic venous leg ulcer.

4. Chapter Four: Method

Predictions of an increased burden of chronic disease resulting from an ageing population have brought with them increasing demands to prevent chronic disease. Equally, the need to contain health care costs has seen health professionals being held accountable for expenses incurred while managing chronic diseases. In an effort to meet both demands the health care industry is increasingly turning to technology to help track patient progress and, more recently, to predict the prognosis and cure trajectories for health care clients.

In previous chapters it was demonstrated that CVI constitutes a major health problem that is present in 10 per cent to 40 per cent of 'western' or 'developed' societies.[21] Chronic leg ulceration, affecting 0.06 per cent to 1.97 per cent of the population[40] is indicative of advanced venous disease and is instrumental in reducing the quality of life experienced by people with CVI..[31, 183] Expenses incurred when managing venous leg ulceration are high for both the health care agencies and the sufferer.[2, 171, 172]

To help reduce the burden of CVI a number of efforts have been made to reach consensus on a description of the disease; to diagnose the disease early; and to objectively measure progress of the diseased. Clinicians can currently diagnose the condition early (duplex and plethysmography); categorise the severity of the disease (CEAP); determine the amount of oedema (displacement or the Leg-o-metre); and measure the dimensions of

any ulceration (planimetry).[18, 41, 190, 193-195, 197, 199, 200, 205, 206, 215, 221, 234, 235, 237, 248, 259, 261, 264-266, 407-409]

However, when it comes to assessing the healing status of venous leg ulcers clinicians are forced to rely on crude colour assessments (Red-Yellow-Black or Red-Yellow-Black-Pink) that use simplistic descriptions to link the colour exhibited to physiological processes.[301, 306, 307, 309, 410] Marketing materials produced by suppliers of wound care products have seen the promotion of a *red* ulcer as a 'health ulcer'; a *yellow* ulcer as an 'infected ulcer'; a *black* ulcers as 'necrotic'; and a pink ulcer as 'newly healed'. Clinicians are encouraged to select products based on this assessment.

Efforts to use technological solutions for the above assessments have met with difficulties. Such systems have been plagued by problems of standardising colour measurement including controlling for different lighting sources, eliminating unwanted reflection and maintaining a constant orientation of the limb. Computer algorithms designed to measure colour have consistently been unable to differentiate the subtle colours exhibited by an ulcer from those of the ulcer edge or the different tissue types found within an ulcer (e.g. granular, wet necrotic).

The intent of this project was to develop a system that overcame the above problems in an effort to provide a clinical assessment tool that could quantify colours manifested by chronic venous leg ulcers.

This project used a descriptive correlation design to develop and test a system that could form the foundation for assessing the progress of venous leg ulcers. For the purposes of the study the project was conducted using three distinct phases. The first phase was to establish and test a system for capturing the colours exhibited by a venous leg ulcer. The second phase was to establish a colour range that resulted from an aggregation of expert opinion and could be used to identify either erythema or wet necrotic tissue. The third phase was to develop and test a system that would outline aggregations of pixels in digital images that fell within either of the colour ranges developed in phase two.

In line with a descriptive study, non-parametric sampling techniques were used for each phase to select either patient or clinician participants. Data was analysed using methods appropriate to this design and included descriptive, correlation and analysis of variance testing. National ethical guidelines were met during participant recruitment, collection and storage of data, and protection of confidential information.

The following chapter details the method used to develop the system and to test its reliability and validity.

4.1. Ethical consideration

Ethical consideration presented by this project was managed using a number of strategies. Permission was sought to conduct the research from the

Flinders Clinical Research and Ethics Committee (approval no. 2001.037) and The Human Research and Ethics Committee of The Alfred Hospital (approval no.156/02).

Patient participants were recruited via an information leaflet and an expression of interest provided in the outpatient waiting area. This was to prevent direct recruitment by the researcher and possible coercion. Any patient wishing to be involved in the study was required to complete the expression of interest section and place it in the collection box provided in the waiting area. The researcher then contacted the person directly and arranged a time to discuss the project. During this discussion potential participants were provided with a plain language statement detailing the project and a consent form (see Appendix H). They were informed verbally that they could withdraw from the study at any time and were provided time to ask any questions. If they agreed to participate the consent form was signed and witnessed.

Expert panel members were invited to participate via a letter detailing the requirements of their involvement. This letter also contained an expression of interest for them to complete if willing to participate (see Appendix E) and a reply paid envelope. Completion of the expression of interest was seen as consent to participate. Clinicians in the leg ulcer clinic were invited to participate using the same method as that used for the expert panel.

All data collected was stored in accordance with the guidelines of the National Health and Medical Research Council of Australia. All personal information collected during the study was kept confidential. Names and contact details of people who expressed interest in the study were stored in a password protected computer file. Participant numbers were assigned to each patient and clinician participant for all data collection sheets and electronic storage. No identifying data was used in the analysis or presentation of results.

During the study consent forms and received data were kept in a locked office. Following the study, consent forms will be stored for a period of fifteen years in a locked storage cabinet at the La Trobe University School of Nursing and Midwifery, Bundoora campus. Data collected will be archived at the same location in accordance with the National Health and Medical Research Council guidelines.

4.2. Operational definitions

The following operational definitions are presented to ensure clarity of concepts being used in the project.

Wet necrotic tissue refers to a visual manifestation presented when during cell death the cell membrane ruptures and the contents of the cell mixes with the surrounding serum giving a yellow appearance to the bed of an ulcer. It is also known as slough.

Erythema referes to a visual manifestation of the skin surrounding an ulcer that is a result of the infilitartion of erythrocytes into the interstitial compartment as part of an inflammatory process

Image capture refers to the technique of using digital technology to capture and store a photographic image.

A Pixel refers to 'picture elements' or dots that are displayed in a rectangular grid on a computer screen. Each is assigned a colour and, when aggregated, form an image.[411]

Clinical expertise has several meanings and is said to incorporate several aspects including patter recognition, intuition and cognition.[412-418] For the purposes of this study clinical expertise is defined as the skills of "a clinician who manages patients with a venous leg ulcer on a weekly basis and is nominated by his / her peers to have expertise in this area of care".

A visit refers to participants attending the outpatient clinic from which data was collected.

An episode of care refers to the management required for one leg ulcer. A participant may have one visit with two episodes of care (i.e. both legs).

4.3. Aim of the project

To develop a system that enables clinicians to easily and objectively measure the different colour manifestations exhibited in the bed of a venous leg ulcer and the surrounding skin. The long-term intent is to establish a clinical tool that can differentiate chronic venous leg ulcers that are following a normal healing cycle from those that become 'trapped' in an inflammatory process.

4.4. Objectives

1. To develop a reliable method for digitally recording the colours exhibited by a venous leg ulcer that:

- could be used in various lighting conditions
- ensures a consistent view of the leg over several episodes of care
- controls for focal length/magnification
- can be easily used in the clinical environment by clinicians.

2. Test the reliability of the above image capture system.

3. Establish a range of colour that experienced clinicians believe represent erythema.

4. Establish a range of colour that experienced clinicians believe represents wet necrotic tissue, or slough.

5. Develop a system that uses image analysis software to identify pixels in a digital photograph of a venous leg ulcer, that fall within the above colour ranges.
6. Use the above image analysis to place an observable border around groups of pixels that meet the colour range criteria in an effort to highlight areas of erythema or wet necrotic tissue evident within the photograph.
7. Test the validity of the above tissue identification system.

4.5. Methods

Due to a lack of previous knowledge and research regarding colours exhibited by chronic venous leg ulcers, and the association between those colours and the different tissue types comprising a venous leg ulcer, a descriptive-correlational framework was used to conduct the study. Descriptive-correlational methodology is known for its ability to collect a large amount of information about a suspected problem area efficiently and effectively. For this reason it is often utilised in situations where a knowledge base is beginning to be developed for a particular area.[419] Evidence from this type of study often directs further research into possible interventions to improve a situation.[419]

This project was undertaken in three phases. The first phase was to establish and test a method for capturing colours exhibited by venous leg ulcers. The second phase was to determine a colour range that experienced clinicians believed represented either erythema or wet necrotic tissue. The third phase

was to develop and test a system that highlighted areas of erythema and wet necrotic tissue evident within a digital photograph of a venous leg ulcer. The following provides a detailed description of each phase.

4.5.1. Phase 1: Capturing colours exhibited by venous leg ulcers

The method for capturing colours exhibited by venous leg ulcers was designed to control for confounding variables identified in previous studies.[268, 270, 380, 395-402] The intent was to develop a system that reduced unwanted reflections; ensured a consistent orientation and magnification of the leg during an episode of care and across episodes; and to adjust colours within a digital image that reflect the amount of illumination under which the image was captured.

4.5.1.1. Reducing reflections and maintaining a consistent magnification

To reduce unwanted reflections and maintain a consistent magnification and orientation of the leg, a 'capture frame' was developed. The frame, affectionately known as 'Ulcer-cam 2', was constructed from acrylic sheeting so that it could be easily wiped with a disinfectant between patients to prevent cross contamination. The frame consisted of a horizontal semi-circular base marked in 5^0 increments (much like a protractor), and a vertical track marked in centimetres that held camera and lighting mounts (see Figure 12). The camera and lighting mounts could move up and down the

vertical track. The track could also move horizontally around the perimeter of the semi-circular base (see Figure 12).

The 5^0 increments in the base enabled the angle of a patient's foot to be recorded on an initial visit (degrees from 0^0) and at subsequent visits. The patient's heel was placed at the apex of the protractor base and their leg rotated until a clear image of the ulcer was seen in the liquid crystal display of the camera. The lateral aspect of the patient's great toe was then aligned with the nearest degree increment and the number recorded (e.g. 80^0). On subsequent visits the lateral aspect of the patient's great toe was placed against the degree increment recorded at the initial visit to ensure a similar orientation of the leg from episode to episode (see Figure 13).

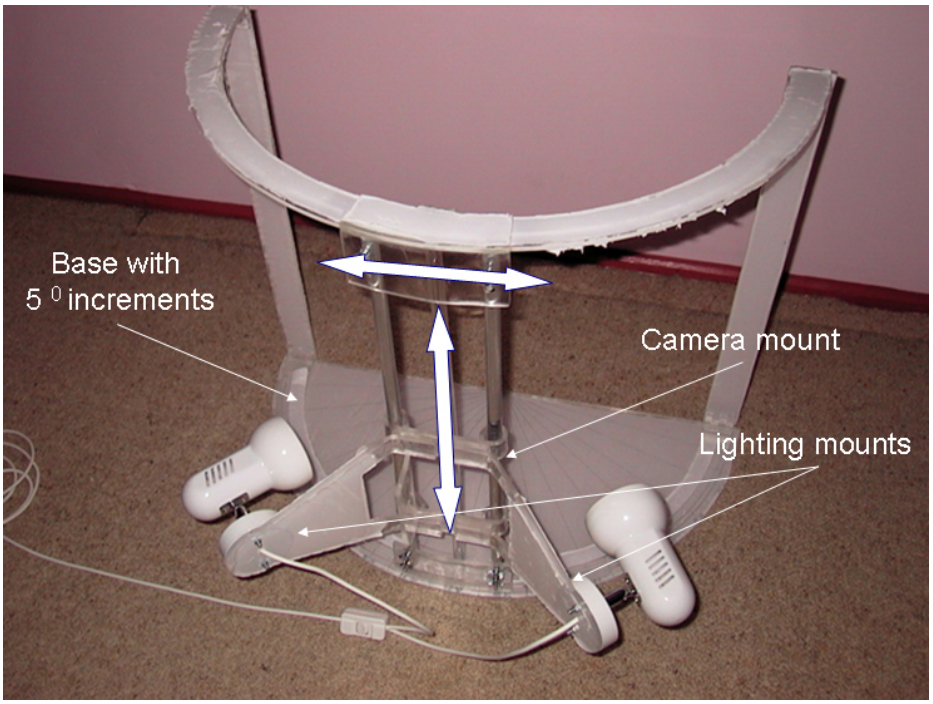


Figure 12. Ulcer-cam

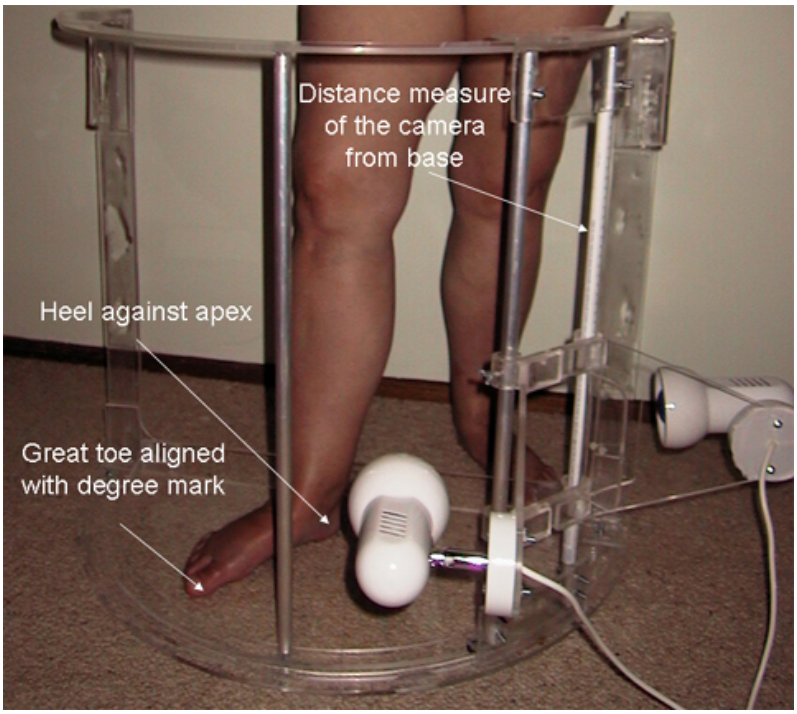


Figure 13. Controlling orientation of the leg

The camera was moved up or down the vertical track until a clear image of the ulcer was visible in the liquid crystal display. The track was then locked and the distance from the base of the frame to the tripod mount on the camera was measured using the ruler attached to the track (see Figure 13). This figure was recorded and used in conjunction with the foot angle (described above) at subsequent visits to establish a consistent orientation and degree of magnification. To eliminate colour or image biases resulting from different cameras, the same camera was used to capture all images. It was a Cannon PowerShot A50 digital camera. This was a 1.3-mega-pixel camera, providing a maximum resolution of 1280 x 960 pixels.

All images were captured at the above resolution and saved as a JPEG file. JPEG is an abbreviation for the Joint Photographic Experts Group who were initially formed in 1986 and issued the JPEG standard in 1992. The standard was approved in 1994 as ISO-10918-1. The compression method used is known as 'lossy compression' which results in some loss of visual process.[411] Although cognisant of potential visual loss, the JPEG format was chosen as it was commonly used by digital cameras and image software, and met one of the project aims; developing a system that could be used in a variety of clinical settings.

4.5.1.2. Illumination

Illumination was provided by two incandescent lamps using daylight globes meeting the *CIE illuminant C* standard adopted by the International

Commission on Illumination.[339] To help reduce unwanted reflections consideration was given to using methods previously implemented by other researchers;[397, 399, 402] in particular setting the camera at 30^0 to the wound surface. However, these methods were rejected because of a concern about potential image distortion. To compensate the lamps were mounted at 30^0 to the camera (see Figure 14). This reduced any shadows and, because of the angle of the light source, reduced any direct reflections from exudate or shiny skin resulting from lipodermatosclerosis or oedema.

To prevent changes to the illumination resulting from minor fluctuations in the power to the lamps or additional illumination from the environment, it was decided that an 'in-shot' colour reference would be used similar to the technique used by previous researchers to account for different amounts of illumination.[396, 398, 401]

The colour reference standard was comprised of cyan, yellow and magenta strips (from Pantone Colour Specifier 1.3U) and a pink and orange strip, all mounted on a green background (see Figure 15). The Pantone colours were used as the primary colour reference by the image analysis software selected for the project. The pink and orange strips were used as a secondary reference to determine if the image had been severely over or under illuminated. The green border provided a contrasting colour to the reference strips and human skin, facilitating easy identification of the reference within an image. When not in use the colour reference was stored in an envelope

that eliminated light. This was to prevent any fading of the reference as a result of continual exposure to light over the life of the project.

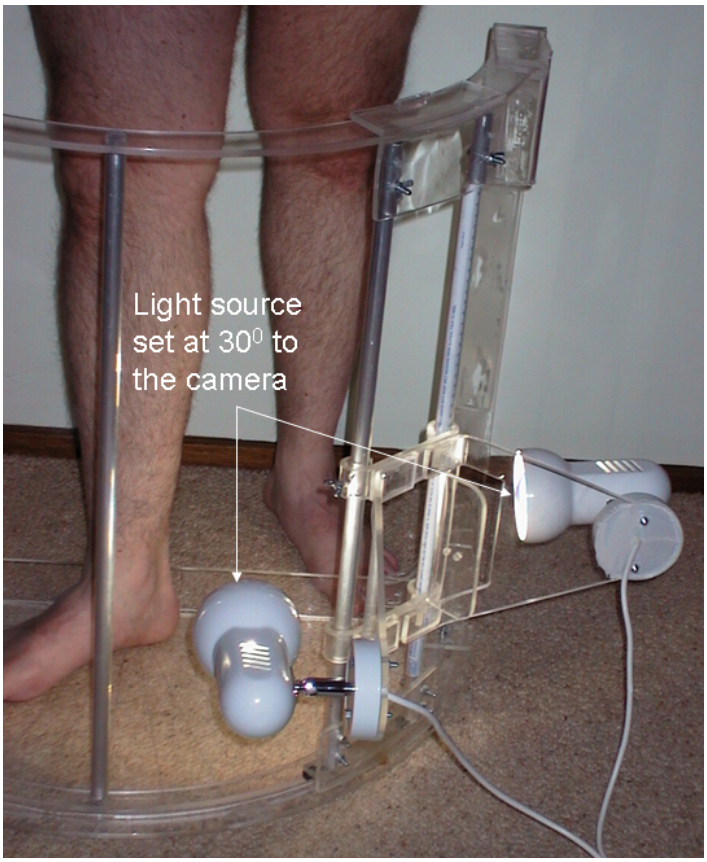


Figure 14. Daylight light source set at 30^0 to the camera

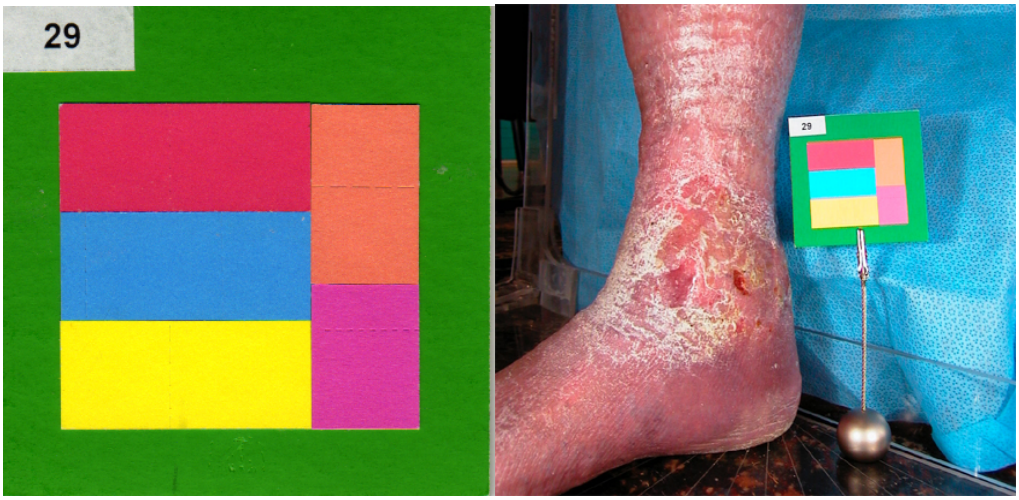


Figure 15. Colour reference example and the reference in situ

4.5.1.3. Colour measurement

The image analysis software chosen for the project was the Adelaide Skin Colour Measurement Program developed by Dr Tim Neild in 1999**.** The software was originally designed to provide an objective measure of burn scars in paediatric patients. Traditionally burn scars are assessed using four parameters; pigmentation, pliability, height and vascularity. The Vancouver Scar Scale, or Burn Scar Index, is often used by clinicians when making such assessments.[420, 421] The Adelaide Skin Colour Measurement Program was validated in a study comparing the assessments made by clinicians using the Vancouver Vascularity Score with colours recorded by the system.[422]

The Adelaide Skin Colour Measurement Program analysed the Pantone colours from the in-shot colour reference (see Figure 15) to determine the level of illumination under which the image was recorded. The hue value for each Pantone colour (cyan, yellow and magenta) formed part of the algorithm used by the software as a reference point for image analysis (see figure 16). The algorithm compared the known hue values of the in-shot reference with the recorded hues of the in-shot reference and calculated the difference in illumination under which the photograph was taken. The hue of each pixel in the image was then adjusted, or standardised to compensate for the recorded illumination difference by the computer algorithm. This provided a hue value for each pixel that would have been recorded if the photograph had been taken under standard illumination conditions (*CIE illuminant C* standard). This process eliminates the need to exclude extraneous light when taking the photograph.

Once the colours were adjusted an area of the digital photograph was selected for colour measurement. For the purposes of this phase the area being examined was confined to the ulcer bed. The area was selected by using the computer mouse to outline the ulcer bed. The software provided a tool for this purpose (see Figure 17). Once the area was defined, the software package measured the hue of each pixel within the border and provided a mean hue and saturation for the area selected (see Figure 17). The hue, saturation and brightness colour space was selected as it had provided the most consistent findings in previous wound colour research.[399, 404]

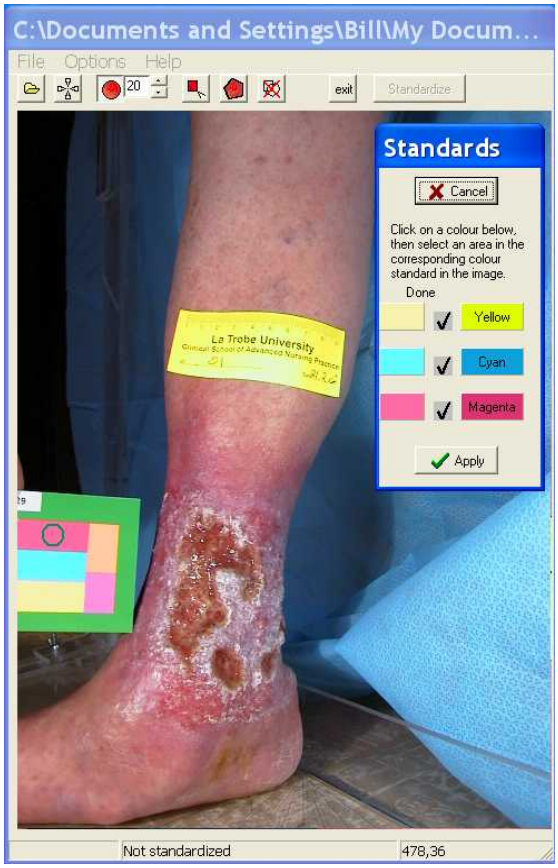


Figure 16. Adelaide Skin Colour Measurement Program interface for standardising the colours of each pixel

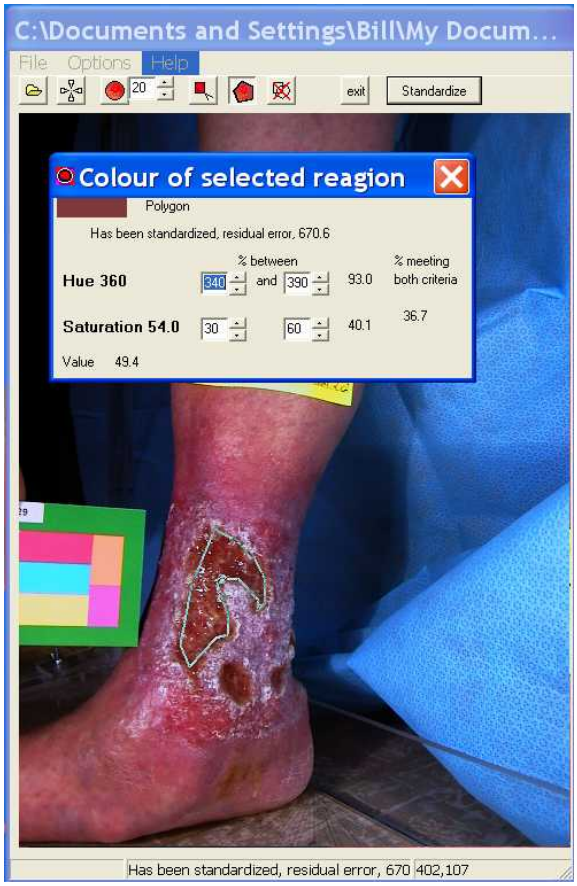


Figure 17. Selection of area to be analysed and the colour summary provided by the Adelaide Skin Colour Measurement Program

A residual error is also provided by the software. This figure represents the total difference between the standard and its true colours after the best possible correction has been applied. It alerts the user to images which effectively could not be corrected satisfactorily, usually due to adverse lighting conditions.

4.5.1.4. Modifications to the method for capturing the image and measuring the colours exhibited

Pilot testing

The system was piloted using two clinicians and two patients over ten episodes of care to capture and measure the colour images. The results are reported in Chapter Five and an article published in the Journal of Wound Care (see Appendix A).

During the pilot it was noticed that both patients found it difficult to stand in the frame and retain their balance for the required time. As the majority of patients with venous leg ulcers are in their sixth to ninth decade it was decided that the above finding would be common for the majority of patients and the frame would need to be changed. Examination of the images also indicated that the gloss finish on the frame produced some unwanted reflections (see Figure 18).

The frame was rebuilt to enable an image to be captured with the patient in a lying or horizontal position. The gloss surface was changed to a matt black

surface which retained the infection control properties of the previous frame but reduced unwanted reflections. Renamed ‘Ulcer-cam2’ the redesigned frame can be seen in Figure 19. The new frame retained the protractor base and camera track features of the initial version, thus enabling the orientation of the leg and degree of magnification to be recorded and reproduced as described above (see Section 4.4.1.1 “Reducing reflections and maintaining a consistent magnification”).

Figure 18. Reflections from the gloss surface of the frame

Figure 19. Ulcer-cam 2

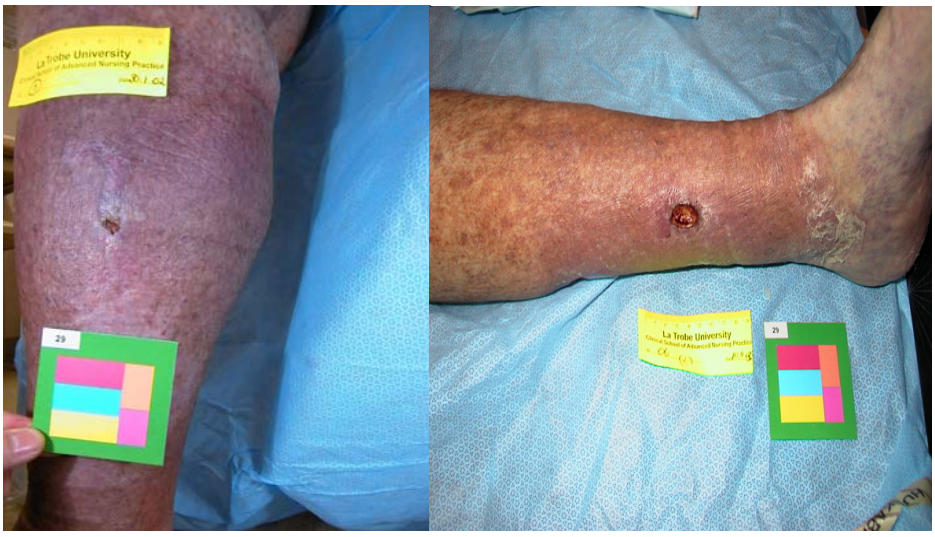


Figure 20. Blue background used in Ulcer-cam 1 and 2

During the pilot it was also noticed that the background provided unwanted distractions and hindered clear visual separation of the patient's leg (see Figure 18). Towards the end of the pilot a blue background was introduced to separate the patient's leg from other similar colours in the clinical background (see Figure 20). Blue provided a contrast to the reds and pinks of skin colour facilitating separation of the leg from other aspects in the photograph. Blue paper towels normally used to wrap surgical equipment for steam sterilisation were used to create the background for all images taken as part of the project. This provided a matt or non-reflective surface that could be discarded after the photographs had been captured for each patient. It is also readily available in the majority of health care settings thus meeting the clinical application aim of the project. This feature was incorporated into the main study.

The pilot also indicated that the residual error figures (generated by the software) were outside acceptable limits indicating that the amount of illumination was greater than the tolerances required for the image analysis. Thirty test images were taken moving the light source away from the leg a centimetre at a time to establish where the amount of illumination decreased to within the required parameters. It was found that the lights had to be placed 35 cm away from the leg before the residual error was consistently within acceptable limits. This however created an image with such poor illumination that it provided very little detail of the leg ulcer.

Following discussions with the software developer (Prof Tim Nield) it was thought that the daylight rated globes may be providing a light frequently outside of the algorithm parameters. A series of images were taken using the inbuilt flash on the camera which consistently yielded a residual error within acceptable parameters. It was felt that as the in-shot reference provided adjustment for illumination (converting colours to hues that would be seen if the image was taken in daylight) that the requirement for daylight rated lights was redundant. Images in the main study were therefore taken using the inbuilt flash on the camera. The light fittings were removed from the camera mount in Ulcer-cam 2.

4.5.1.5. Testing reliability of the system

Reliability refers to the ability of a system to measure a phenomenon in a consistent manner that can be reproduced in different contexts, by different observers.[423] Although specific to the measure being examined, reliability is often tested by conducting trials that involve combinations of a sample of patients, a sample of clinicians and sample of time intervals.[423] Findings from such trials are limited by the representative nature of the above samples, which in turn determines the clinical settings in which an instrument, or system can be reliably used to measure a phenomenon.

To examine the reliability and clinical applicability of the system being examined in this project, two types of analysis were used; intra-observer and inter-observer reliability testing. Intra-observer reliability testing examines the ability of an instrument (or system) to produce consistent measurements

when used by the same clinician over time.[423] Inter-observer reliability testing examines the ability of an instrument (or system) to produce consistent measurements when used by different clinicians over time.[423]

In phase one, intra-observer (test-retest) reliability testing was examined using two forms of analysis. The first examined the ability of the system to capture colour reliably. The second examined the ability of the system to record a photograph of a venous leg ulcer with a consistent orientation and magnification. Inter-observer reliability was examined by repeating the same sets of analysis using photographs taken by different clinicians of the same patient.

4.5.1.6. Intra-observer reliability testing

Intra-observer reliability testing examined the reliability of the system to capture hue, orientation and magnification in a consistent manner when used by the same clinician.

Aim

1. To examine the reliability of the system to produce consistent hue, orientation and magnification measurements within a set of three photographs taken at an episode of care for a patient by the same clinician.
2. To examine the reliability of the system to produce consistent hue, orientation and magnification measurements across photographic sets

taken at each episode of care for different patients by the same clinician.

Participants

For intra-observer reliability testing a convenience sample of participants was recruited from patients attending a venous leg ulcer outpatient clinic at a major metropolitan hospital. Convenience sampling is a non-probability sampling technique that is appropriate for descriptive studies. Following discussions with a biostatistician (see Acknowledgements) it was decided that as the project was a descriptive study a specific number of participants was not required. Whilst convenience sampling does not consider the degree of representativeness of a sample,[419] based on the mean number of patients treated annually over the last three years in the clinic (mean = 51.3) it was felt prudent to collect data from a minimum of twenty patients to help ensure the representative nature of the sample.

Inclusion criteria:

Patients were invited to participate if they had:

- a venous ulcer for more than six weeks
- an ankle brachial index (ABI) of greater than 0.8
- were being managed using a triple layer compression bandaging regime of zinc impregnanted bandage, undercast padding and short stretch compression bandage.
- could read and speak English

- had Caucasian (white) skin colouring.

Exclusion criteria:

Patients were excluded if they had:

- a leg ulcer without a confirmed venous aetiology
- an ankle brachial index (ABI) of less than 0.8
- were being managed with a different dressing regime from that above
- unable to understand English
- had Non-Caucasian skin colouring.

The initial criteria were set to exclude arterial disease and ensure that the colours being measured were that of venous leg ulcers only. The decision to recruit from patients who were being managed with the same dressing regime was made to prevent possible influences that different dressing products may have had on the colour of the ulcer or the surrounding skin (e.g. iodine or silver). The latter was particularly important as the aim was to develop a system that would record the colour of erythema surrounding the ulcer. Equally, the decision to exclude dark skinned participants was made to prevent possible masking of erythema that can occur with this patient cohort.

Initially the researcher had some concern over the criteria to exclude non-English speaking patients as this may affect the representative nature of the sample. However, the criterion was required as there were insufficient funds for translation of the relevant information and consent sheets. A further review of patients attending the clinic over the past two years, who required

an interpreter, revealed that this would potentially exclude less than 3% of the patients, a figure that was considered to be acceptable by the researcher.

Procedure

Once consented, a summary of demographic data was collected using the data sheet shown in Appendix B. Items such as gender; history of specific conditions (deep vein thrombosis, diabetes and rheumatoid arthritis), participant's age; age of the ulcer; size of the ulcer; and their body mass index were collected because of known associations with chronic venous disease.[2, 3, 24, 54, 56, 58, 59, 63, 70, 71, 75] This data was used to assess the representative nature of the sample.

Once the demographic data was collected a set of three sequential photographs of the participant's ulcer were taken using the Ulcer-cam 2 frame. The photographs were taken one second apart to allow time for the shutter to reset. Three photographs were taken to provide a suitable range of images for analysis (when combined across several episodes of care) and limited the impost of capture time on the clinical procedures. For the purposes of intra-observer testing, the photographs were taken by the researcher to eliminate any variation resulting from techniques used by different clinicians.

The angle of the participant's foot, and the distance of the camera from the base of the frame were recorded using the initial data collection sheet (see

Appendix B) immediately prior to the photographs being taken. The type of dressing used was also recorded at this time to ensure that the patient met the inclusion criteria described above. An adhesive label was attached to the patient's medical record to alert clinic staff that the patient had been recruited to the study.

On subsequent visits the participant was placed in the Ulcer-cam 2 frame with their foot and the camera adjusted to the original setting recorded at the first visit. Three sequential photographs were then recorded. The angle of the participant's foot and the camera distance was again recorded, as was the size of the ulcer and the dressing used. The former was recorded to ensure that the settings had not been changed from the initial visit, the latter to ensure that the management of the participant remained within the required selection criteria (see above). Data was recorded using the data sheet in Appendix C.

At the completion of each clinic, the photographs were downloaded to the same computer and each file (photograph) labelled with the participant's number, the date and the clinician who had taken the photograph. The colours of each photograph were adjusted to compensate for difference in illumination, and the mean hue of the ulcer bed measured using the Adelaide Skin Colour Measurement Program. The results were stored in a Microsoft Access® database in preparation for analysis.

Examination of differences of leg orientation and magnification in the photographs captured during a single episode of care was performed by overlaying images and quantifying the amount of difference. Using Adobe Photoshop® a copy of an image (2nd or 3rd) was pasted onto the initial image in a set with the opacity of the pasted image set to 50 per cent. The section of the patient's heel originally aligned with the apex of the protractor in the base of the Ulcer-cam 2 frame was used as the reference point for aligning the images.

Orientation was examined by digitally placing a small colour dot over the external or internal malleolus of the images being compared. The colour selected was blue to contrast with skin colours. When the images were overlaid the distance between the dots was measured in centimetres and the direction of the movement recorded using a clock face model (e.g. 1 o'clock, 2 o'clock etc). The frequency of any change in location of the malleoli was then examined using frequency distribution. Changes to orientation of the ulcer from visit to visit were also performed using the method described above.

Changes to magnification were examined by overlaying the photographs and measuring any area of difference between the ulcer sizes. This was mapped using transparent plastic sheets and quantified using planimetry provided by a device used to measure the surface area of wounds known as Visitrak® (see Chapter Three). This provided an amount of difference in magnification in cm^2.

As it was expected that the ulcer size would change between visits, using the above criteria to measure changes to magnification was not considered valid as it could lead to a type 2 error. A type 2 error occurs if a hypothesis is rejected when it is true.[423] Using changes in ulcer dimensions to determine if the magnification of the photograph had changed may have provided a significant difference between episodes leading to rejection of the hypothesis, when in fact the magnification had not changed. To overcome this limitation the yellow strip of the in-shot colour references was used as the area of comparison between images taken at different episodes. The dimensions of the strip remained constant and therefore enabled an analysis of magnification.

Data analysis

A repeated measure design was used to examine the ability of the system to reliably capture colour, magnification and orientation of a venous leg ulcer. A repeated measure design traditionally refers to studies where the subjects participate in all conditions.[423] For example, instead of using two groups to examine different dressing products, one group of patients would be used and each would be treated with all products. A repeated measure design is principally used when it is difficult to find enough participants for a study.[423] However, this was not the case for the project as the incidence of chronic venous disease and ulceration are high enough to ensure adequate numbers from which to recruit. The design was chosen as it enabled the reliability of the system to be tested by taking a series of three photographs under the

same conditions including the same patient and clinician. The same measurements were again taken when the patient re-presented completing the repeated design format.

It was hypothesised that a system for capturing colours exhibited by venous leg ulcers would be reliable if:

1. *The variation of mean hue recorded in three sequential photographs taken by the same clinician within an episode of care was not significantly different.*

2. *The variation of mean hue recorded in three sequential photographs taken by the same clinician across episodes of care was not significantly different.*

3. *The variation of the orientation and magnification of the ulcer in three sequential photographs taken by the same clinician within an episode of care was not significantly different.*

4. *The variation of the orientation and magnification of the ulcer in three sequential photographs taken by the same clinician across episodes of care was not significantly different.*

The difference in hue, magnification and orientation between each set of three sequential photographs was analysed using an analysis of variance

(ANOVA). An ANOVA enables the differences or variance between more than two groups to be examined. The test compares the amount of variance that could be expected (due to patient differences) to the total variance of the data collected. The difference between expected and total variance is used to provide a ratio known as an F-ratio.

If the variability within photographic sets (1st, 2nd or 3rd photograph) is similar to between groups variance across all photographs then the ratio will be around one. If the variability between groups of photographs were greater than the between groups variance across all three groups the F-ratio will be greater than one.[423] In order to support the above hypotheses the F-ratio within each set of three photographs (taken at each episode) would not be statistically different from the F-ratio between photographic sets.

4.5.1.7. Inter-observer testing

Inter-observer testing examined the reliability of the system to capture hue, orientation and magnification when used by different clinicians.

Aim

1. To examine the ability of the system to produce consistent hue, orientation and magnification when photographing venous leg ulcer measurements within a set of three photographs taken at an episode of care by different clinicians for the same patient.
2. To examine the ability of the system to record a photograph of a venous leg ulcer with consistent hue, orientation and magnification

when used by different clinicians across two different episodes of care for the same patient.

3. To examine the ability of the system to record a photograph of a venous leg ulcer with consistent hue, orientation and magnification when used by different clinicians for different patients.

Participants

A convenience sample of three clinicians (one of which was the researcher) was taken from the nurses who regularly managed patients in a venous leg ulcer outpatient clinic at a major metropolitan hospital. Each nurse was qualified as a Division One nurse in the State of Victoria and had provided care for patients suffering from venous leg ulcers for a minimum of five years. It was felt that selecting these clinicians would decrease the impost on the patient participants as the nurses had established rapport with the patients and understood the procedures of the clinic. A convenience sample was justified by the descriptive nature of the project.

Procedure

Prior to the commencement of the project each clinician observed a ten minute demonstration of how to use the Ulcer-cam 2 frame and digital camera. In addition they were supplied with printed instructions for recording a set of photographs (see Appendix D).

As described above, participants had three sequential photographs of their leg ulcer taken at each visit. To examine inter-observer reliability this was increased to three times each visit giving a total of nine photographs; three sets of three sequential images. The initial set was taken by the researcher (as described in intra-observer testing), and the 2nd and 3rd set were taken by the other two clinicians (one each). To prevent unnecessary discomfort for the participant their leg was left inside the Ulcer-cam 2 frame during the entire photographic procedure. The disposable blue background was also left in situ. To ensure each clinician was responsible for setting the parameters for his / her set of photographs, the patient participants were instructed to move their leg prior to each set being taken and, at the completion of each set, the camera was returned to the base of the slide.

At the completion of each clinic the photographs were downloaded and stored as described above. Each clinician would then measure the colour of the ulcer base, using the Adelaide Skin Colour Measurement Program from the photographs they had taken using the method described previously (see intra-observer testing).

Examination of variation in magnification and orientation was examined using the same procedure described in intra-observer reliability testing. In addition, changes to magnification and orientation were examined across visits. Data was examined for all three clinicians by comparing measurements taken at a participant's second visit with those recorded during their first visit.

Data Analysis

Analysis of the inter-observer data was conducted using correlation coefficients and the same procedures as those used for intra-observer testing but with the additional photographic sets and hue measurements from the other clinicians.

It was hypothesised that a system for capturing colours exhibited by venous leg ulcers would be reliable if:

1. *A correlation coefficient of > 0.8 between the hue values recorded by three clinicians for the same patient during the same episode of care was achieved.*

2. *The variation of mean hue recorded in three sequential photographic sets taken by three different clinicians for the same patient during the same episode of care was not significantly different.*

3. *The variation of ulcer orientation or magnification within photographic sets taken by three different clinicians for the same patient during the same episode of care was not significantly different.*

4. *The variation of ulcer hue, orientation or magnification within photographs taken by three different clinicians across two visits for the same patient was not significantly different.*

Degrees of hue recorded by two sets of clinicians for the same patient were initially examined using scatter plots to estimate the amount of correlation. A scatter plot provides a graphic representation of a numeric relationship between two variables.[423] A correlation refers to relationships or association between two variables of interest.[423] It implies that an increase in one variable is associated with an increase or decrease in another variable. An associated increase is known as a positive correlation, a decrease is known as a negative correlation.[423] For the purposes of this study the degrees of hue measured by two different clinicians for the same patient were examined to see how closely they correlated.

To quantify the amount of correlation between a set of two clinicians a Pearson's product moment correlation coefficient was calculated. This measures the degree of an association by using the amount of shared variance (see above) between two variables. The correlation coefficient is a score between 0 and + 1 or - 1. Zero indicates no association where as + 1 or -1 indicates a perfect association. Generally a correlation coefficient of > 0.8 is considered a very high association.[423] To support the above hypothesis a positive correlation of 0.8 or greater was required.

An ANOVA was also conducted to determine the amount of variation between the degrees of hue, and changes to magnification and orientation recorded for all three clinicians using the same technique as that used for intra-observer reliability testing. In order to support the above hypotheses, the F-ratio within each set of photographs taken by each clinician would not be statistically different from the F-ratio between photographic sets taken for that episode and across episodes.

4.5.2. Phase 2: Establishing a colour range for erythema and wet necrotic tissue

Phase two used a selection of the photographs taken in phase one to develop a range of colour that represented erythema or wet necrotic tissue (see operational definitions 4.2).

Aim

1. Establish a range of colour that experienced clinicians believe represents erythema.
2. Establish a range of colour that experienced clinicians believe represents wet necrotic tissue.

Design

A descriptive design was used to identify a range of colour that experienced clinicians believed represented erythema and wet necrotic tissue. Printed photographs of a venous leg ulcer were used as the medium from which

clinicians were asked to highlight areas that they believed represented each tissue type.

Participants

To establish a colour range that represented erythema and wet necrotic tissue a panel of experienced clinicians was formed. The model had been used in the past by other researchers attempting to build a colour range for wound healing.[397, 398] Potential clinicians were selected using the criteria described in the operational definition for expertise (see Section 4.3 Operational Definitions). Initially, the Australian Wound Management Association was asked to nominate clinicians that they deemed to have such expertise. The Association declined to provide this information citing possible contravention of privacy regulations as the reason.

The Association did advise that a national venous leg ulcer working group was being formed and the names of the committee members would be made public. Participating clinicians were recruited from this working group, plus additional clinicians known to the researcher that met the criteria. A total of ten clinicians (two doctors and eight nurses) were identified and invited to participate via a letter (see Appendix E). Each participant was a registered health care provider in Australia and was currently providing treatment for patients suffering from venous leg ulcers and had been providing this service for a minimum of five years.

Procedure

Once recruited, each expert received a series of twenty colour photographs (18 cm long by 13 cm wide) of venous leg ulcers. The photographs were selected from the researcher's library of venous leg ulcers that had the colour reference included in the image (n = 725). Photographs from the library were placed into one of four categories depicting the phases of wound healing (inflammatory, destructive, proliferative and healed). As the intent was to develop a colour range for erythema and wet necrotic tissue, a random selection of ten photographs from the inflammatory and ten from the destructive categories were used for the expert panel review. Colours in the selected photographs were adjusted to compensate for the illumination under which the image had been taken, using the Adelaide Skin Colour Measurement Program. Each image was then printed using an Epson Stylus CX6500 and Kodak photo paper with a matt finish (A4, 165 g/m^2, 150 microns), two images to a page. A matt finish was selected to reduce reflections from the image surface.

Along with the package of twenty photographs participants were supplied with a blue and red 0.5 mm Uniball micro pen. Participants were instructed to select an environment with even lighting and outline areas of erythema or wet necrotic tissue in the image using the pen supplied (see Appendix F). Erythema was to be outlined using the red pen; wet necrotic tissue was to be outlined using the blue pen. Participants were then instructed to return all photographs to the researcher using the return paid envelope provided.

Data analysis

Once received, each photograph was digitised using an Epson Stylus CX6500 flatbed scanner. The Adelaide Skin Colour Measurement Program was then used to select the areas outlined by the expert panel and measure the mean hue and standard deviation of the selected region measured. The findings were then aggregated for each tissue type (erythema or wet necrotic tissue) across all images and all experts. This provided a mean hue and standard deviation that represented either erythema or wet necrotic tissue. To establish the colour range for each tissue type it was decided to use the mean hue plus one standard deviation either side of the mean. This excluded hues that may be considered 'outliners', or were encountered in a smaller number of patients. The intent was to establish a range that would be exhibited by the majority of venous leg ulcers manifesting inflammation or wet necrotic tissue.

4.5.3. Phase 3: Developing a system to highlight areas of erythema and wet necrotic tissue in a digital photograph of a venous leg ulcer

Phase three tested the validity of a system developed to highlight areas of wet necrotic tissue and erythema within a digital image of a venous leg ulcer. The long-term aim was to develop a system that could quantify the above manifestations proving data for research and clinical decision making.

Aim

1. To develop a system that would highlight erythema and wet necrotic tissue in a digital photograph of a venous leg ulcer without input from a clinician.
2. To test the validity of the areas selected by the computer system.

Procedure

Development of the system

An image analysis technique was developed that highlighted areas of erythema and wet necrotic tissue in a digital photograph of a venous leg ulcer. The criteria used for the selection of areas within the image (pixels) were derived from the colour range obtained from phase two. Previous projects attempting to differentiate tissue types from a digital image have relied on a clinician to outline the areas of interest on a computer screen.[172, 402, 406] Such approaches introduce inter-observer differences which may have confounded any findings. It was felt that by automating the selection of pixels the inter-observer bias could be reduced.

Adobe Photoshop® version 5.5 was used to select pixels that had a hue value that fell within one standard deviation from the mean hue established for either erythema or wet necrotic tissue. Three Adobe Photoshop® functions were used to select areas of erythema or wet necrotic tissue: the 'Info' window; the 'magic wand'; and the 'stroke' function. The 'Info' window

displays the hue, saturation and brightness of any pixel directly under the computer curser. As the user moves the curser around the image the levels for each parameter change in accordance with the colour of the pixel directly beneath the curser.

The ‘magic wand’ tool enables the user to select an area of an image that includes adjacent pixels of a similar colour.[411] The colour of pixels selected is determined by a tolerance level that can be set prior to the procedure (‘Info’ window in Abode Photoshop®). The unit used for tolerance is degrees of hue. The ‘magic wand’ also enables the user to determine if the pixels selected are continuous with each other (touching) or separate. Some preliminary testing indicated that the continuous option needed to be selected to ensure that pixels fell within the colour range but were in a different location in the image (e.g. sections of the foot or leg not affected by the ulcer were not selected).

Once an area of an image was selected, the curser was then placed over the area and the right mouse button clicked. This provided a list of options including the ‘stroke’ function. This function enable the user to place a border around the area selected.[411] The colour and width of the border was determined by the user when the option was selected.

To select an area of a digital venous leg ulcer photograph the following procedure was used:

1. The tolerance for the ‘magic wand’ was set to the degrees of hue that represented one standard deviation either side of the mean hue for the tissue type being selected (erythema or wet necrotic tissue). The continuous function was also checked in this dialogue box to ensure selected pixels were linked.
2. The ‘magic wand’ was then slowly moved over the ulcer under review (peri-wound for inflammation or ulcer bed for wet necrotic tissue) until a pixel was identified (using the ‘Info’ window) that had a hue value matching the mean hue for the tissue type being selected. The left mouse button was then clicked and the software would select pixels that fell within one standard deviation of the mean hue and that were continuous (see Figure 21).

The ‘stroke’ function was then selected and the colour and width assigned for the border. The colour blue was used for erythema and yellow for wet necrotic tissue. Blue was used for erythema to differentiate it from surrounding skin. Yellow was visible when bordering wet necrotic tissue as the surrounding area was often red or pink. The software would then place a border around the pixels selected by the ‘magic wand’ (see Figure 22). The image was saved and given an alternative name to preserve the original. The process was repeated for all twenty photographs from the original set used in phase two. The resulting images were then printed (two to a page) using the same equipment and photographic paper used in phase two.

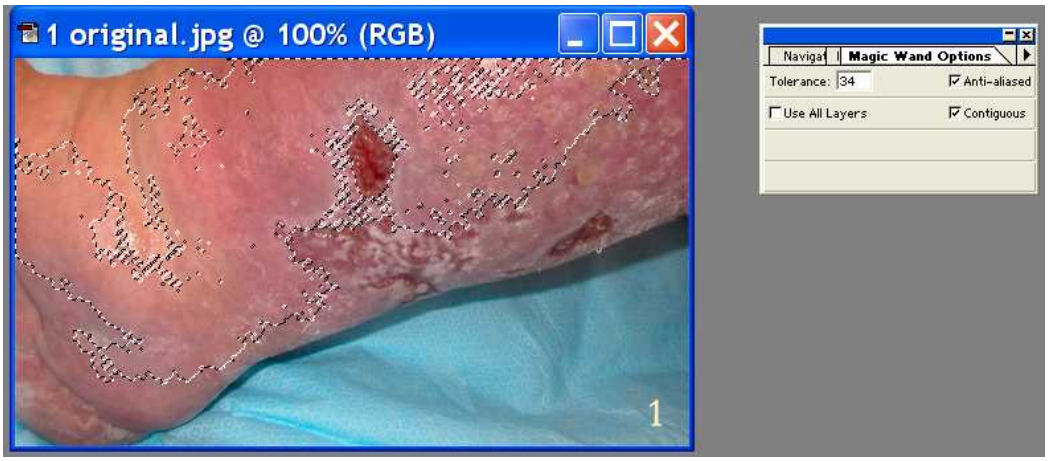


Figure 21. Selection of pixels using the magic wand

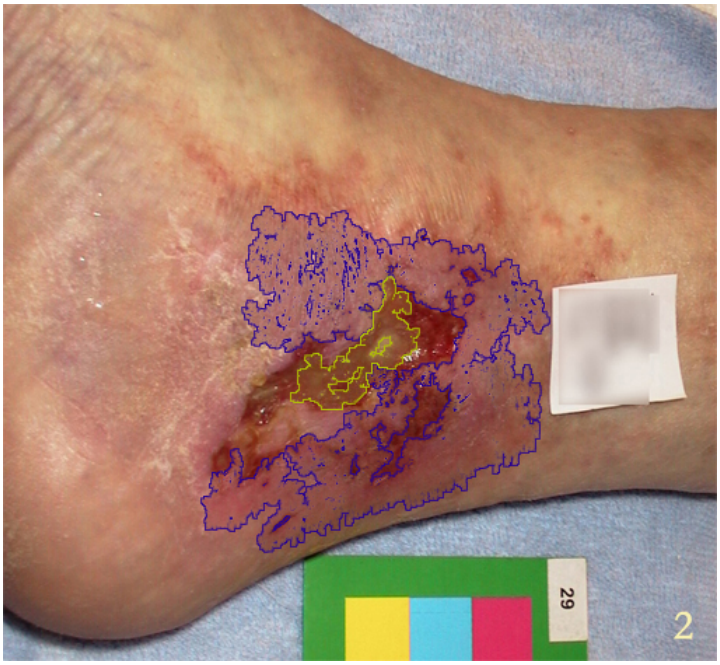


Figure 22. Border placed around different tissue types

Validation of the areas selected by the computer

Validation of the areas selected as either erythema or wet necrotic tissue was examined using two methods. The first compared any difference between areas originally selected by the clinicians in phase two with that selected by the computer. The second asked participating clinicians to indicate the level to which they agreed with the computer selection.

To examine differences between areas selected by the computer with that selected by the clinicians the overlay technique described in phase one was again used to record any areas of difference. The areas of difference were then measured using the grid and planimetry method described in phase one.

To examine the extent to which clinicians agreed with the areas selected by the computer the images were returned to the original expert panel. The sample was comprised of the clinicians recruited for phase two. As data from their original assessments were used to construct the colour ranges representing the two manifestations, it was felt that the original expert panel should be given the opportunity to validate the outcomes. Whilst it would have provided a higher level of confidence to use a different expert panel the number of clinicians with the required expertise was limited. Equally, the possibility of contamination from interactions with the original group was deemed to be high because of frequent interactions between this clinician cohort.

The clinicians were asked to indicate on a Visual Analogue Scale (see Appendix G) the extent to which they agreed with the areas highlighted by the computer software. A Visual Analogue Scale is an instrument that is used when the phenomena being measured ranges across a continuum but cannot easily be directly measured.[424] Given the nature of 'expert opinion' it was felt that this instrument was the most appropriate. The normal conventions were followed with the Visual Analogue Scale set at 100 mm long with anchored text descriptors at each end;[424] in this case 'strongly agree' or 'strongly disagree'. The respondents were also given the opportunity to make comments they felt relevant about the images. A reply paid envelope was supplied for them to return the data collection sheet and the set of photographs.

Data analysis

The analysis examined differences between areas selected by the clinicians and those selected by the computer system, and the degree to which clinicians agreed with the areas selected.

It was hypothesised that for a system to provide a valid selection of erythema or wet necrotic tissue in a digital image of a venous leg ulcer:

1. *The amount of difference between the areas selected by an expert panel and areas selected by computer software would not be statistically different.*

2. *An expert panel would strongly agree with the areas selected by the computer software for each tissue type (erythema and wet necrotic).*

To test the first hypothesis, frequency distribution and mean area (cm^2) was used to examine any differences between the area selected by the clinicians in phase two and the area selected by the computer system. A one way ANOVA was used to determine if there was any statistical difference in the areas of the image selected.

To test the second hypothesis, data from the visual analogue scale were analysed using descriptive statistics including frequency distribution, mean and standard deviation for each image, and the entire photographic set. A one way ANOVA was used to examine variance of opinion between experts for each image to determine the amount of any variation of agreement within the clinician group.

4.6. Chapter summary

This project used a descriptive correlation design to develop and test a system that could form the foundation for assessing the progress of venous leg ulcers. For the purposes of the study the project was conducted using three distinct phases. The first phase was to establish and test a system for capturing the colours exhibited by a venous leg ulcer. The second phase was to establish a colour range that resulted from an aggregation of expert opinion and could be used to identify either erythema or wet necrotic tissue. The third phase was to develop and test a system that would outline aggregations of pixels in digital images that fell within either of the colour ranges developed in phase two.

In line with a descriptive study, non-parametric sampling techniques were used for each phase to select either patient or clinician participants. Data was analysed using methods appropriate to this design and included descriptive, correlation and analysis of variance testing. National ethical guidelines were met during participant recruitment, collection and storage of data, and protection of confidential information.

Chapter Five presents the outcomes of the above analysis and provides a foundation for a discussion of the findings in Chapter Six.

5. Chapter Five: Results

The intent of this project was to develop a system that could overcome the above mentioned problems in an effort to provide a clinical assessment tool that could quantify colours manifested by chronic venous leg ulcers. This chapter reports the findings of the study with reference to the objectives of the study, principally:

1. To develop a reliable method for digitally recording the colours exhibited by a venous leg ulcer that:
    - could be used in various lighting conditions
    - ensures a consistent view of the leg over several episodes of care
    - controls for focal length / magnification
    - can be easily used in the clinical environment by clinicians.
2. Test the reliability of the above image capture system
3. Establish a range of colour that experienced clinicians believe represents erythema.
4. Establish a range of colour that experienced clinicians believe represents wet necrotic tissue, or slough.
5. Develop a system that uses image analysis software to identify pixels in a digital photograph of a venous leg ulcer, that fall within the above colour ranges.

6. Use the above image analysis to place an observable border around groups of pixels that meet the colour range criteria in an effort to highlight areas of erythema or wet necrotic tissue evident within the photograph.
7. Test the validity of the above tissue identification system.

The chapter begins with a description of the demographic data of patients recruited into phase one of the study (see Chapter Four). Although the patient sample was small (n=25), the distribution of gender, age and country of origin of the participants is presented, as is descriptive data specific to the patient's ulcer including ulcer age, size and associated co-morbidities. The intent is to examine the representative nature of the sample prior to further analysis.

The ability of the 'Ulcer-cam 2" system to reliably capture hue, orientation and magnification is then reported. This section begins by describing a pilot undertaken to test the initial prototype. Changes made to the method prior to collection of the study data as a result of the pilot findings are detailed. This is followed by a review of hue, orientation and magnification measurements for each photographic set, and conclusions drawn about the intra-observer reliability of the 'Uulcer-cam 2' system (see Chapter Four). Comparisons are made within photographic sets recorded at an episode; across photographic sets recorded at different episodes; within photographic sets for individual patients; and across photographic sets for all patients. Findings are further explored by an analysis of variance in an effort to establish the statistical

significance of trends identified. A further comparison between photographic sets recorded by different clinicians is presented in an effort to examine inter-observer reliability (see Chapter Four).

Descriptions of the hue and saturation range derived from phase two of the study are then reported. Variations between experienced clinicians recruited for the study is examined for consistency. The mean hue and colour range for both erythema and wet necrotic tissue resulting from aggregation of the findings from all participating clinicians is displayed.

The chapter concludes with an examination of the validity of the above colour range to represent erythema and wet necrotic tissue in a digital image of a venous leg ulcer. Comparisons are drawn between areas highlighted by the computer system and those selected by experienced clinicians. Trends evident in this analysis are then compared to results obtained from a questionnaire asking participating clinicians to document their level of agreement with areas selected by the computer.

Normally hue is reported using degrees of a colour circle that range from 0 degrees to 360 degrees. In this chapter the degrees presented for hue are in some instances greater than 360 degrees. This is because the Adelaide Skin Colour Measurement Program treats hue as a linear measurement adding degrees onto 360 instead of reverting back to zero. Whilst these figures could be altered to represent the colour circle (e.g. 375 degrees becomes 15 degrees) doing so would render analysis of variance invalid. For example,

the variance between 360 degrees and 15 degrees would be marked, whereas the variance between 360 degrees and 375 degrees would be much less. Given the aim of the project, it was decided to retain the linear figures provided by the above software.

5.1. Patient demographics

Twenty-three participants were recruited for phase one of the study. Thirteen were females (56 per cent) and ten (44 per cent) were males. One participant was withdrawn from the study as her hip and knee flexion was insufficient to allow one leg to be positioned inside the capture frame (Ulcer-cam 2). This resulted in a total of twenty-two participants, twelve females (54 per cent) and the remaining ten males (45 per cent). The ages ranged from 50 years to 89 years with a mean age of 69.7 years (SD 10.06 years). An examination of age distribution demonstrated that the majority of patients recruited were 69.5 years of age or greater (see Figure 23).

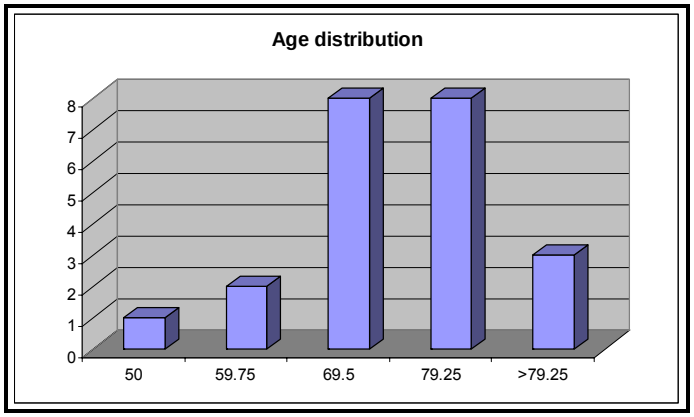


Figure 23. Age distribution of the patient sample

The majority of participants (69.5 per cent) listed their country of origin as Australia. The remaining participants originated from a number of other countries (see Table 10).

Country of Origin	Frequency
Australia	16
Malaysia	1
Sweden	1
Sri Lanka	1
Greece	1
Turkey	1
Switzerland	1

Table 10. Country of origin frequency

At the time of recruitment the basal metabolic rate was calculated for each participant as this variable has been cited as a contributing factor to chronic venous disorders. The basal metabolic rate ranged from 23.42 kg / m^2 to 35.10 kg / m^2 with a mean of 28.72 kg / m^2 (SD 3.48 kg / m^2). Participants were also asked about co-morbidities that are known to be associated with venous leg ulceration, specifically deep vein thrombosis (DVT), rheumatoid arthritis and diabetes (see Chapter One). Nine participants reported that they had not suffered from any of the assigned co-morbidities (40.9 per cent). The remainder had suffered from one or more of the co-morbidities. Only one participant had suffered from all three (see Table 11).

Condition	Frequency
Nil	9
Diabetes	3
Rheumatoid arthritis	5
DVT	4
Diabetes, Rheumatoid arthritis and DVT	1

Table 11. Associated co-morbidities

At the time of recruitment an ankle brachial pressure index (ABPI) was taken for each participant. All participants were above the 0.8 mmHg established as a minimum threshold for the application of compression. The ABPI ranged from 0.9 mmHg to 1.4 mmHg with a mean of 1.08 mmHg (SD 0.13 mmHg) (see Figure 24).

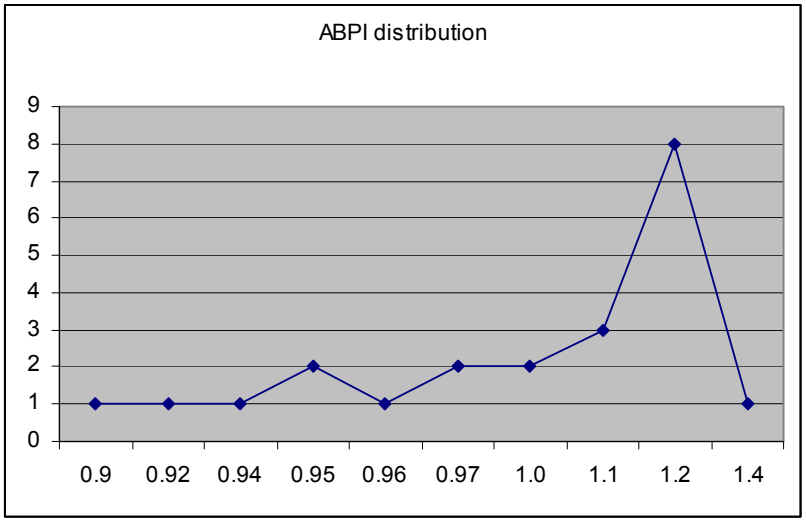


Figure 24. ABPI distribution

5.1.1.1. Initial ulcer assessment findings

From the twenty-two participants recruited a total of twenty-five ulcers were reviewed. The location of the ulcer; the duration that the participant had suffered with the current leg ulcer; ulcer dimensions; and types of wound care products were examined.

Eight possible location options were used to record the location of the venous ulcers during data collection. They included: left and right medial; lateral; anterior; and posterior aspects of the lower leg. The medial aspect of the

lower leg was the most common site with both the left and right medial areas recording the highest frequency (see Table 12). The remainder were located on the left or right lateral aspects. No ulcers were found on the anterior or posterior surfaces.

	Frequency	Per cent	Valid Per cent	Cumulative Per cent
Left lateral	2	8.0	8.0	8.0
Left medial	10	40.0	40.0	48.0
Right lateral	6	24.0	24.0	72.0
Right medial	7	28.0	28.0	100.0
Total	25	100.0	100.0	

Table 12. Frequency of ulcer location

The duration that the patient had been suffering with the current venous leg ulcer was recorded by subtracting the date that the ulcer was first diagnosed from the date that the participant was recruited into the study. On average participants reported that their ulcer had been diagnosed 36.1 months (SD 84.6) prior to being recruited into the study. One participant reported that the ulcer was first diagnosed in 1971 and had never completely healed (see Table 13).

Participant	Ulcer no	First diagnosed	Recruited	Days	Months	Years
1	1	1/1/2003	3/6/2003	64	2.1	0.2
1	2	1/1/2003	3/6/2003	64	2.1	0.2
2	1	11/1/2002	3/6/2003	125	4.2	0.3
3	1	2/17/2003	3/27/2003	38	1.3	0.1
4	1	3/1/2002	4/10/2003	405	13.5	1.1
5	1	5/1/2000	4/10/2003	1074	35.8	2.9
6	1	4/1/2002	4/10/2003	374	12.5	1.0
6	2	4/1/2002	4/10/2003	374	12.5	1.0
7	1	3/1/2003	5/1/2003	61	2.0	0.2
8	1	12/1/2002	5/1/2003	151	5.0	0.4
9	1	11/1/1971	5/29/2003	11532	384.4	31.6
10	1	4/1/2003	5/29/2003	58	1.9	0.2
11	1	2/1/2003	6/26/2003	145	4.8	0.4

11	2	2/1/2003	6/26/2003	145	4.8	0.4
12	1	11/1/1997	7/3/2003	2070	69.0	5.7
12	2	3/1/1986	7/3/2003	6333	211.1	17.4
13	1	3/1/2002	7/31/2003	517	17.2	1.4
14	1	6/1/2003	10/7/2003	128	4.3	0.4
15	1	5/1/2003	7/31/2003	91	3.0	0.2
16	1	6/1/1998	8/21/2003	1907	63.6	5.2
17	1	7/21/2003	8/21/2003	31	1.0	0.1
18	1	3/1/2003	9/4/2003	187	6.2	0.5
19	1	1/1/2001	9/4/2003	976	32.5	2.7
20	1	8/1/2003	9/18/2003	48	1.6	0.1
22	1	6/1/2004	10/23/2004	144	4.8	0.4

Table 13. Durations of leg ulcers

During the initial assessment the size of the venous leg ulcer was measured using the Visitrak® system (see Chapter Four). The area of ulceration varied from 0.4 cm^2 to 38.0 cm^2 with a mean of 6.88 cm^2 (SD 9.32 cm^2). The ulcers were relatively small, with the majority of ulcers (77.3 per cent) assessed as being less than 10 cm^2 (see Figure 25).

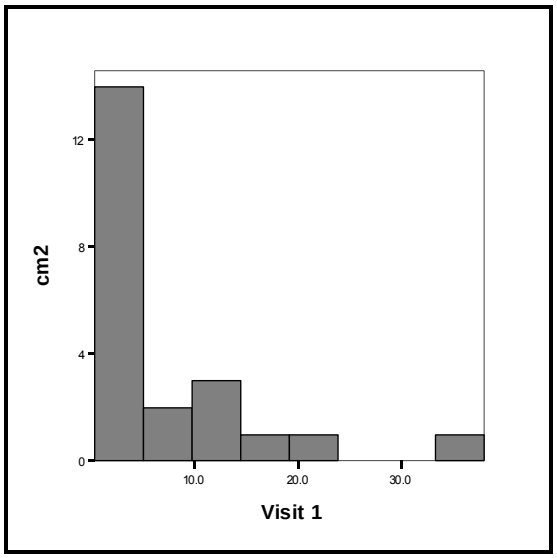


Figure 25. Distribution of ulcer size on the initial visit

When the data pertaining to the types of primary dressing being used to treat the ulcer on the initial assessment were examined it was evident that the

majority of ulcers were being treated with topical zinc oxide in the form of a gauze impregnated bandage. The next most frequently used dressing (n = 2) was a foam product often used to absorb excessive exudate (see Table 14).

	Frequency	Per cent	Valid Per cent	Cumulative Per cent
Alginate	1	4.0	4.0	4.0
Foam	1	4.0	4.0	8.0
Zinc	22	88.0	88.0	96.0
Other	1	4.0	4.0	100.0
Total	25	100.0	100.0	

Table 14. Frequency of products being used as primary dressing

When the type of compression being used was examined it was found that all participants (n = 22) were being treated with short stretch compression bandaging.

5.1.1.2. Comparison of initial ulcer assessment findings with participant demographics

The literature reviewed in Chapter One indicated a number of associations between the demographics of patients suffering from venous leg ulcers and the severity of the condition. In particular, associations have been demonstrated between the patient's chronological age and the age of the ulcer, and / or the size of the ulcer.[9, 11, 13, 15, 16, 34, 51, 73, 75, 82, 86, 118, 124, 131, 151, 161, 318, 425, 426]

To determine the extent to which this sample exhibited the above trend correlations were calculated for the above variables. Correlations between the chronological age of the participant and the duration they had suffered

from the current ulcer were examined first. An initial scatter plot indicated very little correlation between these variables (see Figure 26). This was confirmed with a Pearson correlation coefficient test that yielded a value of 0.118 (see Table 15).

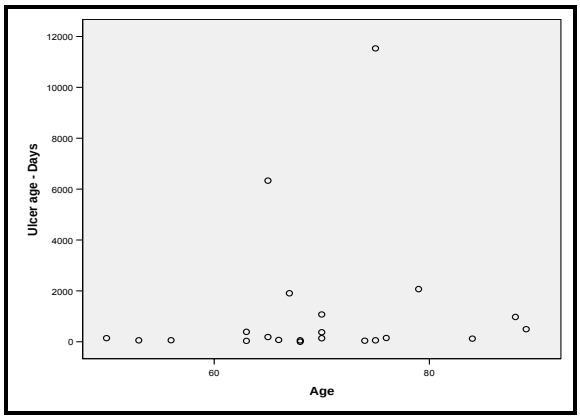


Figure 26. Correlation between the participant's age and the age of the ulcer

		Age	Ulcer age - Days
Age	Pearson Correlation	1	.118
	Sig. (2-tailed)		.601
	N	22	22
Ulcer age - Days	Pearson Correlation	.118	1
	Sig. (2-tailed)	.601	
	N	22	22

Table 15. Pearson correlation of the participant's age and the age of the ulcer

A similar lack of correlation was found between the participant's age and the size of the venous ulcer. A scatter plot (see Figure 27) and Pearson correlation coefficient yielding a figure of 0.171 (see Table 16) confirmed this assumption.

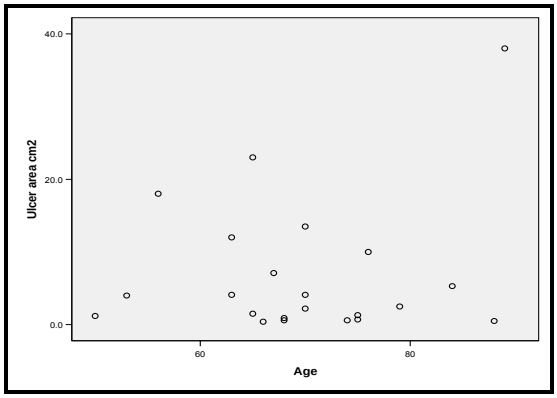


Figure 27. Correlation between the participant's age and the size of their ulcer

		Age	Ulcer size
Age	Pearson Correlation	1	.171
	Sig. (2-tailed)		.448
	N	22	22
Initial visit	Pearson Correlation	.171	1
	Sig. (2-tailed)	.448	
	N	22	22

Table 16. Pearson correlation of the participant's age and the size of the ulcer

5.2. Phase 1: Reliability of the system

The reliability of the system was determined by examining three variables: colour, orientation and magnification. Data for each variable was analysed within each episode of care and between episodes of care to determine the extent of any variation. The extent of variation between photographs taken by the same clinician and between photographs taken by different clinicians was also examined to determine intra-observational reliability (same clinician) and inter-observational reliability (different clinicians).

5.2.1. Pilot study

A pilot study was undertaken to test the practical application and initial reliability of the photographic technique and computer analysis system. Data was collected from a convenience sample of ten episodes of care provided to three patients attending a vascular outpatient department of a major metropolitan hospital. Two participants were male, one female with an age range of 48 years to 76 years (mean 64 years). The ulcers ranged in duration from one year to three years and were principally located on the left medial aspects of the lower leg. Ulcer size ranged from 1.5 cm to 8.7 cm in length and 1.5 cm to 4.6 cm in width. All ulcers in the study were comprised of primarily granular tissue with surrounding skin displaying various degrees of erythema. A summary of the findings can be found in an article published in the *Journal of Wound Care* (see Appendix A).

A total of seven ulcers were photographed, with one ulcer being photographed on two separate visits. To examine the reliability of the system an initial visual observation was made to judge colour, magnification and orientation. The mean hue was calculated and the variance examined. Colour saturation was examined in the same manner.

Visual examination of each set of images demonstrated that the frame (Ulcer-cam) maintained consistent light, and the angle of leg rotation for each photograph during each visit (see Figure 28) and over subsequent visits (see Figure 29).

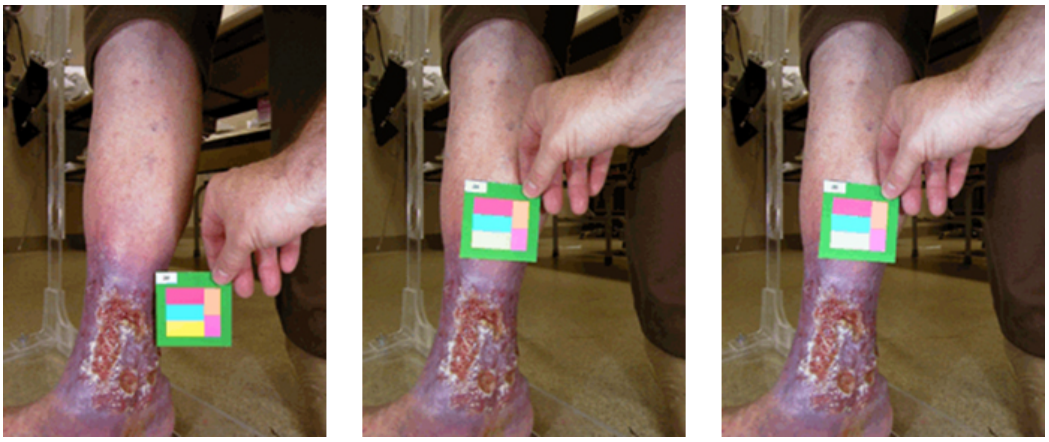


Figure 28. Three sequential photographs taken during one episode using ulcer-cam

Episode 1

Episode 2

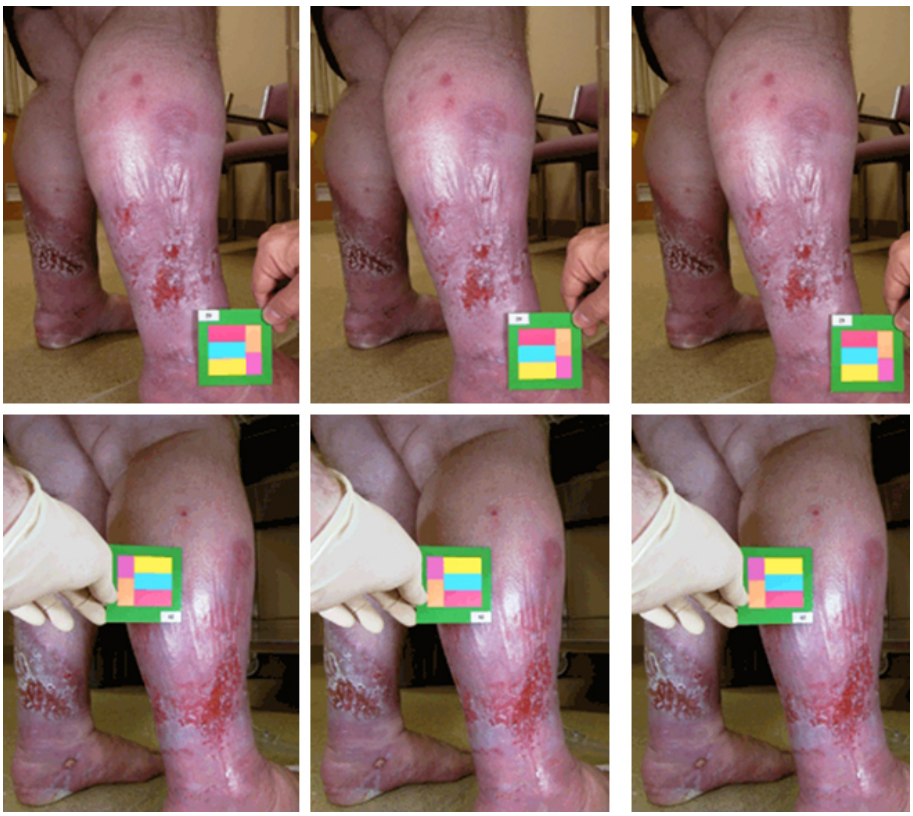


Figure 29. Three sequential photographs taken over two episodes using Ulcer-cam

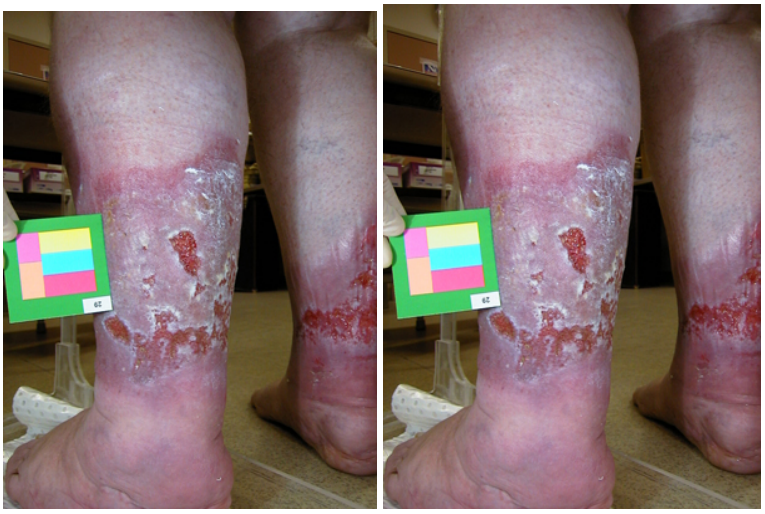
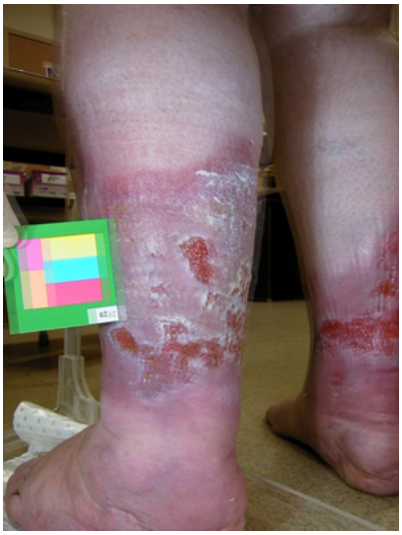


Image 1 Image 2



Combined image

Figure 30. Two sequential photographs with image 2 overlayed on image 1
Note the unwanted reflection evident from leg oedema

Overlaying of the images demonstrated small changes to the location of the leg between each photograph within a set that was indicative of small movement by the patient. Unwanted reflection was also present in three sets of photographs resulting from oedematous skin surrounding the ulcer (see Figure 30).

The colours exhibited by the ulcer bed were at the red end of the spectrum ranging from a hue of 341 degrees to 359 degrees with a mean hue of 350.3 degrees. Small differences in the ulcer bed colour were evident between the three photographs making up a set. The difference ranged from 2 degrees to 4 degrees of hue with a mean difference of 2.5 degrees of hue (see Table 1). The colour of surrounding skin showed a greater variation ranging from 292 degrees to 365 degrees of hue. The difference ranged from 1 degree to 15 degrees with a mean of 4.1 degrees (see Table 17).

Episode number	Ulcer bed	Surrounding skin
1	3	2
2	1	2
3	1	2
4	2	2
5	2	1
6	3	4
7	4	3
8	3	3
9	3	15
10	3	7
Mean	**2.5**	**4.1**

Table 17. Difference in hue measurements for pilot

Colour saturation of the ulcer bed demonstrated greater variation than colour hue. Saturation ranged from 44.9 per cent to 74.3 per cent with a mean of 59.1 per cent. The difference in saturation measurements within each set of three photographs ranged from 1 per cent to 6.8 per cent with a mean of 3.57 per cent (see Table 2). Colour saturation for the skin surrounding the ulcer ranged from 19.2 per cent to 41.4 per cent with a mean of 29 per cent. The difference in saturation measurements for each set of three photographs ranged from 1.3 per cent to 8.1 per cent with a mean of 3.24 per cent (see Table 18).

Episode number	Ulcer bed	Surrounding skin
1	4.4	1.3
2	6.9	1.9
3	1.9	1.7
4	1	2.3
5	2.2	3
6	2.3	2
7	5.6	2.6
8	1.5	2.6
9	6.8	8.1
10	3.1	6.9
Mean	**3.5**	**3.2**

Table 18. Difference in measurements of saturation in pilot study

Whilst on average the hue difference for the ulcer bed was equal to or less than 3 degrees of hue, one set of photographs demonstrated a difference of 4 degrees of hue. The inconsistent hue measurement within each photographic set suggests that the method of capture was not reliable. The reliability of the system was further questioned when colour measurements of the surrounding skin were examined. A mean of 4.1 degrees of difference (and in one instance the differences within a photographic set were as high

as 15 degrees of hue) indicated an unacceptable amount of variation. The larger variation in saturation measurements across the three photographs in each set (mean range of 3.57 per cent) provided a similar further concern about the reliability of the system.

The original images were reviewed for possible explanations of the above variation. Visual examination of the image sets indicated that the position of the in-shot colour key varied between photographs within the same set. The key was handheld and therefore its position changed. In some instances the in-shot colour key was close enough to the light source to appear 'washed out'. It was felt that this may have resulted in a different colour balance being applied to the image prior to the colour being measured, resulting in different hue and saturation results.

This was further confirmed by a review of the 'residual error' (see Chapter Four) specifications supplied by the image analysis software. The software designer recommended that a residual error rate of greater than 100 indicated that the colour swatch had been overexposed to light and was not to be relied upon to balance the colours in the photograph. Examinations of the pilot data revealed the majority of error rates for each photograph exceeded the designr recommendation (see Table 19). The mean error rate was 1342.07 (SD 1327.12) and ranged from 20.2 to 4458 units.

Visit	Error photo 1	Error photo 2	Error photo 3
1	156.6	121.3	38.3
2	41.3	34.9	34.3
3	1693.3	1075.5	1640.8
4	1593.1	1018.4	1605.3
5	74.3	349.5	126.4
6	1151.5	1137.8	1525.8
7	193	24.1	20.2
8	2011.9	2316.7	1848.5
9	1049.4	2546.3	4137.5
10	4072.1	3416.5	4458

Table 19. Residual error readings indicated by photographic analysis software

To help reduce the amount of light reaching the colour reference a series of additional photographs were taken moving the reference progressively further from the light source. To reduce the error introduced by having the colour reference handheld, a weighted clamp (see Figure 31) was used and placed a set distance from the light source. The light source used was the daylight rated globes housed within the photographic frame. A photograph was taken and the hue, saturation and error rate were measured from the colour reference. The colour reference was then moved an additional 5 cm from the light source and the process repeated. A photograph was taken at 5 cm intervals from 10 cm to 30 cm. It was felt that a distance of less than 10 cm would have put the light source too close to a patient's leg and run the risk of burning a patient as the light shades became hot to the touch. Equally, a distance of further than 30 cm would have placed the colour key outside of the photographic frame base and would therefore be in shadow from a patient's leg when used in the clinical setting. To control for extraneous light

all other light sources were excluded by using blackout curtains to exclude daylight and by switching off any room lights.

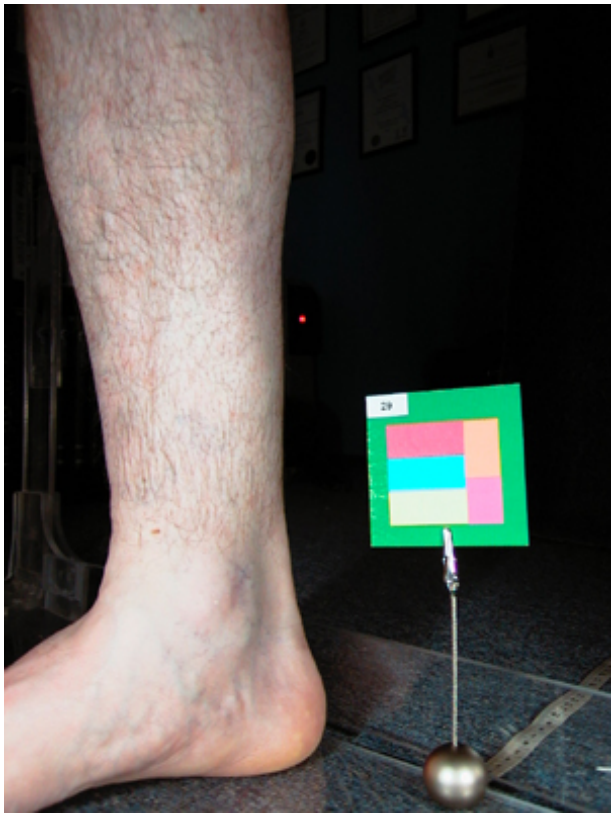


Figure 31. Method used for testing the effect of illumination and different distances from the colour reference

Table 20 illustrates the error rate recorded at distances of 10 cm to 30 cm. Although outside the accepted parameters (less than 100) the trend indicated that the residual error rate was closer to an acceptable range the further the colour key was from the light source.

Light source	Extraneous light	Background	Distance	Residual Error
Daylight globe	Controlled	Nil	10 cm	852.5
Daylight globe	Controlled	Nil	15 cm	889.5
Daylight globe	Controlled	Nil	20 cm	305.5
Daylight globe	Controlled	Nil	25 cm	286.2
Daylight globe	Controlled	Nil	30 cm	160.2

Table 20. Residual error rates at set distance from light source

To test if the above correlation was consistent additional photographs were taken at a distance from 35 cm to 45 cm. The error rate increased and remained substantially outside the acceptable criteria (see Table 21).

Light source	Extraneous light	Background	Distance	Residual Error
Daylight globe	Controlled	Nil	35 cm	606.8
Daylight globe	Controlled	Nil	40 cm	374.9
Daylight globe	Controlled	Nil	45 cm	324.2

Table 21. Residual error rates at set distance from light source

Following further discussion with the software designer it was decided to repeat the test using the in camera flash as a light source instead of the daylight rated globes. The series of photographs demonstrated residual error rates closer to but still outside the acceptable criteria (see Table 22).

Light source	Extraneous light	Background	Distance	Residual Error
Flash	Controlled	Nil	30 cm	133.6
Flash	Controlled	Nil	25 cm	123.5
Flash	Controlled	Nil	20 cm	100.1
Flash	Controlled	Nil	15 cm	111.5
Flash	Controlled	Nil	10 cm	123.6

Table 22. Residual error rates using the in camera flash light source

Discussion with the camera manufacturer revealed that the amount of light released when the camera flash is triggered was determined by the distance the camera was from the nearest object. An in camera beam of light is directed at objects in front of the camera. The amount of light reflected from those objects back to the camera is then recorded by an in camera sensor. The amount of flash light released is then determined by the amount of light reaching the in camera sensor. This is to ensure that objects are correctly exposed when taking photographs.

As the photographic technique had not included a background it was decided to insert a background into the rear of the frame used to photograph the ulcer. It was felt that this would provide the in camera sensor with a set distance and hence control the amount of flash released by the camera flash. Blue non-reflective background was selected to contrast with skin colour and prevent unwanted reflected light (see Chapter Four).

A series of photographs were taken using the technique described above. The residual error rates were all within the acceptable criteria (see Table 23).

Light source	Extraneous light	Background	Distance	Residual Error
Flash	Controlled	Blue	30 cm	53.4
Flash	Controlled	Blue	25 cm	89.1
Flash	Controlled	Blue	20 cm	85.1
Flash	Controlled	Blue	15 cm	82.1
Flash	Controlled	Blue	10 cm	92.9

Table 23. Residual error rates using the in camera flash and background

As the methods used to control for extraneous light would prove impractical in the clinical setting it was decided to repeat the above series without control for extraneous light. The residual error rate for each photograph was again within the acceptable limits (see Table 24).

Light source	Extraneous light	Background	Distance	Residual Error
Flash	No control	Blue	30 cm	54.4
Flash	No control	Blue	25 cm	91.6
Flash	No control	Blue	20 cm	85.5
Flash	No control	Blue	15 cm	92.3
Flash	No control	Blue	10 cm	94.3

Table 24. Residual error rates not controlling for extraneous light source

It was further noted that the photographs taken using the flash at 30 cm from the light source had consistently lower residual errors than the remaining photographs. A further series of photographs at 30 cm was taken to examine if this trend was consistent. The residual error rate ranged from 52.1 to 63.4 with mean of 56.92 (SD 3.967031) (see Table 25).

Light source	Extraneous light	Background	Distance	Residual Error
Flash	No control	Blue	30 cm	54.3
Flash	No control	Blue	30 cm	56.3
Flash	No control	Blue	30 cm	54.2
Flash	No control	Blue	30 cm	55.1
Flash	No control	Blue	30 cm	61.4
Flash	No control	Blue	30 cm	63.4
Flash	No control	Blue	30 cm	54.3
Flash	No control	Blue	30 cm	52.1
Flash	No control	Blue	30 cm	55.7
Flash	No control	Blue	30 cm	62.4

Table 25. Residual error rates at 30 cm from light source

Based on these findings it was decided to use flash as the light source set at a standard distance of 30 cm, and a blue background for the main study. During the pilot it was also discovered that patients who were unsteady on their feet had trouble standing in the capture frame (see Chapter Four). It was further decided that the frame could be used when the patient was horizontal. The clear acrylic used on the frame was also changed to a matt black material to help reduce unwanted reflections (see Chapter Four).

A series of ten photographs were taken using the new frame (Ulcer-cam 2) and colour key to examine any variation in residual error. All recorded error rates were within the range depicted as acceptable by the software designer. The mean error was 56.3 (SD 3.27) with a range from 52.1 to 62.4 (see Table 26).

Light source	Extraneous light	Background	Distance	Residual Error
Flash	No control	Blue	30 cm	57.6
Flash	No control	Blue	30 cm	54.3
Flash	No control	Blue	30 cm	56.3
Flash	No control	Blue	30 cm	54.2
Flash	No control	Blue	30 cm	55.1
Flash	No control	Blue	30 cm	61.4
Flash	No control	Blue	30 cm	62.4
Flash	No control	Blue	30 cm	54.3
Flash	No control	Blue	30 cm	52.1
Flash	No control	Blue	30 cm	55.7

Table 26. Residual error rates at 30 cm from light source using re-developed frame, Ulcer-cam 2

Having established a photographic technique that met the intent of the study and produced residual error rates that were within the parameters established by the software designer, the main data collection for phase one of the study was commenced.

To examine the reliability of the system to consistently capture colour, magnification and orientation two groups of analyses were examined. The first examined the *intra-observer* reliability by analysing variation of colour, magnification and orientation in a set of three photographs taken by the researcher at each participant visit to the clinic. The second examined the *inter-observer* reliability by analysing the same variables across sets of photographs (three photographs in each) taken at each visit; the first taken by the researcher and the second and third sets taken by the same two nurse clinicians working at the clinic (see Chapter Four).

The twenty-two participants recruited for the study attended the clinic a total of forty-four visits resulting in fifty episodes of care (see Table 27). A set of

three photographs were taken by three clinicians during each episode of care resulting in a total of 450 digital photographs. The majority of the photographs were taken a single or double visit which may limited the value of the analysis when compared with images taken across the healing cycle of the ulcer. Data from each episode were used to analyse the intra and inter-reliability of the system.

Participant	No. of ulcers	No. of Visits	No. of Episodes	Comments
1	2	2	4	
2	1	1	1	
3	1	1	1	
4	2	2	2	Different ulcer each visit
5	1	1	1	
6	2	1	2	
7	1	2	2	
8	1	5	5	
9	1	3	3	
10	1	1	1	
11	2	3	4	2 ulcers first visit, 1 ulcer next 2 visits
12	2	3	5	2 ulcers x 2 visits, 1 ulcer x 1 visit
13	1	1	1	
14	1	1	1	
15	1	3	3	
16	1	1	1	
17	1	1	1	
18	1	2	2	
19	1	3	3	
20	1	3	3	
21	1	2	2	
22	1	2	2	
Total	**27**	**44**	**50**	

Table 27. Level of participant involvement in the project

5.2.2. Intra-observer reliability

Intra-observer reliability was tested by examining the variation of hue, orientation and magnification within sets of digital images recorded by the same clinician at each episode of care and across episodes of care.

The analysis was aimed at testing the following hypotheses.

It was hypothesised that a system for capturing colours exhibited by venous leg ulcers would be reliable if:

1. *The variation of mean hue recorded in three sequential photographs taken by the same clinician within an episode of care was not significantly different.*

2. *The variation of mean hue recorded in three sequential photographs taken by the same clinician across episodes of care was not significantly different.*

3. *The variation of the orientation and magnification of the ulcer in three sequential photographs taken by the same clinician within an episode of care was not significantly different.*

4. *The variation of the orientation and magnification of the ulcer in three sequential photographs taken by the same clinician across episodes of care was not significantly different.*

5.2.2.1. Intra-observer reliability for colour measurement

To determine the amount of colour variation between three sequential photographs taken at each visit by the same clinician, the mean hue of each ulcer bed was measured using the Adelaide Skin Colour Measurement Program (see Chapter Four). The variance between hues was then calculated.

As expected the mean hues of the ulcer beds were at the red end of the spectrum. The mean hues ranged from 348 degrees to 394 degrees with an overall mean of 367.47 degrees (SD 8.51 degrees). The variance of the hues within each photographic set ranged from 0.33 degrees to 3.00 degrees with a mean of 0.85 degrees (SD 0.57 degrees). Table 28 details the hues and variance for each set. HueA1 is the first photograph taken in the set, HueA2 the second and HueA3 the third.

Visit	HueA1	HueA2	HueA3	Variance
1	371	372	372	0.33
2	371	371	371	0.00
3	377	378	377	0.33
4	348	351	351	3.00
5	356	356	357	0.33
6	366	367	368	1.00
7	357	356	358	1.00
8	363	361	361	1.33
9	365	366	366	0.33
10	367	365	367	1.33
11	358	357	358	0.33
12	354	355	355	0.33
13	373	374	373	0.33

14	363	361	363	1.33
15	363	363	364	0.33
16	368	369	370	1.00
17	373	373	372	0.33
18	369	368	370	1.00
19	379	378	379	0.33
20	369	371	369	1.33
21	371	373	373	1.33
22	359	361	359	1.33
23	367	369	368	1.00
24	362	364	364	1.33
25	361	360	361	0.33
26	363	364	363	0.33
27	376	378	378	1.33
28	364	365	363	1.00
29	385	386	387	1.00
30	360	362	361	1.00
31	373	373	372	0.33
32	359	358	359	0.33
33	375	376	374	1.00
34	363	363	364	0.33
35	372	372	373	0.33
36	363	362	361	1.00
37	366	369	368	2.33
38	362	362	363	0.33
39	368	366	366	1.33
40	358	357	356	1.00
41	373	374	372	1.00
42	381	380	379	1.00
43	374	372	372	1.33
44	360	360	359	0.33
45	381	381	380	0.33
46	394	393	393	0.33
47	374	373	374	0.33
48	375	373	375	1.33
49	359	360	358	1.00
50	359	361	359	1.33

Table 28. Mean hues and variance of colour for each photographic set

To analyse the variation of colour measurement across the entire collection of photographs taken by the researcher an analysis of variance (ANOVA) was calculated. This yielded an F score of 0.01 ($p = 0.98$) indicating no

significant difference between the hues recorded within each photographic set or across the entire set of photographs (see Table 29).

ANOVA						
Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	1.49	2	0.74	0.01	0.98	3.05
Within Groups	10791.9	147	73.41			
Total	10793.39	149				

Table 29. ANOVA results from intra-observer reliability testing

The absence of a statistically significant difference of colour hues within photographic sets or between photographic sets taken by the researcher enabled the null hypothesis to be rejected and the following hypothesis to be accepted.

A system for capturing colours exhibited by venous leg ulcers would be reliable if:

1. *The variation of mean hue recorded in three sequential photographs taken by the same clinician within an episode of care was not significantly different.*

2. *The variation of mean hue recorded in three sequential photographs taken by the same clinician across episodes of care was not significantly different.*

Based on the acceptance of this hypothesis it was deemed that the system developed was able to reliably capture colours exhibited by venous leg ulcers when the image was taken by the same clinician.

5.2.2.2. Intra-observer reliability for magnification and orientation analysis

Image overlays were used to determine the reliability of the system to maintain a consistent magnification and orientation of the ulcer being photographed, when used by one clinician. The second and third images were digitally pasted over the first image with the opacity of the subsequent images set to 50 per cent using Adobe Photoshop®. The area of difference was then calculated in cm^2 and the variance of each photographic set analysed (see Chapter Four).

Examination of changes to orientation within the set of three sequential photographs taken by the researcher indicated no measurable difference. Figure 32 demonstrates the consistency with which the images were captured. This was constant for all images used in the intra-observer data set yielding no difference.

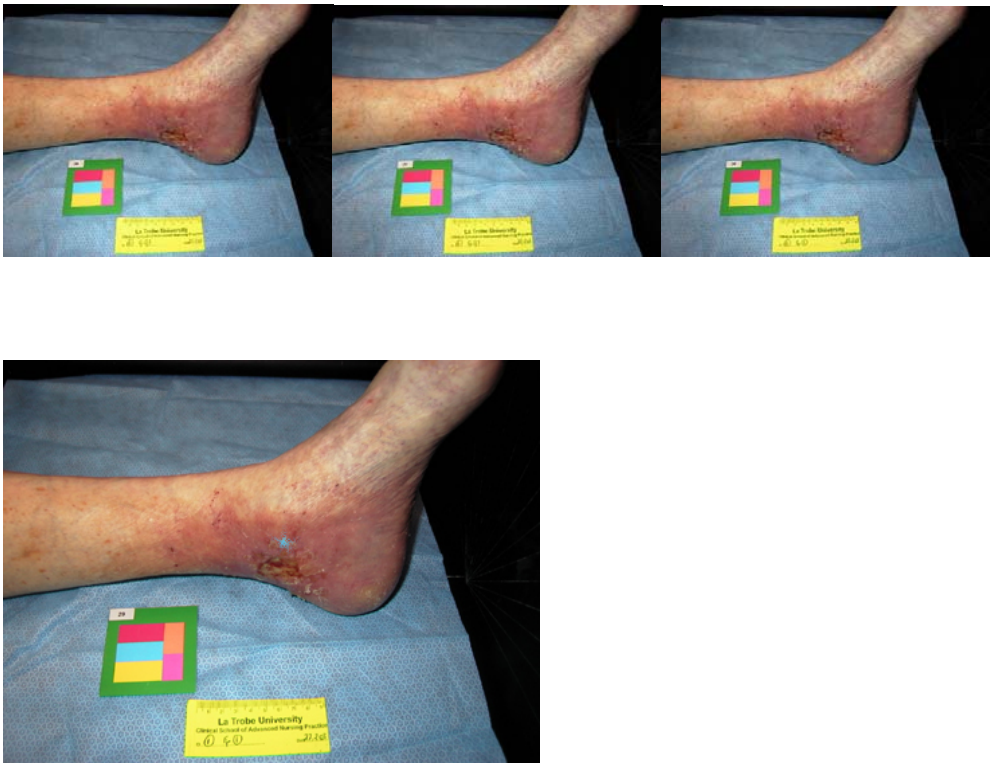


Figure 32. An example of three sequential photographs and the resultant overlaying of all three images. Note the coloured dot over the medial malleolus.

Examination of magnification changes over the three sequential photographs taken by the researcher again indicated no measurable difference (see Table 30). The absence of any measurable difference prevented further analysis.

Participant	Visit	Episode	Image1	Image2	Image3
1	1	1	4.00	4.00	4.00
1	1	2	3.00	3.00	3.00
1	2	3	2.00	2.00	2.00
1	2	4	6.60	6.60	6.60
2	1	5	5.30	5.30	5.30
3	1	6	4.10	4.10	4.10
4	1	7	0.40	0.40	0.40
4	2	8	0.10	0.10	0.10
5	1	9	4.10	4.10	4.10
6	1	10	13.50	13.50	13.50
6	1	11	4.10	4.10	4.10
7	1	12	18.00	18.00	18.00
7	2	13	0.10	0.10	0.10
8	1	14	10.00	10.00	10.00
8	2	15	11.30	11.30	11.30
8	3	16	6.60	6.60	6.60
8	4	17	9.20	9.20	9.20
8	5	18	4.00	4.00	4.00
9	1	19	1.30	1.30	1.30
9	2	20	0.80	0.80	0.80
9	3	21	1.10	1.10	1.10
10	1	22	0.90	0.90	0.90
11	1	23	1.20	1.20	1.20
11	1	24	3.00	3.00	3.00
11	2	25	1.50	1.50	1.50
11	3	26	0.70	0.70	0.70
12	1	27	2.50	2.50	2.50
12	1	28	7.80	7.80	7.80
12	2	29	3.80	3.80	3.80
12	2	30	7.80	7.80	7.80
12	3	31	6.40	6.40	6.40
13	1	32	23.00	23.00	23.00
14	1	33	38.00	38.00	38.00
15	1	34	0.70	0.70	0.70
15	2	35	0.80	0.80	0.80
15	3	36	0.40	0.40	0.40
16	1	37	7.10	7.10	7.10
17	1	38	0.60	0.60	0.60
18	1	39	0.50	0.50	0.50
18	2	40	0.30	0.30	0.30

19	1	41	1.50	1.50	1.50
19	2	42	0.40	0.40	0.40
19	3	43	0.80	0.80	0.80
20	1	44	14.30	14.30	14.30
20	2	45	14.30	14.30	14.30
20	3	46	15.60	15.60	15.60
21	1	47	2.20	2.20	2.20
21	2	48	2.20	2.20	2.20
22	1	49	2.25	2.25	2.25
22	2	50	2.00	2.00	2.00

Table 30. Ulcer size measured in cm^2 across all images used in the intra-observer analysis

Based on the absence of any measurable difference the null hypotheses were rejected and the following hypotheses accepted:

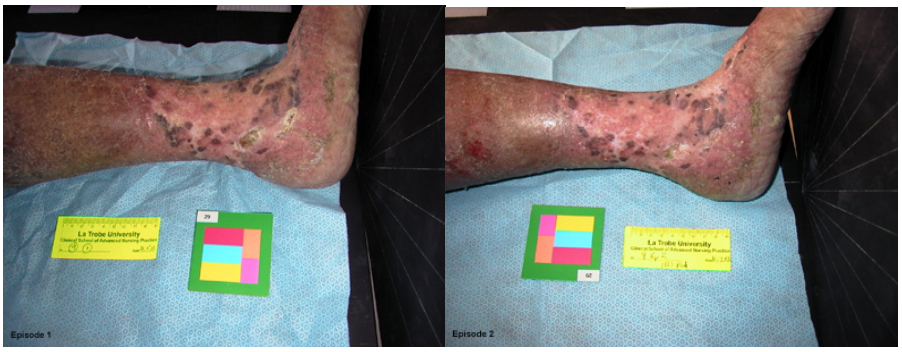
A system for capturing colours exhibited by venous leg ulcers would be reliable if:

1. *The variation of the orientation and magnification of the ulcer in three sequential photographs taken by the same clinician within an episode of care was not significantly different.*

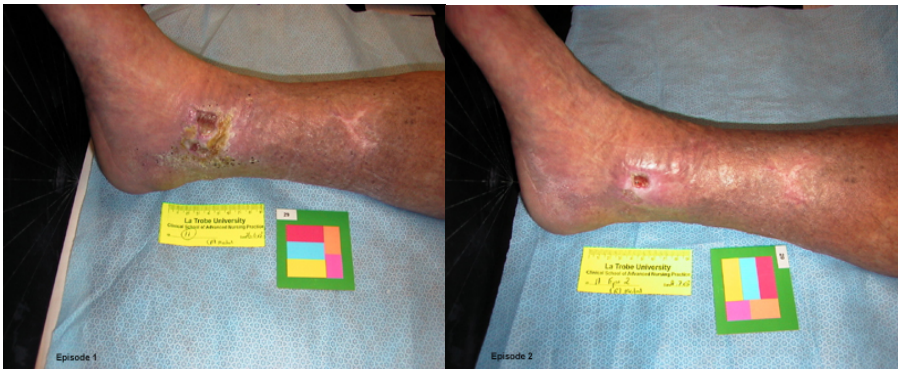
It was further expected that magnification and orientation of the image would not change for each participant visit. The above analysis was repeated comparing these variables across visits for the same participant. As not all participants had two or more visits to the clinic during the data collection period, all data pertaining to single visits were excluded. Participant 4 was also excluded because the two visits had been for two different ulcers. As a small number of participants (n = 3) had visited the clinic on more than two occasions it was decided to limit the analysis to the first and second visit only for consistency. This provided a sample of twelve participants photographed over fourteen episodes of care.

As the above analysis had indicated little difference within episodes of care, the first photograph in the series was used to measure changes to orientation and magnification. As the ulcer size was expected to change over time the yellow strip of the in-shot colour reference was used to judge changes in magnification (see Chapter Four).

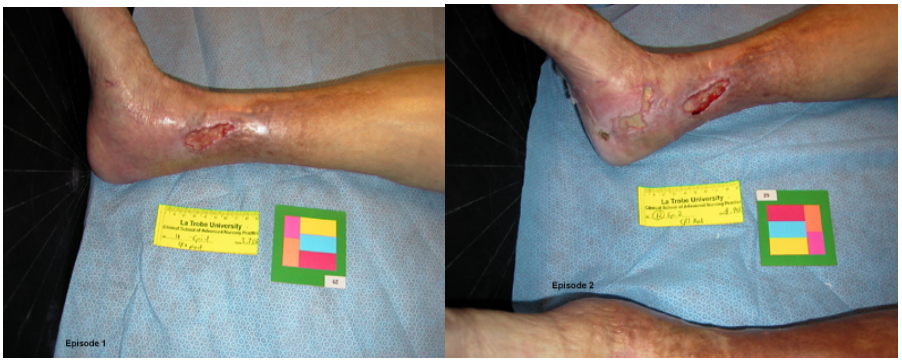
Initial visual assessment of the images taken of the same ulcer over time demonstrated changes to both orientation and magnification. Further examination revealed that the participant's heel had not always been placed on the apex of the base of the frame. As a result the foot had not been placed flat on the base of the frame resulting in a change to the angle of the foot and the degree of knee flexion changed resulting in the leg angle changing. In a small number of images the rotation of the leg had changed (see Figure 33).



Episode 1 Episode 2



Episode 1 Episode 2



Episode 1 Episode 2

Figure 33. Examples of changes to orientation and magnification across participant visits with photographs taken by one clinician

The findings supported the visual assessments with changes to the ulcer orientation ranging from 0.4 cm to 2 cm with a mean of 0.96 cm (SD: 0.51 cm). The direction of the change to orientation was variable with the most frequent (28.5 per cent, n = 4) being an adduction rotation of the leg moving the malleoli in a '6 o'clock' direction. Changes to magnification ranged from 0.14 cm^2 to 2.16 cm^2 with a mean of 0.44 cm^2 (SD: 0.70 cm^2) (see Table 31).

		Orientation		Magnification		
Patient	**Ulcer**	**cm**	**Clock face direction**	**Visit 1 (cm^2)**	**Visit 2 (cm^2)**	**Difference**
1	1	1	8	4.62	2.7	1.93
1	2	1.5	1	5.76	3.6	2.16
7	1	2	6	4.90	4.76	0.14
8	1	0.4	6	4.76	4.76	0.00
9	1	0.4	2	4.76	4.16	0.60
11	1	0.5	6	4.48	4.48	0.00
12	1	1.5	7	3.60	3.6	0.00
12	2	1.2	11	3.60	3.6	0.00
15	1	1	4	4.62	4.62	0.00
18	1	0.8	3	3.60	4.08	0.43
19	1	0.8	5	4.62	4.34	0.28
20	1	1.5	5	4.48	4.76	0.28
21	1	0.4	2	4.90	4.76	0.14
22	1	0.5	6	4.90	4.76	0.14

Table 31. Changes to orientation and magnification across patient's 1st and 2nd visit using images recorded by one clinician

Using the results obtained for magnification only an ANOVA was performed. Although the F score of 2.01 was not statistically significant (p = 0.16) it indicated a higher variation of magnification between visit than was achieved within a single visit (see Table 32). The single variable measured for orientation (difference in centimeters between the malleoli marks between visit one and two) prevented an ANOVA being calculated.

ANOVA						
Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	0.76	1	0.76	2.01	0.16	4.22
Within Groups	9.83	26	0.37			
Total	10.59	27				

Table 32. ANOVA results for magnification across participant visits

Based on the above findings the null hypothesis was rejected and the following hypothesis accepted:

A system for capturing colours exhibited by venous leg ulcers would be reliable if:

1. *The variation of the orientation and magnification of the ulcer in three sequential photographs taken by the same clinician across episodes of care was not significantly different.*

Although not statistically significant, the greater variation in these parameters, particularly magnification, for photographic sets recorded across

participant visits (taken by the same clinician) indicated that the reliability of the system to achieve consistency across clinic visits could be improved.

5.2.3. Inter-observer reliability

Inter-observer reliability was examined by comparing measures for hue, orientation and magnification across three clinicians. The analysis tested the following hypotheses:

A system for capturing colours exhibited by venous leg ulcers would be reliable if:

1. *A correlation coefficient of > 0.8 between the hue values recorded by three clinicians for the same patient during the same episode of care was achieved.*

2. *The variation of mean hue recorded in three sequential photographic sets taken by three different clinicians for the same patient during the same episode of care was not significantly different.*

3. *The variation of ulcer hue, orientation or magnification within photographic sets taken by three different clinicians for the same patient during the same episode of care was not significantly different.*

4. *The variation of ulcer hue, orientation or magnification within photographic sets taken by three different clinicians across two visits for the same patient was not significantly different.*

5.2.3.1. Inter-observer reliability for colour measurement

To examine the extent to which the above findings were replicated when the system was used by different clinicians the above analyses were repeated for the three photographic sets taken at each visit (one recorded by the researcher, the second and third set taken by the same two clinicians in the clinic).

The mean hues of the ulcer bed were again measured using the Adelaide Skin Colour Measurement Program, and the variance calculated for each set. The hue measurements for each set were performed by the clinician taking the photographs as described in Chapter Four.

Once again the mean hues were located at the red end of the spectrum with a range of 350 degrees to 394 degrees of hue with an overall mean of 367.50 degrees (SD 8.45 degrees). The variance between colours recorded from all photographs taken at each visit ranged from 0.25 per cent to 1.44 per cent with a mean of 0.57 per cent (SD: 0.29 per cent). Table 33 details the findings across photographic sets taken at each visit. Hue A represents the initial set taken by the researcher (see above), Hue B and Hue C represent the hues recorded from photographs taken by the other two clinicians.

Visit	HueA1	HueA2	HueA3	HueB1	HueB2	HueB3	HueC1	HueC2	HueC3	Variance
1	371	372	372	372	372	371	371	372	372	0.25
2	371	371	371	371	372	371	371	370	371	0.25
3	377	378	377	378	378	377	377	378	378	0.28
4	348	351	351	350	351	351	351	350	351	1.03
5	356	356	357	356	357	357	357	356	357	0.28
6	366	367	368	367	367	368	366	368	368	0.69
7	357	356	358	356	356	358	357	358	357	0.75
8	363	361	361	361	361	361	360	361	361	0.61
9	365	366	366	365	365	366	365	366	365	0.28
10	367	365	367	367	366	367	366	365	367	0.75
11	358	357	358	358	357	357	357	357	358	0.28
12	354	355	355	354	354	355	355	355	355	0.25
13	373	374	373	374	374	373	373	373	373	0.25
14	363	361	363	363	363	363	363	361	360	1.44
15	363	363	364	363	364	364	364	364	364	0.25
16	368	369	370	368	369	368	368	368	370	0.75
17	373	373	372	373	372	372	373	372	372	0.28
18	369	368	370	369	369	370	369	370	370	0.50
19	379	378	379	379	379	379	379	377	379	0.50
20	369	371	369	369	370	369	369	369	369	0.50
21	371	373	373	371	372	373	373	373	373	0.78
22	359	361	359	360	361	360	361	361	360	0.69
23	367	369	368	369	369	368	369	369	370	0.75
24	362	364	364	363	364	364	364	364	363	0.53
25	361	360	361	361	361	361	360	360	361	0.25
26	363	364	363	363	363	363	363	364	364	0.25
27	376	378	378	377	378	378	376	376	378	0.94

28	364	365	363	365	365	364	364	365	364	0.50
29	385	386	387	385	386	386	386	386	387	0.50
30	360	362	361	362	362	361	360	361	361	0.61
31	373	373	372	373	373	373	373	372	372	0.25
32	359	358	359	359	359	359	359	358	358	0.25
33	375	376	374	374	376	374	375	375	374	0.69
34	363	363	364	363	363	363	363	364	364	0.25
35	372	372	373	372	372	372	372	371	373	0.36
36	363	362	361	363	363	363	363	362	363	0.53
37	366	369	368	366	366	368	366	367	367	1.25
38	362	362	363	362	362	362	363	362	363	0.25
39	368	366	366	367	366	366	368	368	366	0.94
40	358	357	356	357	357	356	358	356	356	0.69
41	373	374	372	373	373	372	374	374	372	0.75
42	381	380	379	381	380	380	381	379	379	0.75
43	374	372	372	374	374	372	374	372	373	1.00
44	360	360	359	360	360	360	360	358	359	0.53
45	381	381	380	381	381	379	381	380	380	0.53
46	394	393	393	394	394	393	394	394	393	0.28
47	374	373	374	374	374	374	372	373	373	0.53
48	375	373	375	375	375	375	374	373	373	0.94
49	359	360	358	359	360	360	360	360	359	0.53
50	359	361	359	359	358	359	360	361	359	1.03

Table 33. Mean hues and variance for all photographs taken at each visit

To analyse the variation of colour measurement across the entire collection of photographs taken an analysis of variance (ANOVA) was again calculated. This yielded an F score of 0.00 (p = 1) indicating no significant difference between the hues recorded within each photographic set or between the sets of photographs (see Table 34).

ANOVA						
Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	3.95	8	0.49	0.00	1	1.95
Within Groups	32114.54	441	72.82			
Total	32118.49	449				

Table 34. ANOVA results from inter-observer reliability testing

To further examine the variation of colours recorded by the three different clinicians a series of correlations were undertaken. Three dimensional scatter plots reviewed an obvious positive correlation between the hues recorded by all three clinicians (see Figure 34). Hue A, B and C represent colours recorded by the three clinicians and the number represents the image. For example, Hue A1 represents the colour recorded by the first clinician for the first image in the series of three.

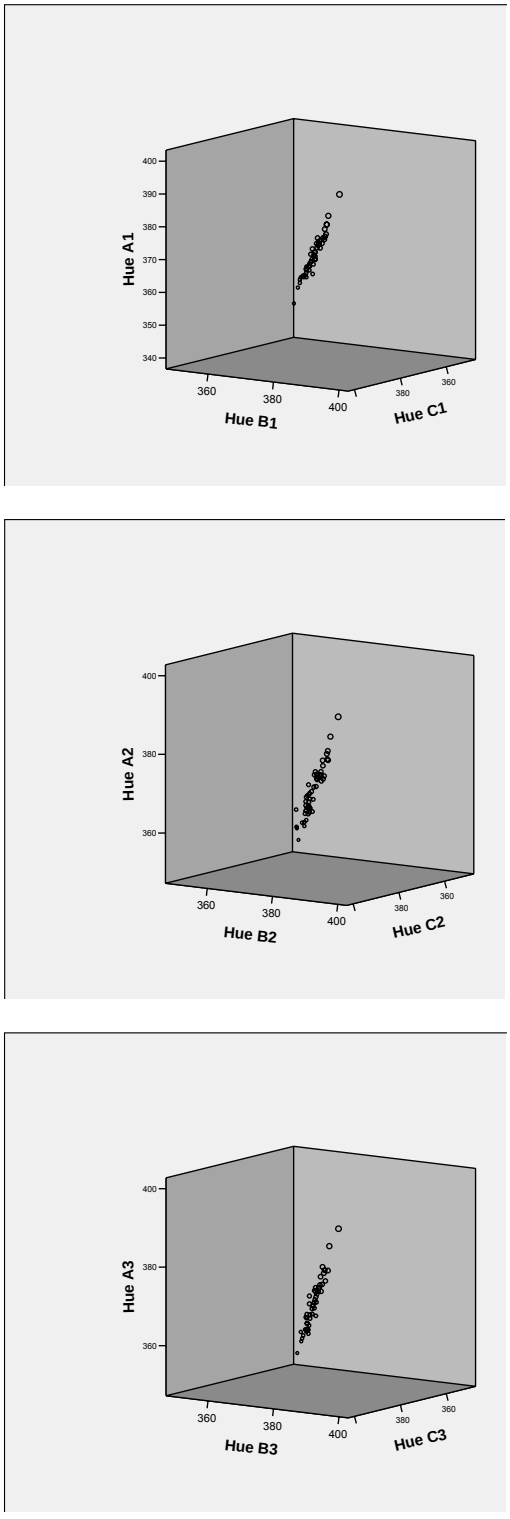


Figure 34 Three dimensional scatter plots of hues recorded by three different clinicians

The degree of correlation was confirmed by calculating a Pearson's product moment correlation coefficient which yielded a coefficient of greater than 0.99 (see Table 35).

		Hue A1	Hue A2	Hue A3	Hue B1	Hue B2	Hue B3	Hue C1	Hue C2	Hue C3
Hue A1	Pearson Correlation	1	.987(**)	.989(**)	.996(**)	.993(**)	.992(**)	.994(**)	.988(**)	.988(**)
	Sig. (2-tailed)		.000	.000	.000	.000	.000	.000	.000	.000
	N	50	50	50	50	50	50	50	50	50
Hue A2	Pearson Correlation	.987(**)	1	.990(**)	.992(**)	.994(**)	.992(**)	.992(**)	.994(**)	.992(**)
	Sig. (2-tailed)	.000		.000	.000	.000	.000	.000	.000	.000
	N	50	50	50	50	50	50	50	50	50
Hue A3	Pearson Correlation	.989(**)	.990(**)	1	.992(**)	.992(**)	.997(**)	.990(**)	.990(**)	.995(**)
	Sig. (2-tailed)	.000	.000		.000	.000	.000	.000	.000	.000
	N	50	50	50	50	50	50	50	50	50
Hue B1	Pearson Correlation	.996(**)	.992(**)	.992(**)	1	.997(**)	.994(**)	.995(**)	.991(**)	.992(**)
	Sig. (2-tailed)	.000	.000	.000		.000	.000	.000	.000	.000
	N	50	50	50	50	50	50	50	50	50
Hue B2	Pearson Correlation	.993(**)	.994(**)	.992(**)	.997(**)	1	.995(**)	.995(**)	.991(**)	.993(**)
	Sig. (2-tailed)	.000	.000	.000	.000		.000	.000	.000	.000
	N	50	50	50	50	50	50	50	50	50
Hue B3	Pearson Correlation	.992(**)	.992(**)	.997(**)	.994(**)	.995(**)	1	.993(**)	.992(**)	.994(**)
	Sig. (2-tailed)	.000	.000	.000	.000	.000		.000	.000	.000
	N	50	50	50	50	50	50	50	50	50
Hue C1	Pearson Correlation	.994(**)	.992(**)	.990(**)	.995(**)	.995(**)	.993(**)	1	.993(**)	.991(**)
	Sig. (2-tailed)	.000	.000	.000	.000	.000	.000		.000	.000
	N	50	50	50	50	50	50	50	50	50
Hue C2	Pearson Correlation	.988(**)	.994(**)	.990(**)	.991(**)	.991(**)	.992(**)	.993(**)	1	.993(**)
	Sig. (2-tailed)	.000	.000	.000	.000	.000	.000	.000		.000
	N	50	50	50	50	50	50	50	50	50
Hue C3	Pearson Correlation	.988(**)	.992(**)	.995(**)	.992(**)	.993(**)	.994(**)	.991(**)	.993(**)	1
	Sig. (2-tailed)	.000	.000	.000	.000	.000	.000	.000	.000	
	N	50	50	50	50	50	50	50	50	50

** Correlation is significant at the 0.01 level (2-tailed)

Table 35. Correlation coefficient across all three clinicians

Based on the absence of a statistically significant difference of colour variation within sets of photographs and between photographic sets taken by different clinicians the null hypothesis was rejected and the following hypotheses were accepted.

A system for capturing colours exhibited by venous leg ulcers would be reliable if:

1. *A correlation coefficient of > 0.8 between the hue values recorded by three clinicians for the same patient during the same episode of care was achieved.*

2. *The variation of mean hue recorded in three sequential photographic sets taken by three different clinicians for the same patient during the same episode of care was not significantly different.*

5.2.3.2. Inter-observer reliability – magnification and orientation

To determine the reliability of the system to maintain a consistent magnification and orientation when used by other clinicians the above analysis was repeated using images captured by all three clinicians in the clinic. The image sets were the same sets used to test the reliability of the system to capture ulcer colours (see above).

Initial visual assessment of the images indicated little difference between the orientation and magnification of images taken by the two clinicians and those taken by the researcher. This was confirmed when images were overlaid (see Figure 35).

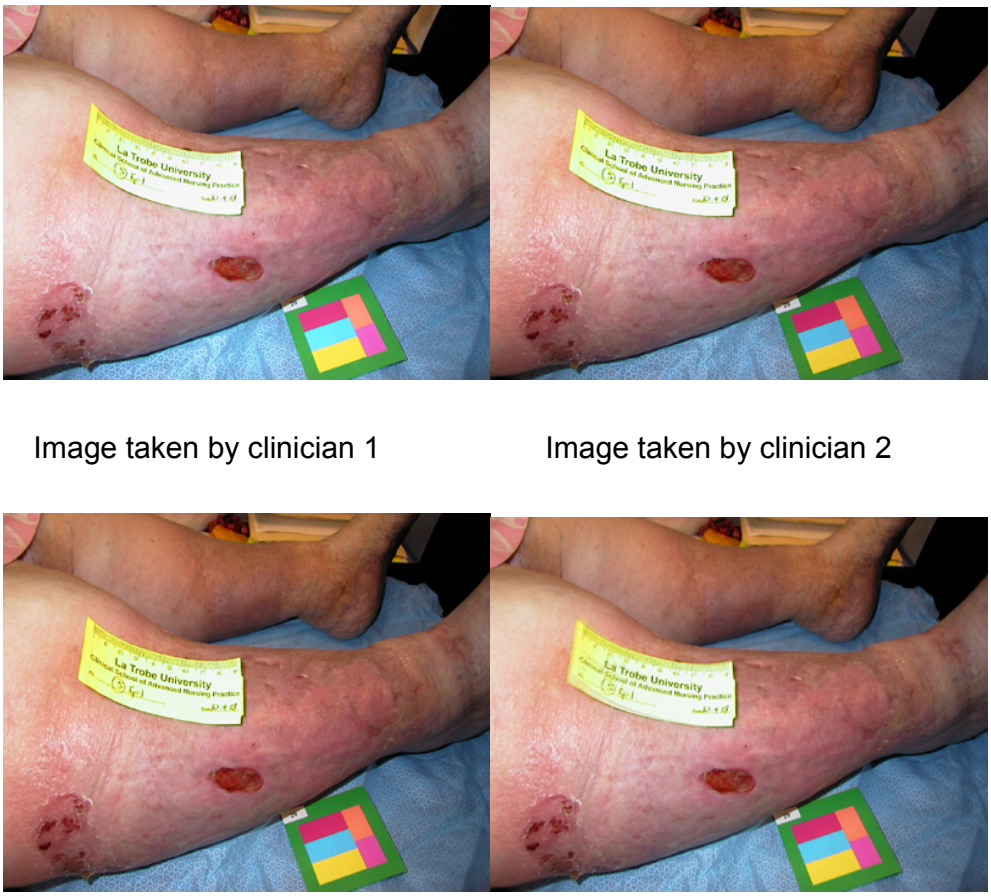


Image taken by clinician 1 Image taken by clinician 2

Image taken by clinician 3 Overlay of images taken by clinicians

Figure 35. Example of images taken by three different clinicians at the same episode

The orientation and magnification difference between photographs taken by the three clinicians were measured using the techniques described previously (see Chapter Four). The findings further supported the visual assessments made. Small differences were found in the orientation of the photographs ranging from 0 cm to 0.3 cm with a mean of 0.02 cm (SD: 0.1 cm). The vast majority of image comparisons yielded no measureable difference (see Table 36).

Participant	Visit	Episode	C1I2	C1I3	C2I1	C2I2	C2I3	C3I3	C3I2	C3I3
1	1	1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1	1	2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
1	2	3	0.0	0.0	0.1	0.1	0.1	0.0	0.0	0.0
1	2	4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2	1	5	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.1
3	1	6	0.0	0.0	0.2	0.2	0.2	0.0	0.0	0.0
4	1	7	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.1
4	2	8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
5	1	9	0.0	0.0	0.1	0.1	0.1	0.1	0.1	0.1
6	1	10	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
6	1	11	0.0	0.0	0.3	0.3	0.3	0.0	0.0	0.0
7	1	12	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
7	2	13	0.0	0.0	0.2	0.2	0.2	0.0	0.0	0.0
8	1	14	0.0	0.0	0.1	0.1	0.1	0.0	0.0	0.0
8	2	15	0.0	0.0	0.0	0.0	0.0	0.2	0.2	0.2
8	3	16	0.0	0.0	0.1	0.1	0.1	0.2	0.2	0.2
8	4	17	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
8	5	18	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
9	1	19	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
9	2	20	0.0	0.0	0.2	0.2	0.2	0.0	0.0	0.0
9	3	21	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
10	1	22	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
11	1	23	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
11	1	24	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
11	2	25	0.0	0.0	0.1	0.1	0.1	0.0	0.0	0.0
11	3	26	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

12	1	27	0.0	0.0	0.2	0.2	0.2	0.0	0.0	0.0
12	1	28	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1
12	2	29	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
12	2	30	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
12	3	31	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
13	1	32	0.0	0.0	0.1	0.1	0.1	0.0	0.0	0.0
14	1	33	0.0	0.0	0.2	0.2	0.2	0.0	0.0	0.0
15	1	34	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
15	2	35	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
15	3	36	0.0	0.0	0.2	0.2	0.2	0.2	0.2	0.2
16	1	37	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
17	1	38	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
18	1	39	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
18	2	40	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
19	1	41	0.0	0.0	0.1	0.1	0.1	0.0	0.0	0.0
19	2	42	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
19	3	43	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
20	1	44	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
20	2	45	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
20	3	46	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
21	1	47	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
21	2	48	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
22	1	49	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
22	2	50	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Table 36. Difference in location of the malleoli between the initial and subsequent photographs

Examination of correlations between the orientations of images across all three clinicians confirmed the above findings. Figure 36 provides a visual representation of the correlation between clinicians (C1 to C3) and the images compared (I1 to I3).

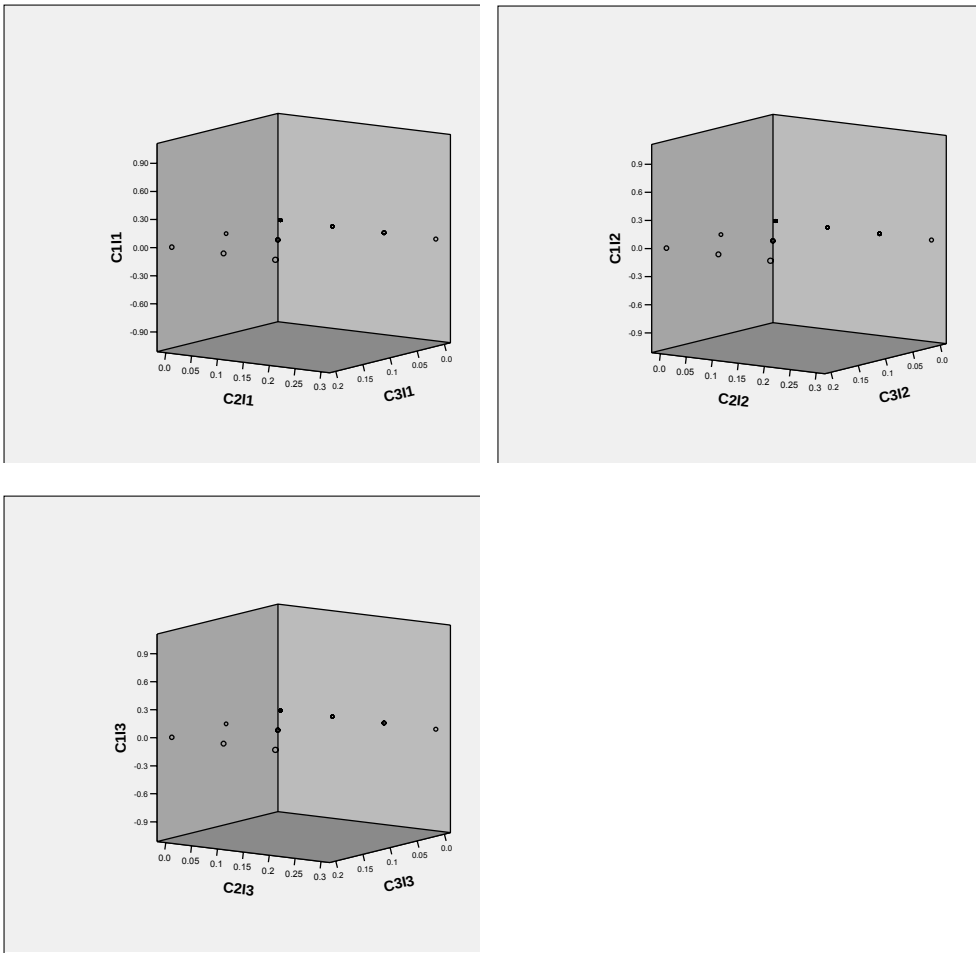


Figure 36. Correlations of orientation measurements across all three clinicians

The number of measurements recording a zero difference (see Table 36 above) rendered any Pearson's product moment correlation coefficient analysis inaccurate (see Table 37). Reduced correlations can be seen between some orientation measurements, for example a coefficient of 0.20 between clinician 2 (image two (C2I2)) and clinician 3, (image two (C3I2)), but these are inaccurate for the reason described above.

Correlations

		C1I2	C1I3	C2I2	C2I3	C3I2	C3I3
C1I2	Pearson Correlation	.(a)	.(a)	.(a)	.(a)	.(a)	.(a)
	Sig. (2-tailed)		.	.	.	.	.
	N	50	50	50	50	50	50
C1I3	Pearson Correlation	.(a)	.(a)	.(a)	.(a)	.(a)	.(a)
	Sig. (2-tailed)	.		.	.	.	.
	N	50	50	50	50	50	50
C2I2	Pearson Correlation	.(a)	.(a)	1	1.000(**)	.203	.203
	Sig. (2-tailed)	.	.		.000	.157	.157
	N	50	50	50	50	50	50
C2I3	Pearson Correlation	.(a)	.(a)	1.000(**)	1	.203	.203
	Sig. (2-tailed)	.	.	.000		.157	.157
	N	50	50	50	50	50	50
C3I2	Pearson Correlation	.(a)	.(a)	.203	.203	1	1.000(**)
	Sig. (2-tailed)	.	.	.157	.157		.000
	N	50	50	50	50	50	50
C3I3	Pearson Correlation	.(a)	.(a)	.203	.203	1.000(**)	1
	Sig. (2-tailed)	.	.	.157	.157	.000	
	N	50	50	50	50	50	50

** Correlation is significant at the 0.01 level (2-tailed)
Cannot be computed because at least one of the variables is constant

Table 37. Correlation coefficient between orientation measurements recorded across clinicians

The findings for magnification demonstrated no measureable difference. The area measurements of each ulcer were the same as the area measured in the initial photograph. The absence of difference prevented further analysis leading to the rejection of the null hypothesis and acceptance of the following hypothesis.

A system for capturing colours exhibited by venous leg ulcers would be reliable if:

1. *The variation of ulcer orientation or magnification within photographic sets taken by three different clinicians for the same patient during the same episode of care was not significantly different.*

Further examination of magnification and orientation changes of images, across visits and across the three clinicians were made. As the above analysis had demonstrated small differences within each photographic set across the three clinicians, it was expected that the findings would reflect the trends identified in the intra-observer reliability testing. This was supported with changes to orientation ranging from 0.5 cm to 1.6 cm with a mean of 0.98 cm (SD: 0.51 cm) (see Table 38).

		Orientation					
		Clinician 1		Clinician 2		Clinician 3	
Patient	Ulcer	cm	clock face	cm	clock face	cm	clock face
1	1	1	8	1	8	1	8
1	2	1.5	1	1.6	1	1.5	1
7	1	2	6	2.2	6	2	6
8	1	0.4	6	0.4	6	0.4	6
9	1	0.4	2	0.6	2	0.4	2
11	1	0.5	6	0.5	6	0.5	6
12	1	1.5	7	1.5	7	1.5	7
12	2	1.2	11	1.4	11	1.2	11
15	1	1	4	1	4	1	4
18	1	0.8	3	0.8	3	0.8	3
19	1	0.8	5	0.8	5	0.8	5
20	1	1.5	5	1.5	5	1.5	5
21	1	0.4	2	0.4	2	0.4	2
22	1	0.5	6	0.5	6	0.5	6

Table 38. Changes to orientation recorded by all three clinicians across participant visits

An ANOVA performed across the findings for all clinicians supported a small but not statically significant difference with an F score of 0.04 (p = 0.9) (see Table 39).

ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	0.023	2	0.01	0.042	0.95	3.23
Within Groups	10.78	39	0.27			
Total	10.80	41				

Table 39. ANOVA of orientation between the three clinicians over different visits for the same participant

As expected, changes to magnification demonstrated no difference to the trend identified in intra-observer testing as there were no differences within photographic sets across the three clinicians (see Table 40).

		Magnification								
		Clinician 1			Clinician 2			Clinician 3		
Participant	Ulcer	Visit 1 (cm^2)	Visit 2 (cm^2)	Diff	Visit 1 (cm^2)	Visit 2 (cm^2)	Diff	Visit 1 (cm^2)	Visit 2 (cm^2)	Diff
1	1	4.62	2.7	1.93	4.62	2.7	1.93	4.62	2.7	1.93
1	2	5.76	3.6	2.16	5.76	3.6	2.16	5.76	3.6	2.16
7	1	4.90	4.76	0.14	4.90	4.76	0.14	4.90	4.76	0.14
8	1	4.76	4.76	0.00	4.76	4.76	0.00	4.76	4.76	0.00
9	1	4.76	4.16	0.60	4.76	4.16	0.60	4.76	4.16	0.60
11	1	4.48	4.48	0.00	4.48	4.48	0.00	4.48	4.48	0.00
12	1	3.60	3.6	0.00	3.60	3.6	0.00	3.60	3.6	0.00
12	2	3.60	3.6	0.00	3.60	3.6	0.00	3.60	3.6	0.00
15	1	4.62	4.62	0.00	4.62	4.62	0.00	4.62	4.62	0.00
18	1	3.60	4.08	0.43	3.60	4.08	0.43	3.60	4.08	0.43
19	1	4.62	4.34	0.28	4.62	4.34	0.28	4.62	4.34	0.28
20	1	4.48	4.76	0.28	4.48	4.76	0.28	4.48	4.76	0.28
21	1	4.90	4.76	0.14	4.90	4.76	0.14	4.90	4.76	0.14
22	1	4.90	4.76	0.14	4.90	4.76	0.14	4.90	4.76	0.14

Table 40. Changes to magnification recorded by all three clinicians across participant visits

This was confirmed with an ANOVA which provided similar findings to those in the intra-observer testing, with an F score of 1.20 (p = .31) indicating a small but not statistically significant variation (see Table 41).

ANOVA

Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	2.28	5	0.45	1.20	0.31	2.33
Within Groups	29.51	78	0.37			
Total	31.79	83				

Table 41. ANOVA of magnification between the three clinicians over different visits for the same participant

Based on these findings the null hypothesis was rejected and the following hypothesis accepted.

A system for capturing colours exhibited by venous leg ulcers would be reliable if:

1. *The variation of ulcer hue, orientation or magnification within photographic sets taken by three different clinicians across two visits for the same patient was not significantly different.*

5.3. Phase 2: Establishing the hue for erythema and wet necrotic tissue

Data collected from a group of clinicians experienced at assessing venous leg ulcers was used to establish a colour range that represented erythema and wet necrotic tissue. The method had been used previously by researchers attempting to build a colour range for wound healing.[397, 398]

Clinicians were selected using the criteria described in the Operational Definitions (see Section 4.3) for expertise and recommendations from the Australian Wound Management Association (see Chapter Four).

A total of ten clinicians were invited to participate. They were drawn from different disciplines (two were doctors and eight were nurses); different geographic locations (one from NSW, four from Victoria, two from WA, one from Tasmania, one from Qld and one from SA); and different clinical settings (two from acute care, six from community care and two from aged care). From the ten invited clinicians, eight agreed to participate providing the following distributions (see Table 42).

Variable	Distribution
Discipline	Doctors (2) Nurses (6)
Location	Victoria (4) WA (1) Qld (1) Tasmania (1) South Australia (1)
Clinical setting	Community care (6) Aged care (2)

Table 42. Distribution of variables for clinicians agreeing to participate

Each participant was supplied with a series of twenty venous leg ulcer photographs and asked to outline areas of erythema and wet necrotic tissue as described in Chapter Four. Responses were received from six clinicians providing a response rate of 75 per cent. Follow up reminder letters were sent to those participants who had not responded but these failed to generate any additional responses. Table 43 details the distribution of the above variables for the responses received.

Variable	Distribution
Discipline	Doctors (1) Nurses (5)
Location	Victoria (4) Tasmania (1) South Australia (1)
Clinical setting	Community care (4) Aged care (2)

Table 43. Distribution of variables for clinicians responding

5.3.1. Colour range identified

Responses from the six clinicians provided a total of 120 photographs with areas of either erythema, wet necrotic tissue or both identified. As clinicians were provided with a printed copy of each photograph on which to highlight the different tissue types the images were re-digitised using a flat-bed scanner. The resulting digital images were used to quantify the hue range evident in the areas outlined by the clinicians (see Chapter Four).

From the 120 photographs provided, a total of 193 highlighted areas were identified: 51.8 per cent (n = 100) representing erythema and 48.1 per cent (n = 93) representing wet necrotic tissue. Each area was selected using the Adelaide Skin Colour Measurement Program and the mean hue and standard deviation calculated. The results from each image were then aggregated across all images to provide a hue range for erythema and wet necrotic tissue.

Results from the image areas highlighted by clinicians as representing erythema provided a range of 360 degrees to 378 degrees with a mean hue

of 9.21 degrees (SD: 3.51 degrees). Colour saturation ranged from 34 per cent to 78 per cent with a mean saturation of 51.01 per cent (SD: 8.84 per cent). Figure 37 illustrates the colour range identified for erythema.

Figure 37. Hue and saturation range representing erythema

Results from the image areas highlighted by clinicians as representing wet necrotic tissue provided a range of 367 degrees to 390 degrees with a mean hue of 18.73 degrees (SD: 6.04 degrees). Colour saturation ranged from 33 per cent to 74 per cent with a mean saturation of 56.89 per cent (SD: 8.27 per cent). Figure 38 illustrates the colour range identified for wet necrotic tissue.

Figure 38. ***Hue and saturation range representing wet necrotic tissue***

For the purposes of phase three it was decided to use the mean hue plus one standard deviation either side of the mean. This excluded hues that could be considered ‘outliers’, or were encountered in a smaller number of patients. The intent was to establish a range that would be exhibited by the majority of venous leg ulcers manifesting inflammation or wet necrotic tissue. For erythema that hue range became 5.7 degrees to 12.7 degrees with a colour saturation of 42.2 per cent to 59.8 per cent. For wet necrotic tissue the hue range became 12.7 degrees to 24.7 degrees with a colour saturation of

48.6 per cent to 64.2 per cent. The resulting colour range for each tissue type is illustrated in Figure 39.

Erythema range

Wet necrotic tissue

.

Figure 39. Colour range selected for phase three to represent each tissue type

The above range was used as the criteria for developing phase three; a computer system that selected areas within a digital image that represented either erythema or wet necrotic tissue.

5.4. Phase 3: Developing a system to highlight areas of erythema and wet necrotic tissue

The intent of phase three was to develop a method that could use the colour range obtained from phase two as a criterion for selecting pixels within digital images. The aim was to develop a system that would highlight erythema and wet necrotic tissue in a digital photograph of a venous leg ulcer without input from a clinician.

Adobe Photoshop® version 5.5 was used to select pixels that had a hue value that fell within one standard deviation from the mean hue established for either erythema or wet necrotic tissue (see Chapter Four). A digital border was then placed around the pixels selected; highlighting areas within the photograph deemed to represent erythema or wet necrotic tissue (see Chapter Four). This process resulted in nineteen out of the twenty images

having areas of erythema highlighted and fifteen out of the twenty images having areas of wet necrotic tissue highlighted.

Once areas of each image had been highlighted as either erythema or wet necrotic tissue the validity of the areas selected were analysed using three methods. The first was a visual examination between the areas selected by the participants and those selected by the computer system. The second was to measure the surface area of each manifestation in all images (participant and computer highlighted) and compare any variations. The third asked participating clinicians to estimate how much they agreed with areas selected by the computer system as either erythema or wet necrotic tissue. The first and second methods examined internal validity whilst the third examined external validity (see Chapter Four).

The analysis was aimed at testing the following hypotheses:

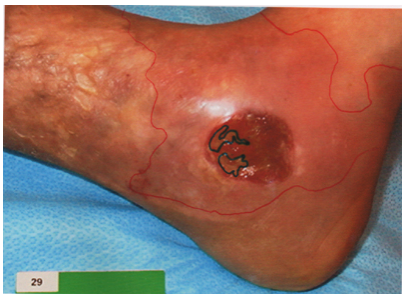
A system to provide a valid selection of erythema or wet necrotic tissue in a digital image of a venous leg ulcer:

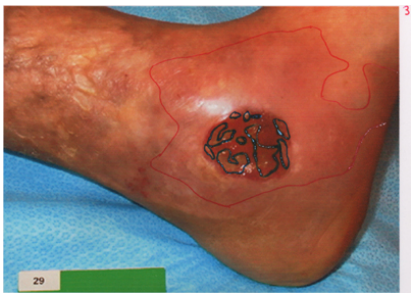
1. *The amount of difference between the areas selected by an expert panel and areas selected by the computer system would not be statistically different.*

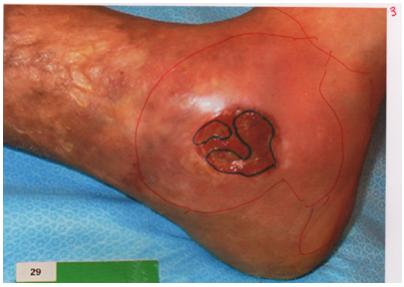
2. *An expert panel would strongly agree with the areas selected by the computer system for each tissue type (erythema and wet necrotic).*

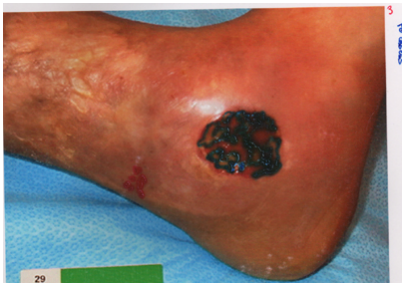
5.4.1. Visual observations

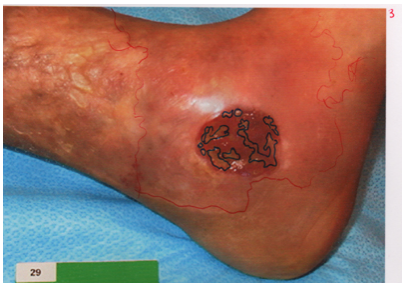
Visual observations indicated some variation between areas selected by the computer using the colour range established and areas selected by the clinicians. The greatest variation was noted when comparing areas of erythema. The visual comparison also highlighted variations between areas selected by clinicians for each image. Figure 40 provides an example of the visual variations evident between clinicians, and between clinicians and the computer.

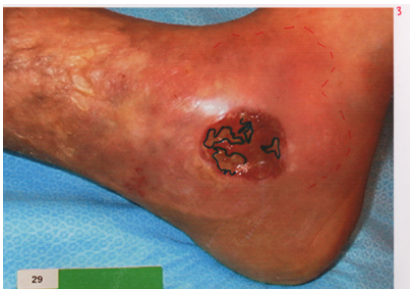

Clinician 1


Clinician 2


Clinician 3


Clinician 4


Clinician 5


Clinician 6

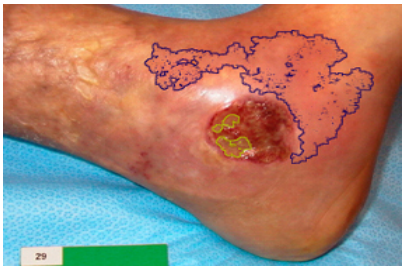
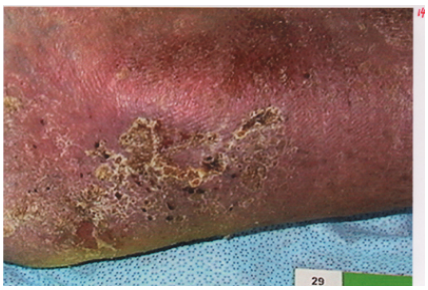

Computer selection

Figure 40. Comparison of areas selected by clinicians and the computer system for image three

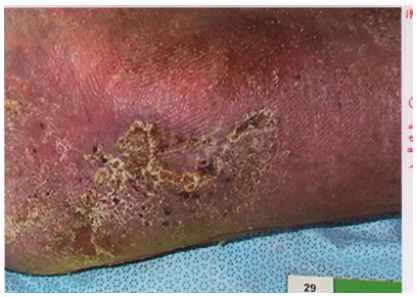
5.4.2. Difference in surface area

To quantify variations in the areas highlighted by the clinicians and the computer system, the surface areas of both manifestations (erythema and wet necrotic tissue) were measured. Variance between the surface areas selected were calculated for each image. An ANOVA was used to determine the statistical significance of the difference between clinicians and between clinicians and the computer system.

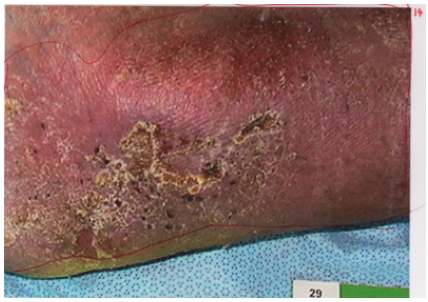
Areas selected as erythema had the largest variation with a mean variance of 70.90 (SD: 70.52). Image 14 (see Figure 41) had the highest level of variance between clinicians, and between clinicians and the computer system with some participants identifying 35 cm^2 to 36 cm^2 of erythema with others believing that erythema was not present (see Table 44).



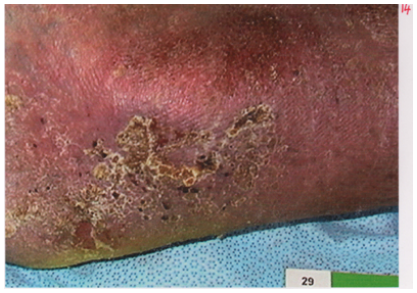
Clinician 1



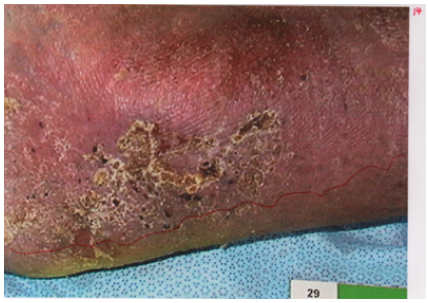
Clinician 2



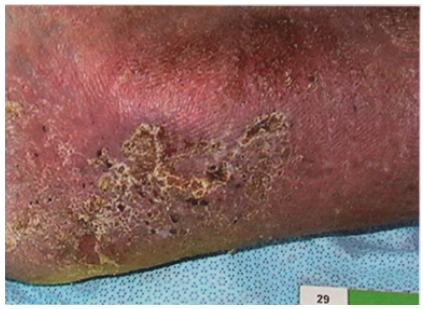
Clinician 3



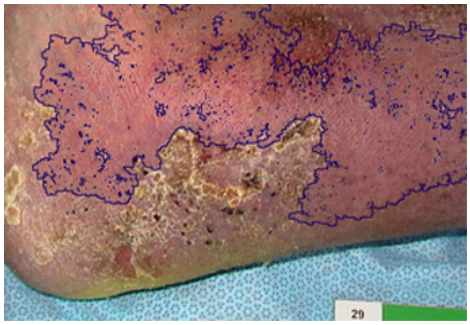
Clinician 4



Clinician 5



Clinician 6



Computer selection

Figure 41. Image with the highest variation of areas selected as erythema

Image	Computer System	Participant 1	Participant 2	Participant 3	Participant 4	Participant 5	Participant 6	Variance
1	26.7	25.2	27.5	26.6	32	0	25	110.86
2	8.4	13.6	17.5	18.3	18.2	15.5	16.8	12.47
3	6.3	24.6	20.6	16.3	0	19.5	13.4	74.34
4	30.8	32	31.4	35.1	0	33.6	24.7	150.33
5	8.3	22.6	22	17.6	0	26.7	21.1	88.71
6	6.9	0	16.3	13.9	13.7	13.3	14.9	33.59
7	5.4	5	5	7	6.1	7.6	0	6.16
8	1.1	23.3	15.5	25.7	24.1	28.7	0	141.11
9	8.7	8.9	8.9	8.7	8.9	8.9	8.7	0.01
10	13.2	9.7	9.4	19.1	0	10.3	12.3	32.77
11	6.8	16.2	14.1	13.5	0	16.2	0	52.45
12	0	3.1	15.9	2.9	0	19	0	65.48
13	8	18.4	17.4	17.4	0	17.7	17.4	49.89
14	24.6	0	0	35	0	36.7	0	308.71
15	16.6	28	3.7	0.9	0	8.9	0	111.84
16	5.2	10.1	8.3	16.4	0	11.5	0	36.71
17	12.6	30.5	28.7	32.2	30.3	29.4	31.7	47.07
18	0.5	0	14.7	5.7	0	5.7	11.7	34.78
19	10.4	0	6	18.2	0	7.3	0	46.31
20	9.6	5.7	5.7	5.5	0	0	0	14.51

Table 44. Variance of surface area identified as erythema by clinicians and the computer system

Areas selected as wet necrotic tissue had much less variation than erythema between clinicians and between clinicians and the computer system. The mean overall variance was 1.76 (SD: 4.57) with surface areas ranging from zero to 12.7 cm^2 being selected (see Table 45). Image 18 recorded the highest level of variance with areas between zero and 12.7 cm^2 being selected (see Figure 42).

Image	Computer System	Participant 1	Participant 2	Participant 3	Participant 4	Participant 5	Participant 6	Variance
1	0	0	0	0	0	0	0	0.00
2	0.7	0.3	0.5	0.6	0.5	0.9	0.5	0.04
3	0.4	0.5	1.5	2	1.9	1.3	0.6	0.45
4	0.15	0.1	0.1	0.1	0.3	0.3	0.1	0.01
5	6.1	7	7.6	6.4	6.4	6.6	6.6	0.24
6	1.2	0	2	2	3.4	2.1	0.1	1.46
7	0.1	1.5	0.2	0.1	0.1	0.2	0	0.28
8	0.2	1.2	3.8	1.6	4.2	4.2	1.8	2.62
9	0.7	0.9	1	1	1.1	1.1	1	0.02
10	0.1	0	0	0	0	0.1	0	0.00
11	0.8	1.5	1.9	0.8	0.4	0.8	0.1	0.38
12	3.6	7.1	7.4	7.3	0	8.2	0	12.90
13	0.5	0.2	0.4	0.5	0.4	0.5	0.4	0.01
14	0	0	0	0	0	0	0	0.00
15	0	0	0.2	0	0	0.2	0	0.01
16	0	0.2	0.2	0.1	0	0.4	0.2	0.02
17	0	0.2	0.4	0.1	0	0.4	0.3	0.03
18	6.8	5.2	5.2	5.7	0	12.7	1.3	16.88
19	0.3	0.2	0.2	0.1	0.1	0.7	0.2	0.04
20	0.1	0.1	0.1	0	0	0.1	0	0.00

Table 45. Variance of areas selected as wet necrotic tissue

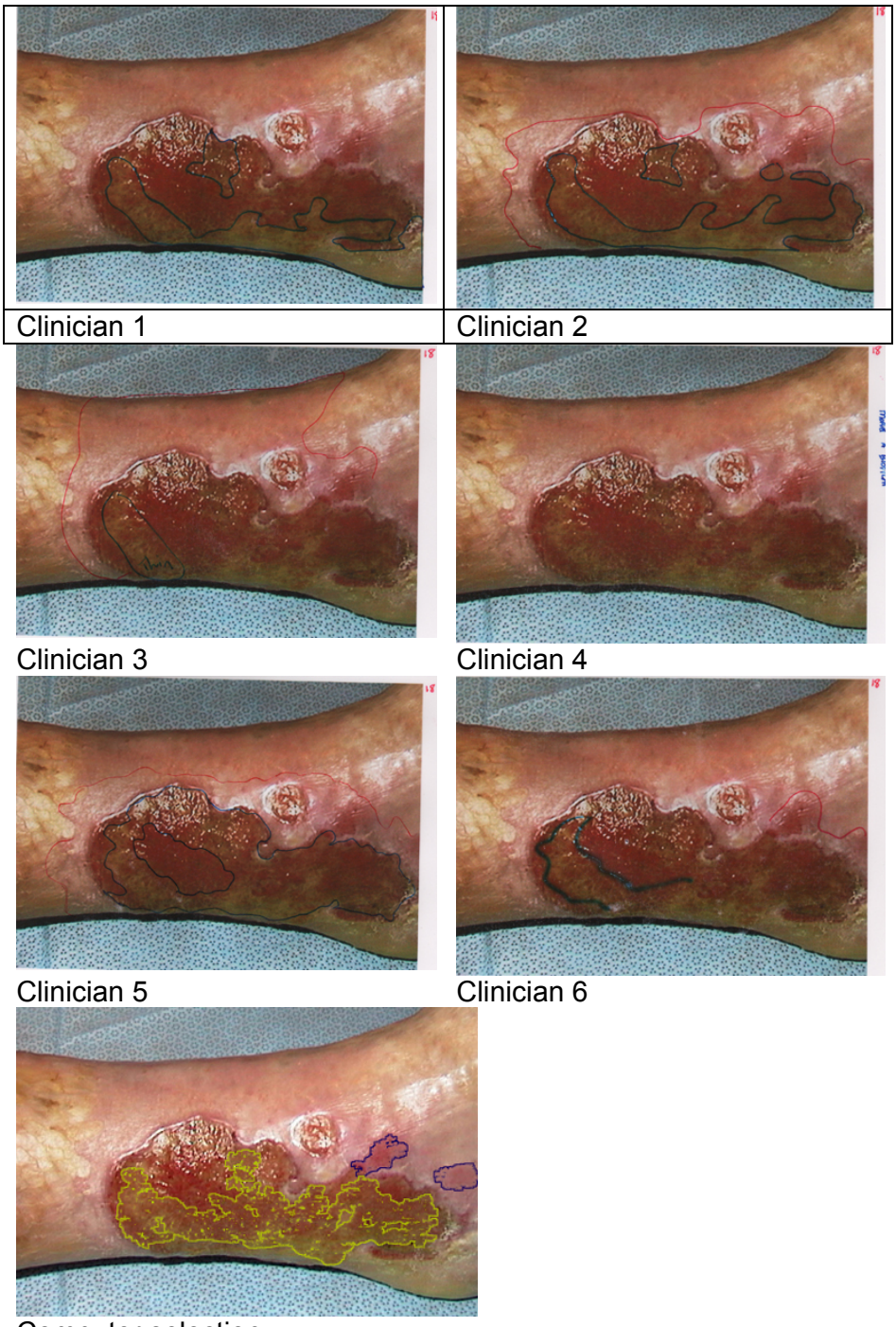


Figure 42. Image with the highest variation of areas selected as wet necrotic tissue

An analysis of the above variations indicated a statistical significance between the areas selected as erythema by individual participants and between the participants and the computer system. The significance between participants was down to p = 0.02 and between the participants and the computer system p = 0.01 (see Table 46).

ANOVA	Between participants					
Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	1499.29	5	299.85	2.79	0.02	2.29
Within Groups	12223.94	114	107.22			
Total	13723.23	119				

ANOVA	Between participants and the computer system					
Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	1598.309	6	266.38	2.61	0.019	2.16
Within Groups	13562.75	133	101.97			
Total	15161.06	139				

Table 46. Analysis of variance for areas selected as erythema

Variations between the areas selected as wet necrotic tissue by individual participants and between participants and the computer system were not statistically significant (see Table 47).

ANOVA	Between participants					
Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	24.13	5	4.82	0.87	0.49	2.29
Within Groups	627.05	114	5.50			
Total	651.18	119				

ANOVA	Between participants and the computer system					
Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	25.17	6	4.19	0.79	0.57	2.16
Within Groups	703.46	133	5.28			
Total	728.64	139				

Table 47. Analysis of variance for areas selected as wet necrotic tissue

Based on the above findings the following hypothesis was **rejected** and the null hypothesis accepted for the manifestation of **erythema only**.

For a system to provide a valid selection of erythema in a digital image of a venous leg ulcer:

1. *The amount of difference between the areas selected by an expert panel and the areas selected by the computer system would not be statistically different.*

The findings for the manifestation of wet necrotic tissue demonstrated no statistically significant difference between the areas selected by the computer system and those selected by participating clinicians. Based on these findings the following hypothesis was accepted and the null hypothesis rejected.

For a system to provide a valid selection of wet necrotic tissue in a digital image of a venous leg ulcer:

1. *The amount of difference between the areas selected by an expert panel and the areas selected by the computer system would not be statistically different.*

5.4.3. Level of agreement between participating clinicians and areas selected by the computer system

To further examine validity images with areas of erythema and wet necrotic tissue highlighted by the computer system were returned to the participating clinicians to judge their level of agreement. Participants were asked to indicate their level of agreement on a visual analogue scale (VAS) ranging from ‘strongly disagree’ to ‘strongly agree’ (see Chapter Four).

5.4.3.1. Erythema

Overall results for the areas highlighted as erythema by the computer system indicated that the mean VAS for all images was 5.63 out of a possible 10, with 10 indicating strong agreement and zero indicating strong disagreement (see Table 48).

Image	Participant 1	Participant 2	Participant 3	Participant 4	Participant 5	mean	SD	variance
1	3.1	8.1	6.9	7.1	9.6	6.96	2.42	5.84
2	1.8	6.8	7.7	8.2	9.5	6.80	2.97	8.82
3	0.7	2.0	8.4	1.2	9.9	4.44	4.34	18.87
4	6.4	7.6	7.7	7.1	9.3	7.61	1.07	1.15
5	1.1	1.1	7.7	3.5	3.0	3.27	2.72	7.39
6	9.3	3.1	6.1	5.4	9.8	6.73	2.79	7.76
7	0.9	7.5	9.6	9.3	9.8	7.43	3.75	14.04
8	8.4	2.6	2.1	1.2	0.6	3.00	3.14	9.85
9	1.1	9.6	1.0	2.3	2.0	3.20	3.65	13.29
10	3.2	9.1	3.6	5.6	9.4	6.17	2.95	8.72
11	0.7	9.1	2.6	2.9	2.9	3.63	3.17	10.07
13	0.9	8.9	7.6	3.4	2.1	4.59	3.52	12.40
14	0.9	2.3	7.3	7.4	7.7	5.10	3.26	10.66
15	0.7	5.9	8.5	5.6	9.6	6.06	3.45	11.91
16	1.1	8.1	10.0	5.9	9.3	6.86	3.60	12.93
17	8.6	8.9	5.9	5.6	3.1	6.43	2.40	5.75
18	9.1	4.3	4.6	3.1	5.7	5.34	2.29	5.23
19	1.2	8.1	1.4	5.9	9.6	5.26	3.83	14.65
20	8.6	8.4	8.9	5.7	9.1	8.13	1.38	1.90

Table 48. VAS scores recorded when participating clinicians were judging areas of erythema

The image receiving the lowest level of agreement amongst participating clinicians differed from that identified in the above section (see “Difference in surface area”). Image 8 had the lowest level of agreement with a mean score of 3.0 (SD: 3.14) out of a possible 10 (see Figure 43). Image 20 had the highest level of agreement with a mean score of 8.13 (SD: 1.38) out of a possible 10 (see Figure 44).

When variance between the opinions of participating clinicians judging erythema were examined, it was Image 3 (see Figure 45) that had the highest level of variation indicating the most divided opinion. Image 20 (see Figure 46) had the lowest level of variation indicating a degree of consensus

between the opinion of the participating clinicians and the areas selected by the computer system (see Table 48 above).

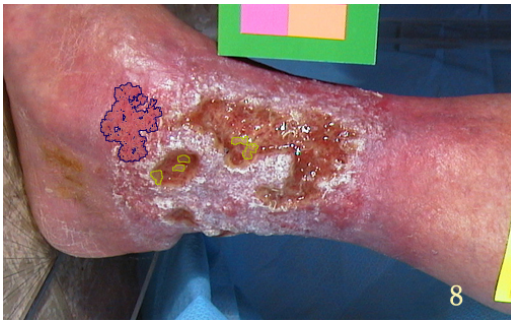


Figure 43. Image yielding the lowest level of agreement between participating clinicians and the computer system for erythema

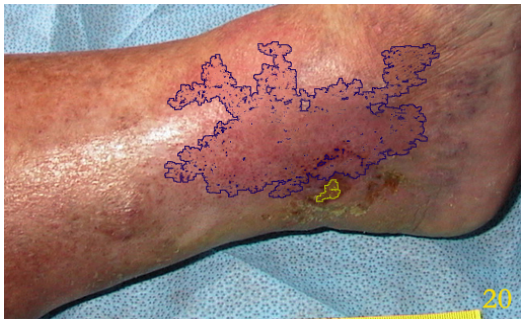


Figure 44. Image yielding the highest level of agreement between participating clinicians and the computer system for erythema

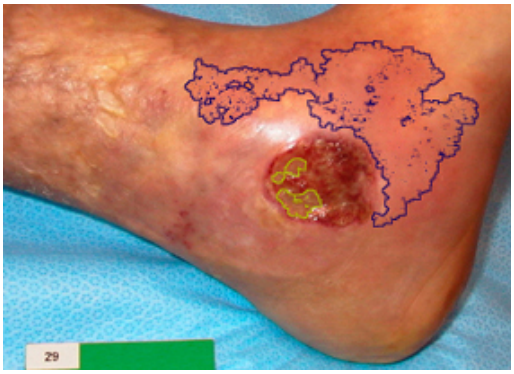


Figure 45. Image with the most divided opinion between judging clinicians for erythema

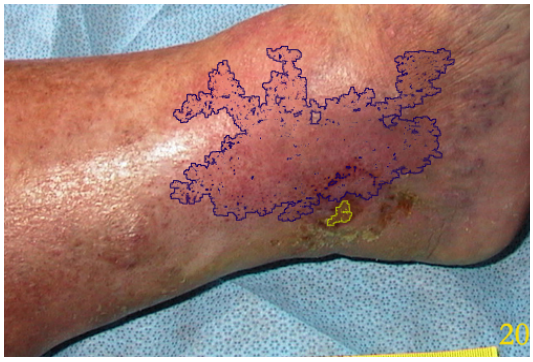


Figure 46. Image with the highest level of consensus between judging clinicians and highest agreement score

An analysis of variance between the opinions of clinicians judging areas of erythema selected by the computer system indicated no statistically significant difference (see Table 49) indicating a significant level of agreement between clinicians assessing the images.

ANOVA						
Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	39.87	4	9.96	1.39	0.24	2.47
Within Groups	642.77	90	7.14			
Total	682.64	94				

Table 49. Variance between the opinions of participating clinicians judging areas of erythema selected by the computer system

5.4.3.2. Wet necrotic tissue

When scores for the areas selected by the computer system as wet necrotic tissue were examined a slightly higher level of agreement between participating clinicians and the computer system was evident. The mean VAS score for all images was 6.27 (SD: 2.40) out of a possible 10 (see Table 50).

Image	Participant 1	Participant 2	Participant 3	Participant 4	Participant 5	mean	SD	variance
2	7.1	9.3	0.0	2.3	9.6	5.67	4.32	18.66
3	8.2	6.4	6.4	8.4	9.6	7.81	1.38	1.91
4	8.6	8.3	10.0	8.1	9.8	8.94	0.89	0.79
5	9.3	9.8	10.0	8.1	8.9	9.23	0.74	0.54
6	8.9	9.3	6.4	7.1	9.0	8.16	1.28	1.65
7	9.3	4.1	8.7	9.1	9.7	8.19	2.33	5.42
8	5.9	2.4	5.0	2.5	0.7	3.31	2.11	4.47
9	2.1	0.5	1.8	2.8	1.3	1.70	0.87	0.75
10	0.5	2.7	0.8	3.6	9.6	3.46	3.70	13.68
11	8.9	0.9	7.3	3.7	0.6	4.27	3.76	14.11

12	1.6	4.6	8.2	3.2	0.4	3.61	3.04	9.22
13	8.8	2.5	9.8	6.9	9.1	7.41	2.94	8.66
18	8.7	4.4	4.1	6.4	9.6	6.67	2.47	6.12
19	8.9	2.9	8.7	9.1	9.6	7.84	2.81	7.89
20	8.3	9.1	7.9	4.9	9.4	7.90	1.81	3.28

Table 50. VAS scores recorded when participating clinicians were judging areas of wet necrotic tissue

Image 9 (see Figure 47) had the lowest level of agreement with a mean score of 1.7 (SD: 0.87) out of a possible 10. Image 5 (see Figure 48) had the highest level of agreement with a score of 9.23 (SD: 0.74) out of a possible 10 (see Table 50 above).

When variance between the opinions of participating clinicians judging wet necrotic tissue was examined, it was Image 2 (see Figure 49) that demonstrated the highest level of variation and hence the most diverse opinions. Image 5 (see Figure 50) demonstrated the highest level of consensus with a variance of 0.74 (see Table 50 above)

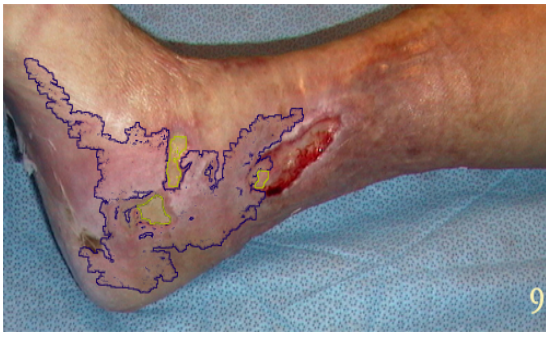


Figure 47. Image yielding the lowest level of agreement between participating clinicians for wet necrotic tissue

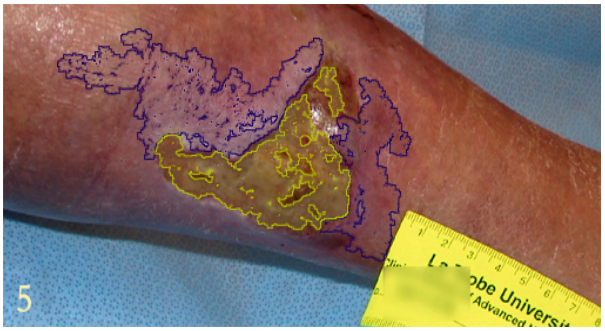


Figure 48. Image yielding the highest level of agreement between participating clinicians for wet necrotic tissue

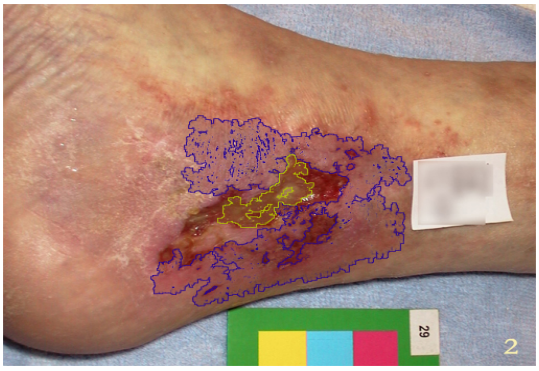


Figure 49. Image yielding the most divided opinion between participating clinicians judging wet necrotic tissue selected by the computer system

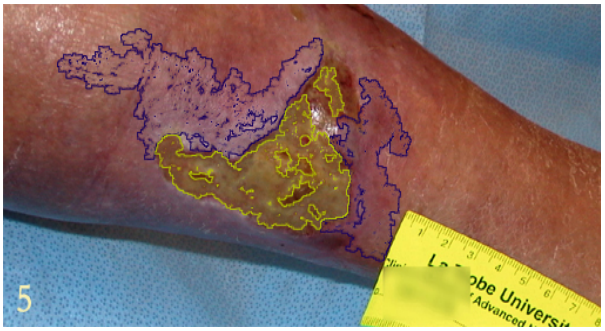


Figure 50. Image yielding the highest level of consensus between participating clinicians for wet necrotic tissue

An analysis of variance between the opinions of clinicians judging areas of wet necrotic tissue selected by the computer system indicated no statistically significant difference (see Table 51) indicating a significant level of agreement between clinicians assessing the images.

ANOVA						
Source of Variation	*SS*	*df*	*MS*	*F*	*P-value*	*F crit*
Between Groups	42.68	4	10.67	0.99	0.41	2.50
Within Groups	751.17	70	10.73			
Total	793.85	74				

Table 51. Variance between the opinions of participating clinicians judging areas of wet necrotic tissue selected by the computer system

With a mean VAS score of 52 per cent to 62 per cent of agreement between areas identified by the computer systems and participating clinicians it was decided that the overall consensus was not high enough to indicate 'strong agreement'. Although there was no statistically significant difference between the levels of agreement between clinicians, the high level of variation for individual images led the researcher to believe that the participating clinicians did not consistently see the areas highlighted by the computer system to be a valid representation of the two manifestations.

Based on these findings it was decided to **reject** the following hypothesis and accept the null hypothesis.

For a system to provide a valid selection of erythema or wet necrotic tissue in a digital image of a venous leg ulcer:

1. *An expert panel would strongly agree with the areas selected by the computer system for each tissue type (erythema and wet necrotic).*

Based on these findings it was deemed that the areas selected by the computer system as representing erythema were not valid representations. Whilst the analysis for wet necrotic tissue was more favourable, with the absence of significant difference in surface area selected by the computer system and the clinicians, and a higher level of clinician agreement with areas selected by the computer system, the criteria established for the above hypothesis (strongly agree) was not met and then areas highlighted by the computer system as wet necrotic tissue were deemed to be invalid.

5.5. Chapter summary

The aim of this project was to enable clinicians to easily and objectively measure the different colour manifestations exhibited in the bed of a venous leg ulcer and the surrounding skin. To that end a three phase method was developed to:

1. Establish a reliable method for digitally recording the colours exhibited by a venous leg ulcer.
2. Establish a range of colour that experienced clinicians believe represent erythema and wet necrotic tissue.

3. Validate a computer system that identifies pixels in a digital photograph of a venous leg ulcer that fall within the above colour ranges and highlights the identified area with a border.

The findings suggest that the aim of the first phase was met with small variations between the hues recorded for individual images. This trend was evident for images within a photographic set recorded at each episode, within photographic sets recorded over two or more visits for the same patient, and across all images collected for the study.

Equally the aim for phase two was met with the establishment of a colour range that represented colours of erythema and wet necrotic tissue within a digital image of a venous leg ulcer. The range developed incorporated the variables of both hue and saturation providing a comprehensive colour representation of the areas outlined by participating clinicians.

The findings for phase three indicate that using the above colour range as a criterion for selecting pixels as a representation of either erythema or wet necrotic tissue has limited validity. This is particularly true for erythema with a significant difference in surface area being selected by the computer system and participating clinicians. This was reinforced with participating clinicians only in partial agreement with areas identified by the computer system as erythema. For wet necrotic tissue the above colour range would appear to have a slightly higher level of validity as evidenced by the absence of any significant difference in the surface area selected by the computer system

and participating clinicians. The trend was reinforced with a higher level of participating clinicians agreeing with the areas selected by the computer system.

The findings indicate that the system developed for photographing venous leg ulcers (Ulcer-cam 2) can reliably record the hue, orientation and magnification of the wound. Further, the findings suggest that a group of experienced clinicians are prepared to identify areas of erythema and wet necrotic tissue from a printed photograph and that the areas outlined can be converted to a range of colour indicative of each manifestation. The findings do not support the notion that the above colour range can be used as an algorithm for an image analysis system to select areas within a digital photograph to represent each tissue type.

The significance of the above findings will be addressed in the following chapter. Comparisons will be drawn between samples from other studies and the representative nature of the patient cohort recruited for this project. Possible rationales for the reliability of Ulcer-cam 2 will be explored along with the potentials of a system that captures colours of a venous leg ulcer in a reliable fashion. Equally, explanations for the limited validity of the colour range identified from experts to identify areas within a digital image that represent erythema and wet necrotic tissue will be discussed.

6. Chapter Six: Discussion and conclusion

The need to develop consistent approaches to the assessment of long-term or chronic wounds has never been higher. Institutional and personal financial costs associated with the management of this wound type are expensive, as is the impact of reduced productivity and quality of life on the sufferer and the society in which he or she lives.[8, 75, 208, 247, 253, 318, 326, 327, 425] As populations throughout the world age, and the associated cost of health care continues to escalate, the burden created by patients suffering from chronic wounds is projected to increase.[27, 55, 75, 107, 156, 165, 166, 168-170, 427]

In previous chapters it has been demonstrated that venous leg ulceration arising from CVI is a major contributor to the population of patients suffering from chronic wounds. Whilst the reported population prevalence of venous leg ulceration is 0.06 per cent to 1.97 per cent, the percentage of chronic wounds resulting from this wound type are often high. A recent study conducted in Germany by Coerper et al.[428] found that out of 7051 lower leg ulcers surveyed, 1349 (20 per cent) were attributable to CVI. With annual cost estimates ranging from US$775 million to US$1 billion in the United states, and from £294 million to £949 million in the United Kingdom, health providers are keen to explore more efficient treatment options for this patient cohort.[166, 168, 169]

Research aimed at identifying factors that contribute to the chronic nature of venous leg ulceration has identified a number of contributing variables.

These have included: an underlying ongoing inflammatory process; mechanical changes to the veins resulting in leukocyte entrapment; a higher predisposition in female patients; and lifestyle practices that lead to reduced mobility and / or obesity.[4, 160, 290, 429] It has been postulated by the author and others that there is a need to develop a reliable suite of assessment techniques that collect data concerning the above variables and, more importantly, alert the clinician to the presence of developing chronicity early in the healing cycle.[208, 232, 234, 255, 258, 262, 267, 278, 290, 317, 327, 329, 330, 400, 430-432]

This thesis has attempted to contribute to the above endeavour by developing and testing the reliability and validity of a method for recording and using digital colour photographs to identify two principle manifestations of inflammation; erythema and wet necrotic tissue. The following chapter discusses the findings of this project in an effort to determine the degree to which this aim was met.

In order to provide a foundation for the ensuing discussion the chapter beings with a description of the study limitations including sampling techniques, sample size and data collection methods. A comparison between samples from other studies and the representative nature of the patient cohort recruited for this project are then examined. The reliability of a developed system (Ulcer-cam 2) is explored, along with the potentials such a system offers wound care clinicians. The validity of the colour range identified from experts to identify areas within a digital image that represent erythema and wet necrotic tissue is discussed and possible explanations for the findings

presented. A summary of conclusions derived from the findings are stated and the chapter concludes with an exploration of further research options arising from the findings.

6.1. Study limitations

Whilst every effort has been made to reduce the number of limitations when conducting this study, as with any study a number of limitations still need to be considered when discussing the findings. These include: the sampling technique used to select the patient and clinician cohorts; the recruitment strategies used for both groups; the techniques used to digitise the images; and the level of controls implemented for data collection.

6.1.1. Potential bias

The use of a convenience sampling technique limits the application of the findings of this study to the general population of patients with venous leg ulceration. Using a convenience sample of patients to test the reliability of the Ulcer-cam 2 system may have introduced biases into the sample.[332, 423] An example is the country of origin bias evident in the findings. A high percentage 69.5 per cent (n = 16) of patients recruited for the study were born in Australia. The hue range identified may therefore have a race bias. Colours displayed in the skin of Caucasian Australians may differ from that of non-Australian Caucasians, limiting the application of the findings to the latter cohort. The exclusion of patients with dark skin from the study introduces a

similar bias. Colour ranges of brown through black pigmented skin may have introduced a number of different hues that altered the hues found. Once again the application of the findings to this cohort is therefore limited.

Selecting a convenience sample of patients from the same clinical venue also reduces the ability to generalise the findings to the population of patients suffering from venous leg ulcers. The degree of inflammation and wet necrotic tissue exhibited by the patient cohort may different from other patient cohorts in different geographic catchment areas. For example, patients in more humid climates may demonstrate a great range of erythema or different hues of wet necrotic tissue related to higher moisture content in the air. Any conclusion drawn about the colour ranges established from the findings of this study to represent the above manifestations will need to be tempered by the limitations imposed by the geographic bias of the patient sample used.

The selection process used to choose the panel of experienced clinicians may have also introduced bias into the findings. Whilst measuring expertise is often subjective, relying on a professional organisation of peers to nominate potential participants may have prevented clinicians unknown to the organisation being nominated. For example, the absence of an allied health professional being nominated could be more a reflection of the organisational membership distribution, rather than a true representation of personnel with venous ulcer management expertise within Australia.

6.1.2. Technological limits

The findings are further limited by the technology used to digitise the image. The digital camera used to record images for the first phase of the study has inbuilt parameters specific to the manufacturer. Whilst the use of an in-shot reference was used to control for different lighting conditions, any attempts to replicate the findings using the Ulcer-cam2 system with other cameras would require additional reliability testing. Specific inbuilt manufacturer parameters in different cameras may influence the hues and saturations captured in ways that may not be completely compensated.

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Equally, the techniques used to convert digital images to printed copies and return the printed copies to a digital image, are limited by parameters specific to the manufacturer of the technology used. For example, the flat bed scanner and printer used to print the images from which the colour range for wet necrotic tissue and erythema were derived are affected by the algorithms used by Epson Pty Ltd. The use of in-mage colour standards and subsequent computer correction attempts to minimize differences between different technologies, but it will seldom be com,pletely successful. Therefore the application of the findings from this study is limited to the technology used to capture and reproduce the digital images.

6.1.3. Sample size

The size of both the patient and clinician cohort are small. Whilst the patient sample number was determined using longitudinal data derived from the recruiting clinic, the number is still small (n = 23) and therefore limit the

application of the findings to the larger population of patients suffering from venous leg ulceration. Larger sample populations reduce the potential of bias being introduced and enhance the ability of the findings to be generalised to the broader population of patients with venous leg ulcers.[332, 423]

Two samples of clinicians were recruited for the study. The clinicians collecting the digital images to test the reliability of Ulcer-cam 2 and the panel of experienced clinicians. The first sample was a convenience sample drawn from nurses working in the clinic from which the patients were recruited and only number three. The small sample may have reduced the amount of variation between clinicians. For example, the nurses who collected the digital images were closely involved with the project and therefore their understanding of the techniques used may have been more acute than for nurses from other clinical sites. The small sample size and the single site of recruitment limit the application of the findings to other clinician cohorts.

The size of the experienced clinician panel was also small. It is hard to be any more certain about the representative nature of the sample because of the absence of established registers for clinicians with venous leg ulcer assessment experience. However, a sample size of eight would appear to be small in comparison to a membership number of 4000 for the organisation asked to nominate clinicians with this type of expertise. Any attempts to claim that the colour range identified by the clinician sample in this study was representative of the greater population of clinicians assessing venous leg

ulcers would need to be tempered by concerns that the sample size was insufficient to be representative.

6.2. Discussion of the findings

The findings of this study are discussed with reference to the stated objectives:

1. To develop a reliable method for digitally recording the colours exhibited by a venous leg ulcer that:
    a. could be used in various lighting conditions
    b. ensures a consistent view of the leg over several episodes of care
    c. controls for focal length / magnification
    d. can be easily used in the clinical environment by clinicians.
2. Test the reliability of the above image capture system
3. Establish a range of colour that experienced clinicians believe represents erythema.
4. Establish a range of colour that experienced clinicians believe represents wet necrotic tissue, or slough.
5. Develop a system that uses image analysis software to identify pixels in a digital photograph of a venous leg ulcer, that fall within the above colour ranges.
6. Use the above image analysis to place an observable border around groups of pixels that meet the colour range criteria in an effort to highlight areas of erythema or wet necrotic tissue evident within the photograph.
7. Test the validity of the above tissue identification system.

6.2.1. The reliability of the method to digitally record the colours exhibited by a venous leg ulcer

Given the limitations imposed by the small patient sample size it was felt prudent to begin the discussion by examining the degree to which the patient sample compares to the larger population of patients suffering from venous leg ulceration. This is followed by an examination of the ability of Ulcer-cam 2 and the image capture system developed to reliably record the colours exhibited by a venous leg ulcer.

6.2.1.1. Representative nature of the patient sample

Whilst a representative sample was not required to meet the aim of this descriptive study, a review of the patient sample against previous studies is presented to examine the degree to which the sample represents the wider population of patients suffering from venous leg ulceration. It is done to determine the level of confidence with which the findings could be extrapolated to the wider population.

The majority of studies examining the prevalence of CVI and the resulting manifestations report a higher prevalence in the older age cohorts.[2, 5, 12, 20, 22, 43, 46, 50, 56, 68, 69] Nelzen et al.,[54] when determining the prevalence of venous leg ulcers in Skaraborg, reported a prevalence of 1.5 per cent for subjects aged 60 years to 79 years and 3.2 per cent for subjects aged 80 years to 89 years. Findings from this study are consistent with this trend with an age

range of 50 years to 89 years, and a mean age of 69.7 years (SD 10.06 years). The age distribution of the patient sample demonstrates a similar finding with the majority of the patients being older than 69.5 years and 50 per cent of the sample being 79.25 years or greater.

When considering the gender distribution of patients suffering from venous leg ulceration the majority of studies report a higher prevalence amongst females.[5, 6, 20, 27, 36, 40, 43, 72] Whilst some studies have demonstrated equivalence between the sexes,[24, 150] and others would argue that this is artificially high due to the propensity of women to seek medical help earlier,[3, 20] the trend is consistent. The gender difference is said to equalise as the age of the patient increases.[3] Although the limitation of sample size precludes any definitive conclusions, findings from this study support the female bias reported above with a slightly higher number of females (54 per cent, n = 12) than males (45 per cent, n = 10).

Previous studies have indicated a higher prevalence of venous ulceration in people residing in industrialised or developed countries.[27, 40] It is argued that the lifestyle promulgated by these societies contributes to reduced exercise, obesity and resulting venous hypertension. Studies examining the prevalence of CVI and associated manifestations amongst people who have moved from developing countries to developed countries support this assertion.[44-47] Although limited by the sample size, a small number of participants in this study (18 per cent, n = 4) reported a country of origin that could be considered as ‘developing’ and therefore expected to have a lower prevalence of venous ulceration. The fact that they were currently suffering

from a venous ulcer may support the above assertion that an association exists between prevalence of the condition and country of residence rather than country of origin. However, the small number limits the confidence with which the conclusion is drawn.

Body Mass Index (BMI) has been associated with chronic venous disease and resulting ulceration in a number of previous studies.[1, 4, 14, 21, 29, 36, 58, 59, 83, 106, 144, 201, 290] Danielsson et al.[58] concluded that overweight patients (BMI > 25 kg / m^2) were more likely to have skin changes and ulceration than patients with a BMI of less than 25 kg / m^2. The findings from this study supports this trend with participants recording a BMI ranging from 23.42 kg / m^2 to 35.10 kg / m^2 with a mean of 28.72 kg / m^2 (SD 3.48 kg / m^2). In fact the majority of patients (86 per cent) had a BMI of greater than the 25 kg /m^2 established by Danielsson et al.[58] as the threshold for developing venous ulceration.

A number of associated underlying diseases have also been associated with venous ulceration, principally deep vein thrombosis (DVT), rheumatoid arthritis and diabetes.[3, 75, 63] Scott et al.[63] found that 45per cent of patients with CVI had a history of DVT compared to 4 per cent in a control group. Although the occurrence of each of these co-morbidities was evident in the findings of this study a large percentage of participants (40.9 per cent, n = 9) reported an absence of any of the above. Only 22.7 per cent (n = 5) reported suffering from rheumatoid arthritis, 18 per cent (n = 4) reported a history of DVT and 13.6 per cent (n = 3) reported that they suffered from diabetes.

These findings are contrary to the above studies and may indicate that other factors such as obesity are a better predictor of venous ulceration for patients within Australia. Alternatively, the small sample size of this study may have been insufficient to manifest trends previous identified in larger population based studies.

A number of authors have argued that prevalence of co-morbidities such as diabetes in patients suffering from leg ulceration results in a 'mixed' underlying aetiology; a combination of both arterial and venous disease.[4, 8, 9, 11, 15-17, 34, 52, 54, 76, 80, 84, 85, 92, 93, 97, 106, 109, 113, 123, 175, 179, 207, 225, 253, 260, 291, 299, 408, 433-436] This assertion was not supported by the findings of this study. The ankle brachial index (ABPI) recorded for patients recruited into this study ranged from 0.9 mmHg to 1.4 mmHg with a mean of 1.08 mmHg indicating that the majority, if not all participants, had limited arterial insufficiency. Although these findings do not exclude arterial disease they do indicate that advanced venous disease was the most likely underlying aetiology. As diabetes is the underlying aetiology most often associated with arterial insufficiency, the small number of participants reporting a history of diabetes in this study (13.6 per cent, n = 3) may account for this trend. Equally, the small sample size may have excluded patients of mixed aetiology resulting in the higher ABPI recordings.

Predictable trends regarding the location, amount of surface area, and duration that the patient has suffered with an ulcer have been reported in previous research.[259, 261, 262, 264, 269, 273, 290, 325, 327, 431, 436-438] The results from

this study support previously identified trends. For example, venous leg ulceration has been found to be principally located in the gaiter region (the medial and lateral aspects of the distal leg).[2, 8, 242] Moffatt et al.,[9] when examining 113 patients recruited from a defined geographic area of inner London, found that the majority of ulcers were located on the medial malleolus, of the inner aspect of the gaiter region. Similarly, all ulcers in this study were located in the gaiter region with the majority being located on the medial aspects of the leg. This area is where the venous vasculature is the most superficial and therefore prone to minor trauma which acts as a precursor to ulceration in patients suffering from CVI. This is the most probable explanation for the frequency for this area in the findings of this study.

Surface area dimensions identified in previous studies report a mean surface area of 6 cm^2 with 18 per cent to 48 per cent greater than 10 cm^2. [90] The mean surface area for ulcers recorded in this study was 6.88 cm^2 with 22 per cent (n = 5) greater than 10 cm^2 demonstrating a similar trend to previous studies. When ulcer duration is examined similar parallels are evident. A review of leg ulcer studies by Persoon et al.[90] identified that the duration of ulceration ranged from one week to 63 years with 40 per cent of ulcers existing for more than one year and 10 per cent more than five years. Whilst the range of ulcer durations for participants in this study was not as large as that identified by Persoon et al.,[90] the identified range of one month to 31.6 years is indicative of the very long durations reported by patients suffering from venous leg ulceration. This is confirmed in this study with 22.7 per cent

(n = 5) of participants having suffered with the current venous leg ulcer for greater than five years; similar to the findings of Persoon et al.[90]

The ulcer treatments used for the patients in this study reflect contemporary options cited in clinical guidelines literature. Topical zinc on venous leg ulcers has been found to enhance re-epithelialisation, decrease inflammation and reduce bacterial growth in both patients with a zinc deficiency and those without.[439] The use of zinc bandages as the primary dressing is also in keeping with recommendations made by a multidisciplinary panel examining the treatment of venous leg ulcers based on a comprehensive literature review in 2006.[192] This review recommended that dressings should be selected that maintain a continual moist wound healing environment. Zinc impregnated bandages meet this recommendation by providing a moist interface that does not dry out over time. It would therefore be logical to expect that the majority of patients with venous leg ulceration be treated with topical zinc. The findings from this study support this assertion.

Equally, the use of multi layer compression bandaging to treat all patients recruited to this study is in keeping with clinical guidelines for venous leg ulcer management. A review undertaken for the Cochrane Collaboration,[440] examining research on compression for venous leg ulcers, concluded that venous leg ulcer healing was increased when compression is applied. The use of high compression systems comprised of three to four layers was found to provide better compression than low compression or single layer systems. The fact that all patients recruited for this study were treated with short

stretch multi layer compression bandaging is in keeping with these guidelines.

Whilst the above findings suggest similarities between the patients recruited for this study and other studies, the results obtained by correlating the participant's age with ulcer severity failed to support this assertion. Previous studies have demonstrated a linear association between the patient's age and the duration and / or size of their venous leg ulcer.[9, 11, 13, 15, 16, 34, 51, 73, 75, 82, 86, 118, 124, 131, 151, 161, 318, 425, 426] For example, Moffatt et al.[9, 104, 161] found that as the patient's chronological age increased the duration that they suffered from a given ulcer and the surface area of that ulcer also increased. Findings from this study did not support this association. No significant correlation was demonstrated between the participant's age and the duration of their ulcer or the surface area of the ulcer. The most likely explanation is that the size of the sample was insufficient to demonstrate this association. Equally, it may suggest that for patient populations within the region sampled (Melbourne Australia) such associations are not evident. Difference between the Australian context and that of the regions within Europe, where the majority of previous population studies have been conducted, may be contributing to a decreased association between age and ulcer severity. Additional research would be required to explore the difference in findings in order to support the above assertion.

Overall, the patients recruited to this study provided some similarities to patients recruited to previous studies. The age distribution, associated BMI,

underlying venous disease, and ulcer characteristics such as location, duration and surface area are in keeping with findings from previous studies. Equally, the presence of underlying autoimmune disease, DVT and diabetes in the patients recruited for this study is consistent with previously identified co-morbidities of venous leg ulceration. The treatments being used to treat the participant's ulcer, principally topical zinc and multi layer low stretch compression, is consistent with recommended clinical guidelines. The absence of correlations between the patient's age and the duration and surface area of their ulceration could be attributed to the predominance of Australian born participants which differs from other studies, but is most likely a result of the smaller sample size and the resulting absence of adequate representation.

6.2.1.2. Reliability of Ulcer-cam 2 and the associated capture method to record a consistent digital image of a venous leg ulcer

For the purposes of this study the reliability of the system examined three aspects; the hues, the magnification and the orientation. It was felt that for the system to be reliable each aspect should be recorded in a consistent manner within a single episode of care with a single clinician and across episodes of care with different clinicians. It was further expected that the system could be easily used in the clinical setting with minimal need for specialised equipment.

The development of reliable systems for capturing the colour of skin changes is not unique to this project. As early as the 1980s systems designed to measure an erythemal index following radiation treatments was available.[335, 393, 441] Equally, reliable systems for capturing the colour displayed by skin lesions, principally melanomas, have been available since that time.[382-394] However, as researchers have sought to transfer these developments to the capture of visual manifestations of wounds they have been plagued with a number of confounding variables.

As described in Chapter Three, these variables included: differing capture devices (cameras); different light sources; unwanted reflections; and colours displayed by different types of wounds at different times in the healing cycle. To help control for such variables researchers have implemented a number of interventions or controls. These have included increasing the sophistication of the camera used,[396-398] using mechanisms for fixing the distance between the camera and the wound;[268, 270, 380, 395, 400] the use of in-shot references to control for different lighting conditions,[396, 398, 401] and using camera angles that reduce unwanted reflections.[397, 399, 402] Findings generated by using the Ulcer-cam 2 frame, digital camera and the Adelaide Skin Colour Measurement Program reinforce the use of the above techniques and provide an alternative method for reliably recording wound images.

Using a digital camera and an in-shot reference as part of the system developed for the study enabled a consistent representation of the hues

displayed by the venous leg ulcers photographed to be recorded. The hue consistency achieved was demonstrated within an episode and across episodes, and across different clinicians using the system. For example, hues recorded in each set of digital images captured during an episode of care achieved a difference that was not statistically significant ($F(2,147) = 0.01$, $p = 0.98$). Equally, the variation between hues captured by different clinicians during the same episode of care was not statistically different ($F(8,441) = 0.006$, $p = 1$). The ability of the system to capture venous leg ulcer hues in a reliable fashion across different images and across different clinicians supports the notion that standardising the capture device (camera) and including an in-shot reference provides suitable controls for recording the colour of a wound when using digital technology.

Incorporating the Ulcer-cam 2 frame into the capture system enabled the distance between the camera and the wound surface to be fixed, as recommended by previous studies.[397, 399, 402] Just as previous researchers have been able to provide a consistent magnification when photographing other wound types, this project was able to capture images of venous leg ulcers that did not significantly vary in magnification. In fact any variations were too small to measure using the tools implemented in this project.

Similar outcomes were found with regards to the orientation of the wound within the photograph. Orientation within an episode of care did not differ significantly between images or between clinicians. Whilst the variation of orientation was higher when examined across different episodes of care it

was still not statistically significant (F (1,26) = 2.01, p = 0.16). Both findings are similar to those achieved by other methods described in the literature.[397, 399, 402] For example, Jones and Plassmann[401] were able to demonstrate similar magnification and orientation outcomes when recording wound images using their MAVIS® system

Using the Ulcer-cam 2 frame also enabled sufficient lighting to be achieved using the existing flash unit provided on the camera without creating unwanted reflections. The frame enabled the camera to be stationed at 30 degrees to the wound plane as recommended by Arqvist, Hellgren and Vincent[402] to prevent unwanted reflections from wound exudate or shiny skin resulting from tension associated with oedema. An example can be seen in Figure 51 where an obviously oedematous leg was photographed. The image is evenly illuminated and the unwanted reflections from tight skin over the oedematous areas seen in previous studies are not evident in this photograph.

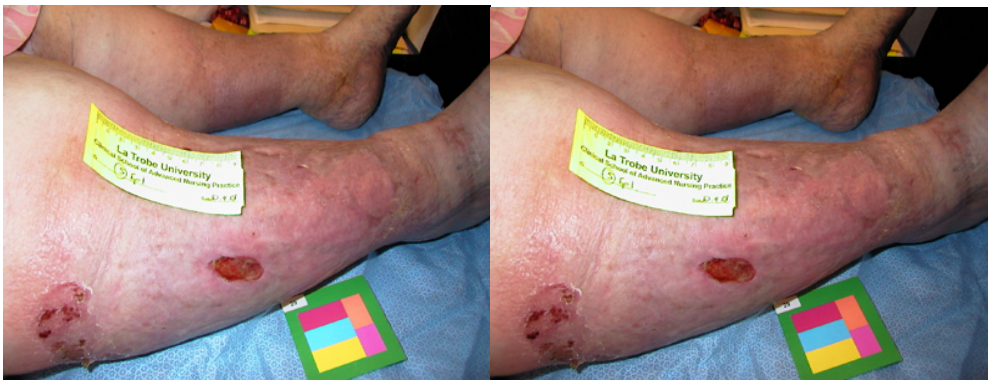


Image taken by clinician 1 Image taken by clinician 2

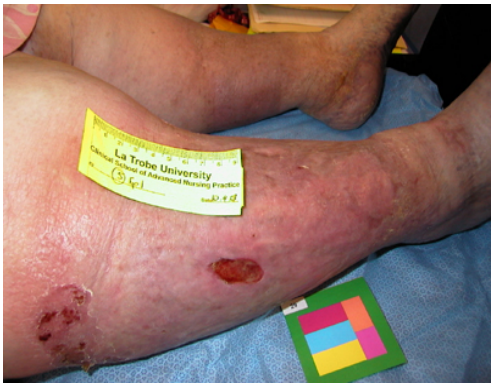


Image taken by clinician 3

Figure 51. Example of the Ulcer-cam 2 frame providing sufficient illumination while controlling for unwanted reflection resulting from oedematous skin

Whilst the reliability of the system developed for this study to record hue, magnification and orientation is similar to that achieved by other studies the method developed would appear to be easier to implement in the clinical setting. Common to the studies cited above[397, 399, 402] is the need for sophisticated equipment to capture and analyse the image. Whilst the Ulcer-cam 2 frame and the Adelaide Skin Colour Measurement Program is needed to replicate the reliability provided by the system used in this study, the degree of sophistication is less than that used in previous studies.

For example, in order for Boardman et al.[399] to achieve a consistent magnification they fitted a pair of high energy light emitting diodes to project light in front of the camera. To standardise for distance between the camera and wound the user was required to move the camera towards the wound until the two lights converged. The Ulcer-cam 2 frame achieved the same magnification consistencies without the need for specialised equipment such high energy light emitting diodes. In addition, the frame provided the added benefit of a consistent orientation of the leg and ulcer as well as a consistent magnification.

Equally, the Ulcer-cam 2 frame enabled even illumination of both the ulcer and leg using the standard in-built flash available on most digital cameras. The results were obtained without the need for a ring flash as suggested by Boardman et al.[399] or polarising filters as recommended by Mekkes and Westerhof.[397]

The level of sophistication used in the Ulcer-cam 2 and the Adelaide Skin Colour Measurement Program is less than that of other studies. For example, MAVIS® (Measurement of Area and Volume Instrument), developed by Jones and Plassmann[401] required a dedicated room with sophisticated equipment costing several thousand English pounds. Likewise the system used by Boardman et al.[399] used a sophisticated video capture device and a computer equipped with frame grabbing technology. Such systems are often beyond the capacity of many health care providers.

The continued development of digital technologies has given rise to a number of new portable innovations in the area of wound image capture. Since the data was collected for this study a number of new products have become available. For example, Silhouette (see Figure 54) is system that uses an infrared scanning device attached to a portable digital assistant (Palm Pilot ®) to generate a three dimensional image of a wound. Whilst reliability testing is still to be completed on this system the degree of sophistication is clearly evident. Predicted item costs of approximately A$6000 plus additional costs for the required software and computing system, will probably mean that such a system is again not readily available to clinicians.

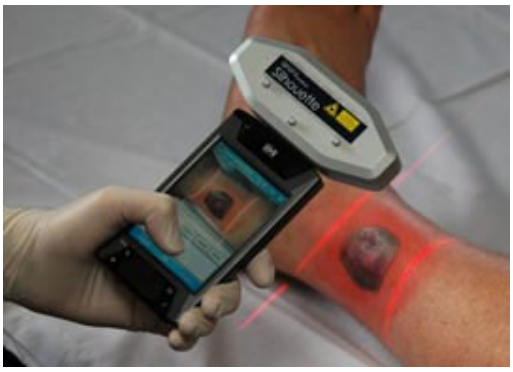


Figure 52. Silhouette wound image system
(Retrieved from http://gadgets.boingboing.net/2007/09/04/silhouette-mobile-po.html on 28/05/2008)

Whilst similar criticism could be levelled at the Ulcer-cam 2 and the Adelaide Skin Colour Measurement Program used for this project the level of required sophisticated equipment is less. The Ulcer-cam 2 frame could be produced with limited tooling or be commercially developed for a modest cost in comparison with the above systems. Equally the computer technology required to operate the Adelaide Skin Colour Measurement Program is minimal as it could be run on most desktop or laptop computers. Therefore it could be argued that the system developed for this project would achieve a higher degree of penetration into clinical settings because of low set-up costs and level of equipment sophistication.

The above assertion is further supported by the reliability of the system to achieve consistent results between different clinicians. Although limited by the small number of clinicians (n = 3) recruited, the findings demonstrated that the variations of hues ($F(8,441) = 0.006$, $p = 1.95$), orientation and magnification ($F(2,39) = 0.04$, $p = 0.95$) of the image recorded between clinicians was not significantly different. The limited variation suggests that the level of sophistication used in this system is consistently and easily

managed by clinicians when capturing a venous leg ulcer photograph. Further research is needed to determine if this trend continues with larger populations of clinicians.

Equally, studies examining clinician's opinions regarding the 'ease of use' when implementing the Ulcer-cam 2 and the Adelaide Skin Colour Measurement Program system is required to support the above assertion. Clinician perception of the utility of the Ulcer-cam 2 and the Adelaide Skin Colour Measurement Program were not examined as part of the project. With hindsight this may have provided further insights into the application of the system in the clinical setting.

Overall, the findings suggest that objectives one and two were met by the system developed for this study. Despite a lower level of sophistication than methods used by other researchers, the system has demonstrated a reliable alternative for capturing the hue, magnification and orientation of venous leg ulcer photographs. The reliability was demonstrated during an episode of care and across episodes of care. It was also evident across different clinicians using the system. The lower level of sophisticated equipment needed for the Ulcer-cam 2 and the Adelaide Skin Colour Measurement Program may ensure that the system becomes more readily available in the clinical setting than other systems. Further research is needed to support this assumption.

6.2.2. Colour range identified by clinicians to represent erythema and wet necrotic tissue

The intent of this phase was to go further than previous studies by providing a finer measurement of the hues that experienced clinicians believed represented two visual manifestations common to inflammation; erythema and wet necrotic tissue. Until this study was undertaken the colour used to describe each manifestation was generally limited to two major categories of the colour spectrum, principally red and yellow.[298, 301, 306, 307, 309, 310, 325, 410] Where attempts have been made to measure more subtle hues the studies have used varied wound types principally created in animals such as pigs or rabbits.[257, 299, 329, 403, 404, 442]

The findings from this study provide insights into these previously unexplored areas. The data are derived from the human assessment of venous leg ulceration of human subjects, all of which have not previously been explored. The colour range identified provides new insights into the subtle hues being used by experienced clinicians when assessing this wound type, again not previously available. In addition, the variation of responses from the participating clinicians questions the often promoted ‘subjective’ nature of clinical assessment and raises questions about the nature of using an expert opinion to arrive at representative colour ranges.

6.2.2.1. The colours identified

Examination of the hues identified by the panel of experienced clinicians for erythema reveals hues that could be typically linked to the descriptions of this manifestation in the literature. Erythema is indicative of infection or inflammation and is often described as a deep red colour.[96, 255, 258, 300-309] The depth of a colour is determined by the saturation of the colour at a given hue and brightness level.[443] The saturation range identified for erythema was 34 per cent to 78 per cent (see Figure 55). This range provides for varied representations of erythema from the lighter red associated with beginning inflammation or the outer area of inflammation, to the intense reds associated with advanced inflammation.

Figure 53. The range identified by experienced clinicians to represent erythema

Although parallels were evident between the colour range identified as erythema and written descriptions of the manifestation, it was felt that further comparisons were required to determine the accuracy of the range identified.

Erythema is most frequently quantified by researchers examining the effects of ultraviolet radiation on the skin or testing topical products for allergic inflammatory responses. The majority of such studies measure light reflected from the skin using a reflectance spectrophotometer or reflectance colorimeter.[444-454] This technology emits light (either Red-Green for the

former or white for the latter) and then measures the amount of light that is reflected by the skin. The amount of reflected light is then measured and converted to an 'erythema index'. The erythema index is based on the assumption that erythema is due to vasodilatation which in turn increases the amount of erythrocytes and haemoglobin in an area. Haemoglobin absorbs green light and reflects red light. By subtracting the amount of reflected green light from the amount of reflected red light the index can be calculated.[455]

In an effort to compare the colour range identified as erythema from the findings of this study with other studies, an erythema index was first calculated. This was achieved by converting the HIS findings recorded in this study to RGB using Adobe Photoshop® and then subtracting the red values from the green values. This method has been used in the past as a cost-effective method of calculating an erythema score.[455]

Using the minimum and maximum values an erythema index (EI = green-red) of -86 to -138 was calculated. This is lower than the findings of other researchers. Sertao and Sparavigna[455] used the above method to calculate an erythema index for 348 Caucasian patients distributed across Italy. The level of visible erythema was first classified into four grades: 0 = absent; 1= slight; 2 = moderate; 3 = intense; and then the erythema index for each calculated. They found that the erythema index for each level was: level 0 = 41 (± 10); level 1 = 51 (± 16); level 2 = 54 (± 23); and level 3 = 49 (± 18). Each level is higher than that established for this project. Even the lowest

erythema index of 31 is higher than the minimum erythema index of -86 identified as erythema by the panel of experienced clinicians.

A similar trend is evident when the erythema index established for this study is compared with results from induced erythema studies. Werner et al.[456] examined the erythema indexes of volunteers who were given first degree burns to their calves. They found an average erythema index of 19 (±2) which is still higher than the index calculated from the findings of this study.

When the findings are compared to studies that have used colour parameters to measure erythema in preference to an erythema index, a similar outcome is evident. Shai et al.[398] found that 'clean' wounds displayed a cyan of 20, magenta of 94, yellow of 87, and black of 12. It could be expected that erythema would display similar hues to that of a clean wound. When the mean hue and saturation of the range identified for erythema is converted to a CMYK colour range it yields a C = 0, M = 55, Y = 46 and K = 0. This constitutes a less saturated red than the findings from the Shai et al.[398] study (see Figure 56).

Clean wound colour range from the Shai et al.[398] study

Mean hue range from this study converted to CMYK colour for erythema

Figure 54. Comparison of red colours found by this study with that found by Shai et al.[398]

Similar findings are evident for the colour range identified for wet necrotic tissue; principally a less than expected saturation. The literature describes a yellow colour as representative of wet necrotic tissue, or slough. Examination of the visual range identified (see Figure 57) reflects more of a red / brown hue than a traditional yellow. When compared with educational material prepared to assist the decision making of clinicians the colour is quite different (see Figure 57).

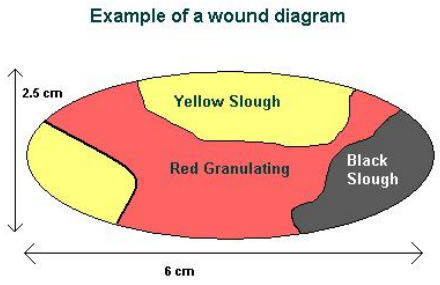


Figure 55. Visual comparison between the range identified as wet necrotic tissue and the colour used to depict this tissue in an example of educational material
(Retrieved from http://www.lhsc.on.ca/wound/assessment.htm)

Once again when the mean range is compared to colours identified by other studies a reduced saturation is found. Shai et al.[398] found that 'unclean wounds' displayed a cyan of 0, magenta of 0, yellow of 70, and black of 5. If we assume that an unclean wound will display large amounts of wet necrotic tissue then the colour range should be similar to the range identified for this study. When the mean hue and saturation of the range identified for wet

necrotic tissue is converted to a CMYK colour range it yields a C = 0, M = 50, Y = 58 and K = 0. This is again different from the figures found by Shai et al.[398] and produces a similar but less saturated colour (see Figure 58).

Unclean wound colour range from the Shai et al.[398] study

Mean hue range from this study converted to CMYK colour

Figure 56. Comparison of yellow colours found by this study with that found by Shai et al.[398]

A number of explanations could account for the lower than expected saturations for both erythema and wet necrotic tissue. The underlying pathophysiology of venous ulceration, the technique used to quantify the colours highlighted by the panel or the colour space used could all provide alternative explanations.

As mentioned previously research studies quantifying wound colours have not focused on venous leg ulceration. The underlying physiology of chronic venous disease, specifically the accompanying hyper pigmentation and skin degradation,[84, 89, 100, 110, 178, 242-245, 288-290] may contribute to the lower colour saturations. The darker pigmentation of the peri-malleolar skin resulting from hemosiderine, or iron deposits left in situ when erythrocytes break down in the subcutaneous tissues[86] may darken the colours exhibited, particularly erythema of the surrounding skin. The often dehydrated nature of the skin surrounding a venous leg ulcer may also decrease the amount of

erythrocytes reaching the superficial layers. When accompanied with the underlying venous hypertension the reduced amount of erythrocytes and haemoglobin reaching the superficial tissues surrounding the ulcer would reduce the colour saturation of the hue resulting from the inflamed response.

The less saturated hues for wet necrotic tissue may be associated with the amount of accompanying exudate. The chronic nature of venous ulceration often results in long-term areas of wet necrotic tissue, leg oedema and high volumes of exudate.[41, 308, 316, 317] The ulcer beds are usually 'wet' with the surrounding skin dry and scaly. The high volumes of exudate would ensure that the wet necrotic tissue is hydrated. Hydrated wet necrotic tissue would appear to have lower colour saturation than dry tissue as the exudate would reflect light. Other wounds containing necrotic tissue such as pressure injuries, arterial ulceration, or the infected or non-clean wounds described by Shai et al.[398] may not have the accompanying level of exudate and therefore the saturation of the tissue may appear greater.

The varied colour production algorithms used to collect data for this project may have also resulted in less than expected colour saturation for erythema and wet necrotic tissue. As digital imagery has become 'mainstream' a number of algorithms have been developed to analyse these images. Whilst the Red-Green-Blue (RGB) colour space has been used as the foundation for such algorithms the findings to date have not been reliable. Van der Valk and Snater[405] were not able to discriminate grades of erythema any better than the human eye using the RGB colour space. Jones and Plassmann[401] concluded that the RGB level of measurement was unable to distinguish

between the colour of a wound and the colour of skin, or the colour of a wound and the colour of connective tissue. Mekkes and Westerhof[397] found that simple RGB thresholds were not enough to identify a given tissue type. In particular the system was unable to determine the difference between the colour of granulation tissue, surrounding skin and newly formed epithelium.

The Cyan-Magenta-Yellow –Black (CMYK) colour space has received little attention in wound colour research however the findings indicate a potential reliability. As described earlier, Shai et al.[398] were able to use the CMYK colour space to identify clean from dirty wounds. As described in Chapter Three, the use of the Hue-Saturation-Brightness (HSB) has provided more promising results. Hansen et al. [404] were able to use colour to differentiate the severity of a pressure injury. Injuries with a blue / grey appearance were more significant than injuries that rapidly assumed a reddish appearance, followed by a gradual reduction in the redness over a period of several hours. Boardman et al.[399] used HSB to compare colours exhibited by non-infected and infected wounds. They identified that non-infected wounds exhibited a peak of red hue in the mid range of hues, which decreased as healing continued. Infected wounds, on the other hand, exhibited a distinct increase in the peak of red hue range.

Findings from this study were derived from images that were produced using all three colour algorithms. This mixture of colour representations may have introduced variables that led to the lower than expected saturations for each manifestation. The process of capture, transfer and printing may have

degraded or altered the colours originally exhibited by the ulcer resulting in the final hue range identified by the experienced panel of clinicians. For example, images were collected using digital technology that represents colour using an RGB algorithm. The hue estimates identified by clinicians to represent erythema or wet necrotic tissue were collected via printed images using a CMYK colour algorithm. When making the assessments, participating clinicians used human colour perception represented by the HSB colour algorithm. The images were then converted back to a digital image using a scanner that uses RGB to represent colour. Once digitised the hues were calculated by measuring the colours exhibited in the highlighted areas using HSB colour parameters. The resulting alteration to colours captured in the original images may have rendered the colour range identified by the clinician panel as invalid. Thus, when clinicians were asked to review the areas identified by the computer they only partially agreed with the selections.

Given the paucity of research examining the colour of erythema or wet necrotic tissue of venous leg ulceration it is hard to draw firm conclusions. The erythema and wet necrotic tissue indices identified developed from the results of this study may result from the colour space used to represent and measure each manifestation, or may represent the hue bias evident in venous leg ulceration. Further research is required to support either assertion.

6.2.3. Consistency between the opinions of the clinician panel when selected areas of erythema and wet necrotic tissue

The subjective nature of clinical decision making is often cited in the literature.[299, 376, 413, 415, 457, 458] The findings from this study provide support for this assertion only when the clinicians in this study were judging wet necrotic tissue. This was demonstrated by the absence of any significant difference between the areas identified by clinicians as wet necrotic tissue, and supported by visible similarities (see Figure 59).

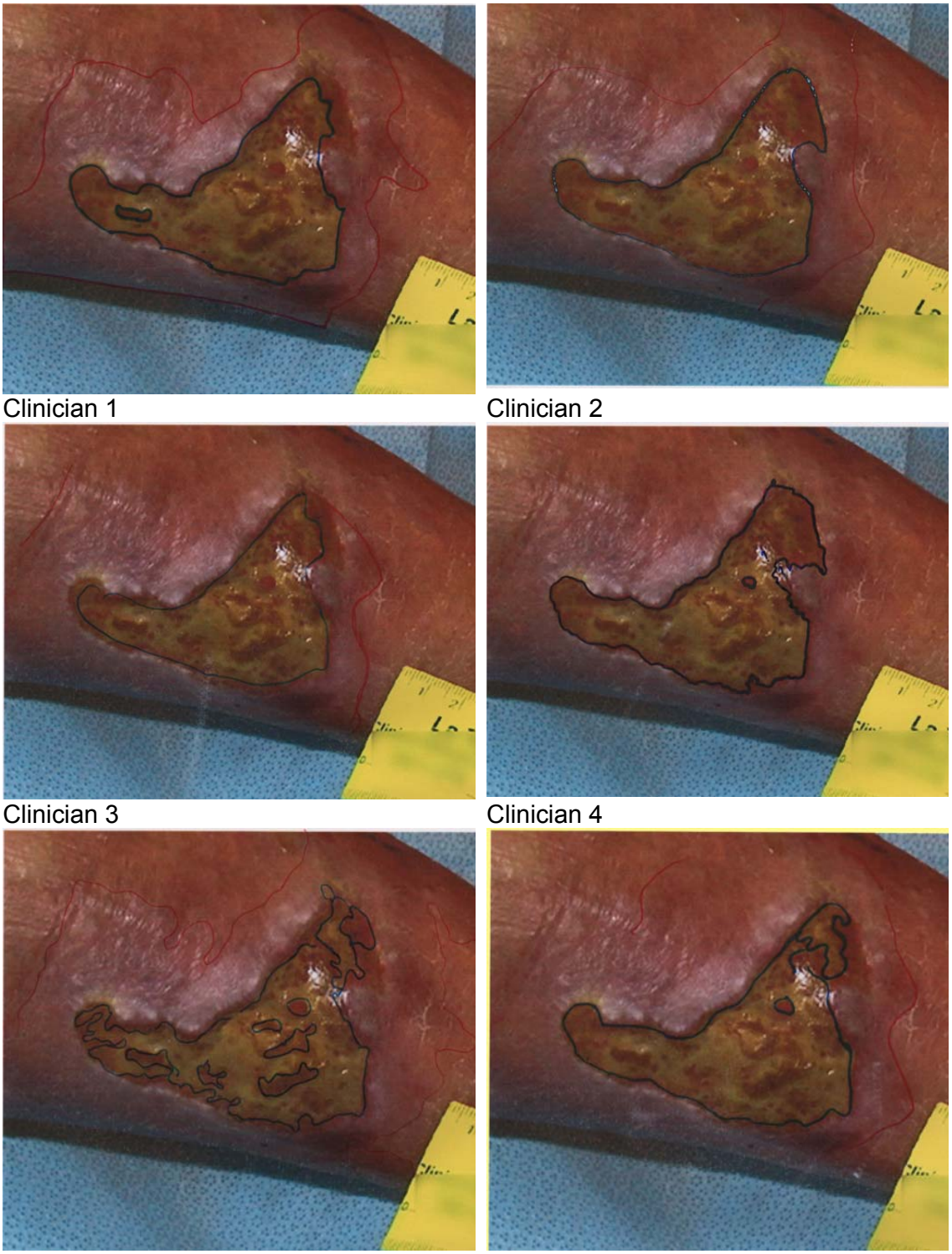
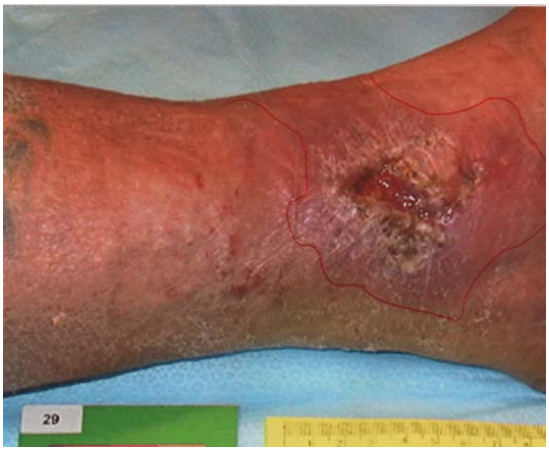
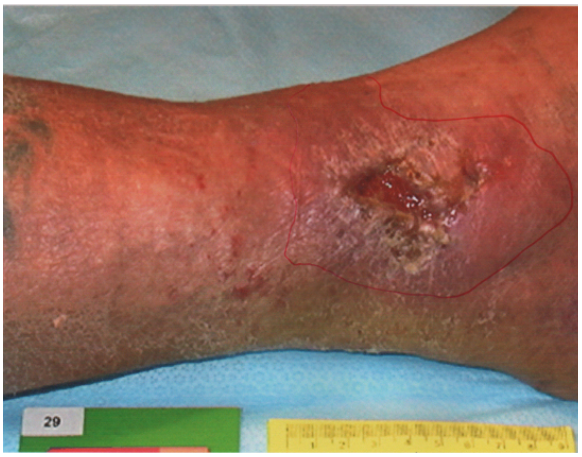


Figure 57. Example of similarity between clinicians when selecting wet necrotic tissue

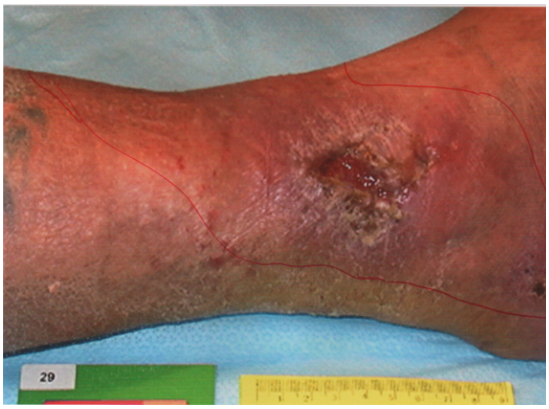
However, when the areas selected as erythema were examined a number of differences were evident. The areas identified as representing erythema by each clinician were significantly different, and visual examinations demonstrated differences (see Figure 60).



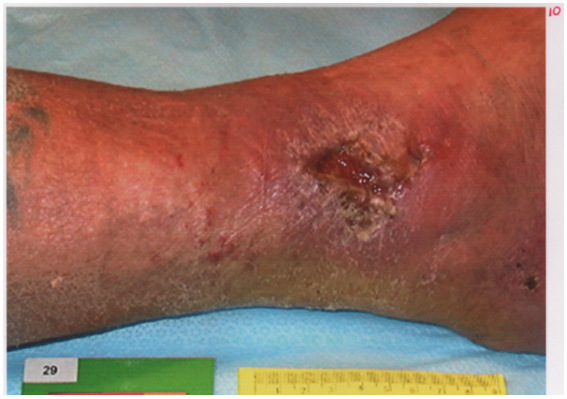
Clinician 1



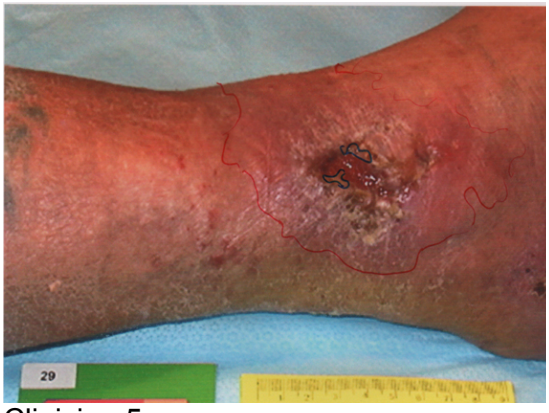
Clinician 2



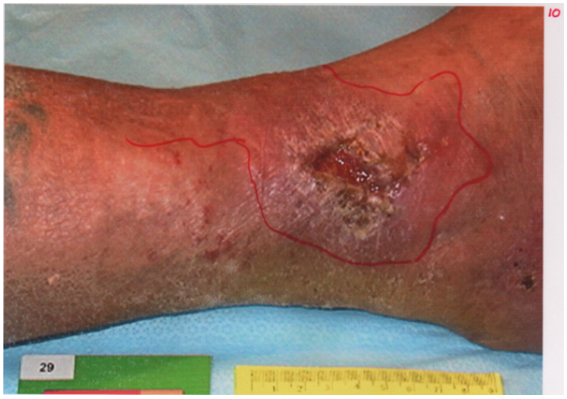
Clinician 3



Clinician 4



Clinician 5



Clinician 6

Figure 58. Example of similarity between clinicians when selecting erythema

The absence of significant variations between clinicians identifying wet necrotic tissue may be related to the ease of delineating this manifestation. When located adjacent to the pink / red hues exhibited by normal Caucasian skin the contrast would be high. The subtle hues of red exhibited by erythema may prove harder to delineate when contrasting with surrounding skin as the contrast in colours is low.

This finding is supported by other researchers. For example, Jones and Plassmann[401] when using the RGB colour space, concluded that the level of measurement provided by MAVIS® was unable to distinguish between the colour of a wound and the colour of skin, or the colour of a wound. Mekkes and Westerhof[397] found that simple RGB thresholds were not enough to identify a given tissue type. In particular, the system was unable to determine the difference between the colour of granulation tissue, surrounding skin and newly formed epithelium.

The subtle hue variation of erythema is obviously harder to differentiate from the surrounding skin or the granular tissue of an ulcer bed. This in turn increases the subjective nature of the assessments being made by the clinician leading to a greater variation in the areas selected within the digital images. On the other hand the contrast between the colour of wet necrotic tissue and skin or granular tissue facilitates identification of the tissue type and recognition of the border. This in turn reduces the subjectivity and improved consensus between observers.

Although not significant there still were variations in the areas selected for wet necrotic tissue as well as erythema. If we accept the notion put forward by Byrne and Hilbert[333] (see Chapter Three) that colour perception is a separation of physical entity (colour representing) and psychological experience (colour feeling) then any criteria derived from the opinion of clinicians will by its nature be varied. Whilst it could be argued that the display of colours generated by the physical entity (e.g. light reflection and light reception) should be similar across patients and clinicians, the introduction of a psychological process in the perception of colour introduces variation.

Each clinician would have brought their 'experience package' to the assessment. This would have included variables that could not be controlled. Previous experiences with colour, previous experiences with leg ulceration, current fatigue levels and ambient lighting in which the assessment was made, are examples of variables that would influence the areas selected by the clinicians.

Differing levels of agreement between clinicians have been found in other studies. Lorentzen et al.[310] found only 'moderate' agreement between clinicians using the Red-Yellow-Black system of wound colour assessment when judging 120 wound photographs. Vermeulen et al.[309] found 'moderate' to 'good' levels of agreement for a sample of doctors and nurses using the same system to judge photographs of wounds. Johnson[291] found low

intrarater reliability of clinicians using wound colour as a criterion for assigning a wound status index score.

The problem faced by the type of research is the absence of a 'gold standard' for assessing erythema or wet necrotic tissue. Clinician and contextual differences makes judging the accuracy of the assessment difficult. Further research using a larger sample size of clinicians is required to help reduce the influences that these confounding variables have on the development of clinician derived indexes such as the erythema and wet necrotic tissue hue ranges generated by this project.

6.2.4. The validity of areas selected as representing erythema and wet necrotic tissue by the computer system

The third phase of this project was to help remove the degree of subjectivity described in the previous section by having the computer system select areas that represented the manifestations of erythema and wet necrotic tissue. The differences between areas selected by clinicians and those selected by the computer system would suggest that this aim was only partially met. This assertion is further supported by the moderate level of agreement indicated by clinicians when asked to judge the areas selected by the computer system for both manifestations.

6.2.4.1. Computer system Vs clinician

When comparisons were made between the areas selected by the computer system as erythema with those selected by the clinicians the difference was significant indicating that the initial criteria developed for the computer system selection were an inaccurate representation of the hue range displayed by this manifestation. Either clinicians participating in the study failed to provide a sufficient range of hues in the areas traced on the images, or the criteria used for the algorithm (mean hue plus or minus one standard deviation) provided an insufficient tolerance required to represent this manifestation.

Attempts were made to increase the correlation between areas selected by clinicians and the computer system by increasing the criteria from one to two standard deviations from the mean hue. When the modified algorithm was used the entire leg was often selected including unaffected skin. Thus, one standard deviation produced an insufficient area whilst two standard deviations failed to discriminate between unaffected skin and areas of erythema.

The above trend was not evident when the areas selected by the computer system as wet necrotic tissue were compared with those selected by the clinicians. The difference was not statistically significant suggesting that the hue criteria being used to select this manifestation were more accurate than with erythema.

The findings provide further support for the assertion made in the previous section; principally the reduced contrast between the hues of erythema, granular tissue and normal skin make it difficult for clinicians to differentiate erythema in a digital image. This is supported by the variations of areas selected by different clinicians when asked to outline this manifestation (see Chapter Five). Collapsing the different hues to a mean hue and one standard deviation provided an insufficient range to select all pixels displaying the hues deemed by *some* clinicians as representing erythema. Increasing the criteria to two standard deviations only increased the range to such an extent that the computer system was unable to differentiate the different tissue types.

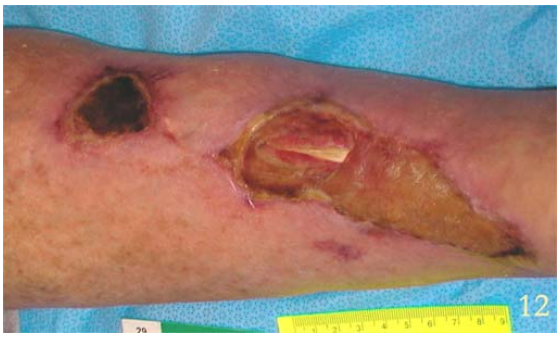
The absence of significant difference for wet necrotic tissue adds further support to the above assertion. The contrast between the yellow of this manifestation and the red of the ulcer bed or surrounding skin has assisted the clinicians to select wet necrotic tissue in a digital image. This has in turn provided a more discrete hue range which when converted into criteria for the computer system has resulted in areas being selected that more closely represent those selected by the clinicians. Although more research is needed to confirm this assumption, the results comparing computer system selections with those of clinicians indicate that using 18.73 degrees of hue plus or minus a standard deviation or 6.04 degrees is a valid criterion for selecting wet necrotic tissue in a digital image.

6.2.4.2. Clinician perception

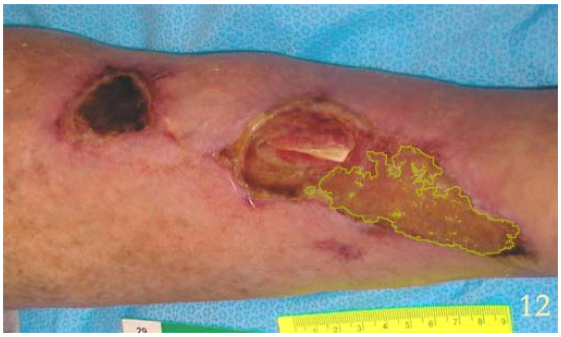
Clinician perception of the accuracy with which the computer system was able to select areas of erythema and wet necrotic tissue was evaluated using a visual analogue scale to examine the level of agreement (see Chapter Four). Given the findings achieved when comparing the difference between areas selected by the computer system and those selected by the clinicians (see above), it was expected that the level of agreement would vary. It was further expected that the level of agreement would be higher for areas selected by the computer system as wet necrotic tissue than for areas identified as erythema. The findings support this assertion with a higher level of agreement achieved for wet necrotic tissue (6.27 degrees out of 10) than for erythema (5.63 degrees out of 10).

What was not expected however was the moderate level of agreement achieved when clinicians were asked to judge the accuracy with which the computer system had selected areas of wet necrotic tissue. The absence of a significant difference between the areas of wet necrotic tissue selected by the clinicians and those selected by the computer system during the second phase would suggest that the level of agreement during the survey should have been higher (remembering also that the images judged by the clinicians in phase three were the original images used in phase two (see Figure 61)). Asking clinicians to judge the same series of photographs containing highlighted areas of wet necrotic tissue that were not significantly different from the areas originally highlighted by themselves should have resulted in a

high level of agreement. Whilst higher than erythema, it could be argued that just over 60 per cent is not indicative of a high level of agreement.



Phase 2



Phase 3

Figure 59. Example of photographs sent to clinicians during phase two and three

The findings suggest that even when criteria derived from the judgement of clinicians is used to develop an automated identification system; and that system selects areas similar to that of the clinician, he / she will only agree with the area selected 60 per cent of the time. A number of explanations for this outcome are possible with the most likely being either a different reproduction of the original photographs for phase three a change to the clinician's observation of the photographs as a result of changes to visual perception; or as a reflection of the clinician's desire to retain some clinical decision making autonomy.

6.2.4.3. Photographic reproduction

Although the photographs for phase three were reproduced using the same printer as that used for phase two, minor variations in the colours produced may have resulted in the clinicians observing areas of wet necrotic tissue not seen in the earlier phase. As suggested previously the capture, printing, re-capture and measurement techniques used for this study (see Chapter Four) may not have accurately reflected the original manifestations presented in the ulcer. The same could be true for photographs replicated in different phases. Additional controls that measured the colours reproduced on each set of photographs would have helped reduce the possible confounding influence of this variable and would need to be included in any future studies.

6.2.4.4. Changes to visual perception

As described in Chapter Three the perception of colour is influenced by a number of variables both physical and psychological. It is possible that the presentation technique used for phase three influenced the visual perception of the clinicians judging the accuracy with which the computer system had selected each manifestation.

In particular, the influence of bordered areas within the photographs used in phase three may have influenced the observations made by the clinicians. The inclusion of borders in an image has been shown to play an important part in visual perception. Using a concaved card Bloj et al.[363] were able to demonstrate that the inclusion of a border enabled subjects to differentiate areas of illumination in an effort to determine depth. By using borders, Kingdom and Moulden[459] were able to isolate cerebral areas responding to different areas of illumination. Van Es et al.[362] demonstrated that border recognition enable humans to maintain colour constancy by comparing areas of interest with surrounding regions and making cerebral changes to compensate for different levels of illumination. Albert[460] and Zhaoping[461] describe how a border normally belongs to one of the two regions adjacent to the border. They demonstrated that humans use surface perceptions to assign ownership to a border. When borders were hard to define the subjects alternated ownership over time.

The use of borders to delineate areas as either erythema or wet necrotic tissue may have therefore influenced the perception of the observer. It may have encouraged them to pay closer attention to areas immediately adjacent

to the border. Equally, it may have changed their perception of the level of illumination in areas adjacent to the border and thus changed their perception of its significance.

The preconceptions of the observing clinicians may have also played a part in the judgements made in phase three. As mentioned in Chapter Three, Treisnman et al.[364, 365] found that subjects given verbal descriptors such as "orange carrot or blue lake" made significantly more illusory preconceptions about the colour than subjects given feature descriptions such as "orange triangle or blue ellipse". Given the experience level of the clinicians, it may be that they were making judgements based on preconceptions (i.e. other ulcerated legs) when assessing the photographs in phase two. A bordered area may have encouraged them to put aside these preconceptions and focus on the actual visual display.

Using the images from phase two in phase three may have also enabled clinicians to see additional cues not previously noticed. Familiarity with visual stimuli has been demonstrated to enrich the neural representations of such stimuli. Epstein et al.[462] used magnetic resonance imagery to scan the cerebral activity of volunteers when viewing digital images that had a high or low degree of familiarity. They believed that scenes familiar to the subject have a variety of cerebral representations enabling the subject to recognise them from a range of different viewpoints. They described this as an "enriched neural representation" (p. 3681).

As the clinicians had seen the photographs used in phase three previously in phase two, they may have already developed a degree of familiarity with the image. If Epstein et al.[462] are correct, any familiarity with the image would have enabled the clinicians to scan recognised sections of an image and focus their attention on other previously unseen aspects. The intent would be to enrich the neural representation of each image as described by Epstein et al.[462] The change in focus may have in turn changed the clinician's opinion about the representation of each manifestation resulting in them disagreeing with areas selected by the computer system which was in turn based on their earlier assessments.

6.2.4.5. The influence of clinical decision making autonomy

The complex array of variables that influence clinical decision making is often cited as impediments to designing systems that replicate expert opinion. Following a comprehensive literature review in 2006 Lee et al.[463] concluded that diagnostic practice was a compilation of information seeking behaviour that utilised communication interactions and cognitive functions to arrive at a decision. The decision was influenced by a number of variables including personal, psychological and structural variables. Thus the ability of clinicians to accurately replicate previous clinical decisions when confronted with similar cues (in this case an ulcer photograph) is limited by the influence of the above variables. For example, when assessing the ulcer photographs for a second time the participating clinicians may have been drawing from experience gained in the intervening time (personal), had a different level of fatigue (psychological) or undertaken the assessment under different lighting

conditions (structural). Each of the above variables may have resulted in the lower than expected level of agreement.

Other authors would argue that the above findings are a representation of a reluctance of clinicians to give up their autonomy when making clinical decisions. Brehm[457, 458, 464, 465] first described this response as 'reactance theory' in 1966. The principle assertion of reactance theory is that when a person is recommended to take a specific action they become motivated to react in a way that affirms their freedom to choose. Proponents of the theory point to common examples that illustrate a reluctance of clinicians to follow evidence based recommendations.

Grol and Grimshaw[466] highlighted the failure of clinicians to wash their hands despite evidence that illustrates an association between increasing nosocomial infection rates and cross contamination perpetuated by clinicians. When examining why interventions aimed at improving the quality and safety of medication administration are often ignored by physicians, de Almeidia Neto and Chen[457] concluded that physicians elected not to follow 'best practice' recommendations as it threatens their freedom to choose. Fogarty,[458] when examining patient behaviour, concluded that reactance theory provided the best explanation for patients refusing to cooperate with medical treatments.

A reluctance to follow evidenced based recommendations may be further heightened when such recommendations are presented in the form of

computer assisted systems. Sittig et al.,[467, 468] when examining emotional responses to a computer based order entry system, found that respondents expressed feelings of guilt, anger, sadness, hostility and disgust towards having to use the system. They concluded that clinicians felt that the computer system was punishing them because when the user stepped outside of established guidelines their decisions were questioned by the computer system via a prompt.

Buller-Close et al.,[469] when evaluating the effects of an emergency department expert charting system, found low compliance amongst treating clinicians. As an example, they cited that the system was used for only 39 per cent of eligible paediatric patients. They concluded that physicians believed that using a "computerised assistant to manage these common problems [was] an admission of lack of knowledge or skill" (p. 649). Agostini et al.[470] asked clinicians to identify barriers to using a computer based reminder when prescribing sedation for older patients. Three barriers were identified: time needed to read the reminder; the role of clinical experience; and the content of the reminder. In regard to the second barrier, clinical experience, the respondents felt that reminders eroded the prescribing autonomy of the clinician. One respondent stated "if the patient needs sleep I can decide whether to order a drug or not" (p. 34).

A similar perceived reduction of clinical decision making autonomy may have accounted for the lower than expected propensity for clinicians to agree that the computer system had accurately selected areas of wet necrotic tissue.

When asked to indicate their levels of agreement participants may have seen the potential of such automation as a threat to their rights to determine assessment criteria when examining venous leg ulcers. Having made this decision they would be less likely to agree with the computer system in order to limit the findings and reduce the threat.

The complex nature of clinical decision making makes it difficult to come to any definitive conclusions. Certainly the absence of consensus between participating clinicians and the computer system with regard to areas identified as erythema was to be expected given the significant difference in areas selected by each party. The unexpected modest rate of agreement indicated by clinicians reviewing areas of wet necrotic tissue may be explained by the complex interactions of variables influencing this process or a more deep seated psychological motivation to retain the freedom of choice. Further research is required to explore possible explanations for this anomaly.

6.3. *Conclusion*

The research reported in this thesis has been motivated by the significant health problems created by CVI. It is based on a number of supported assertions derived from physiology, pathology, psychology, sociology and health science research. The platform has been used to justify the need for more objective visual assessments of venous leg ulceration in an effort to improve the management of this client cohort. The findings contribute to this goal by providing insights into an effective method for recording the colours

manifested by venous leg ulcers; the range of colours seen as significant by experienced clinicians; and the difficulties encountered when tyring to automate the clinical decision making process of clinicians assessing this manifestation.

For the purposes of the project, CVI has been defined as structural and functional abnormalities of the superficial and deep leg veins resulting in venous hypertension which in turn manifests as a discrete set of signs and symptoms. Symptoms cited have included pain, heaviness, leg tiredness, cramps, itching and restless leg syndrome. Signs cited have included telangiectasia, reticular or varicose veins, leg oedema, and skin changes such as pigmentation, lipodermatosclerosis, eczema and ulceration.

Central to the thesis is the assertion that CVI is most frequently caused by abnormalities of vein walls and valves arising from an abnormal *inflammatory* process. The inflammation is either primary in origin with an unknown aetiology, or secondary to a previous injury, principally deep vein thrombosis. Skin changes resulting from CVI, specifically leg ulceration, are influenced by the abnormal inflammatory process resulting in complications such as repeated infections and delayed healing. The visual manifestations resulting from the inflammatory process are recognised by experienced clinicians as indicators of developing complications or delayed healing.

6.3.1. The significance

The long-term nature of CVI and the resulting skin changes creates both a substantial personal and societal impost. For the sufferer the condition is often accompanied by a lowered quality of life exacerbated by the physical manifestations of leaking exudate, odour, pain, interference with sleep, and leg deformity. To compensate sufferers often choose to lead of a life of social isolation and loneliness.[19, 75, 90, 106, 162, 167, 176, 177, 471, 472] In addition, sufferers often have to pay for their management creating an additional burden on the quality of life they can afford. Personal costs have been estimated to be in excess of 14 per cent of their weekly income[174] imposing a significant financial burden on an estimated 67 per cent of patients[173] with manifestations resulting from this disease. Accompanying time lost from work, and an inability to retain paid employment further add to both the financial and quality of life burdens experienced by these patients.[162, 173, 177]

For the providers of health care finding the necessary resources for this client cohort is becoming increasingly difficult. Estimates of the financial impost of this disease on health care costs have been substantial. Figures in excess of US$1 billion[167], £949 million[168, 169] or A$600 million[2, 172] have been cited by studies quoting direct costs only.

As the population of the world ages this burden will only increases as the prevalence of CVI is highest in the sixth, seventh and eighth decade of life.[2, 5, 12, 20, 22, 43, 46, 50, 56, 68, 69] The immediate effect will be felt in developed countries where the rates of obesity are increasing as the inhabitants

consume highly refined diets and opt to follow sedentary lifestyles.[5] As developing countries move to adopt the 'ways of the west' it can be expected that similar health patterns found in developed countries will predominate. This will in turn increase the prevalence of CVI throughout the world.

Although a significant health problem, the attention received by sufferers of CVI is often less than other disease states. As the manifestations of the disease don't threaten life or limb the impact is often overshadowed by more life threatening diseases such as cardiovascular disease or diabetes. This has in turn limited the allocation of resources to conduct the large population based research needed to provide prevalence detail and judge the efficacy of different treatment options.

6.3.2. The challenge

Clinicians wishing to establish clear criteria for the diagnosis of CVI and the resulting clinical manifestations are confronted with an array of options derived from research of varying rigour. This is most keenly felt when assessing the status and healing progress of venous leg ulcers. Assessment schemes relying on the recognition of colour, exudate levels and changes to dimension predominate in the literature.[1, 4, 5, 9, 20, 22, 34, 38, 40, 47, 54, 75, 89, 100, 101, 109, 110, 141, 159, 164, 183, 208, 288-290, 310, 313, 322, 324-328, 396, 400, 403, 407, 425, 430-434, 437, 471, 473-476] The techniques have often not undergone rigorous validation and rely heavily on the subjective opinion of the clinician. It has been argued that as the prevalence of venous leg ulceration increases along with the associated

cost more rigorous assessment criteria are required. Criteria based on objective parameters that can be replicated across different clinicians in different clinical settings are required to assist the implementation of cost-effective care.

6.3.3. The project aim

The intent of this study was to develop a system that enables clinicians to easily and objectively measure the different colour manifestations exhibited in the bed of a venous leg ulcer and the surrounding skin. To achieve this aim a three phase study was implemented. The first phase was to develop and test a system for recording the colours exhibited by a venous leg ulcer. The second phase was to use the images captured to establish a colour range that experienced clinicians believed represented different tissue types. The third phase used the colour range derived from the above clinician cohort to develop a computer system that could identify and highlight different tissue types in a digital photograph of a venous leg ulcer and test the validity of the areas selected.

To help limit the scope of the project two predominant tissue types were selected as the foci; erythema and wet necrotic tissue. These tissue types were selected because the presence of both had been reported in the literature as a common manifestation of inflammation. Inflammatory processes have been reported as the underlying physiological mechanism frequently found in slow to heal or chronic wounds, in particular venous leg ulceration.[3, 5, 13, 15, 19, 30, 37, 80, 86, 127, 128, 130, 135, 223, 296, 313, 314, 477, 478] It was

hoped that by meeting the aims of this study a system could be developed in the future that would provide a clinical tool that could be used to differentiate between chronic venous legs ulcers that follow a normal healing cycle and those that become ‘trapped’ in an inflammatory process and hence slow to heal.

6.3.4. The findings

The findings from the study suggest that the aim has only partially been met. The Ulcer-cam 2 frame and the accompanying photographic capture system developed have produced findings that suggest it provides a consistent and reliable method for capturing the colours exhibited by venous leg ulcers and the surrounding skin. The reliability of the computer system would seem to be consistent within an episode of care and across different care episodes. Equally, the reliability of the computer system to capture colour appears to be consistent when used by different clinicians during the same episode. The findings support the assertion that the computer system developed has both intra-observer and inter-observer reliability.

The Ulcer-cam 2 frame also appears to provide a consistent magnification of the ulcer and orientation of the leg. This is demonstrated by the absence of any difference within an episode, and the lack of any statistically significant differences across episodes of care. The same trend is found when examining photographs captured by different clinicians, again suggesting both intra- and inter-observer reliability.

The image capture system is easy to use and can be implemented in a variety of clinical settings. The cost of training and specialised equipment is low using the relatively 'low tech' approach underpinning the system. The ability to reliability photograph venous leg ulceration over time, providing a library of sequential, standardised photographs could in itself provide support for clinical decisions.

The colour range identified for erythema and wet necrotic tissue by experienced clinicians recruited for this study provide new insights into the observations being made by this cohort. Until this study had been performed wound colour had been confined to gross hue representations of principally red, yellow, black and pink.[305, 309, 310, 410, 433] Understanding of the judgements being made by clinicians when observing subtle differences within a broad hue range (e.g. red) have to date not been explored. The findings from this study provide early insights into the range of hue, brightness and saturations being used when clinicians judge two wound manifestations, namely erythema and wet necrotic tissue.

The range identified for each manifestation has also provided insights into the variation of perceptions between clinicians. Standard variations of 3.51 degrees for erythema and 6.04 degrees for wet necrotic tissue suggest that opinion between experienced clinicians is varied. This assertion is further supported by a statistically significant difference in the areas highlighted by clinicians in the photographs as representing erythema. Interestingly, the colour range with the largest standard deviation (wet necrotic tissue) did not

demonstrate a significant difference in the surface area identified by the participating clinicians. This suggests that the hue range for wet necrotic tissue (yellow) is broad but easier to recognise, whilst the hue variation for erythema is smaller but harder to recognise.

The findings from this project suggest that the contrast between the hues of wet necrotic tissue and the surrounding wound bed or skin are easier to differentiate than the contrast between the hues of erythema and the surrounding hues of wound bed or skin. Such findings require further exploration as the ability to recognise the more subtle differences in erythema may be a critical cue being used by experienced clinicians when judging the progress of venous leg ulcers. If so, data from such studies could be used to inform approaches to diagnostic criteria and clinician education.

When the hue range identified by participating clinicians was used to develop a computer system that could highlight areas of erythema or wet necrotic tissue in a digital photograph of a venous leg ulcer it would seem that the criteria has limited validity. This assertion is initially supported by the statistically significant difference in surface area identified as erythema by the clinician and that identified by the computer system. It is further confirmed by the lower than expected level of agreement (5.63 out of 10) indicated by clinicians when asked to judge the accuracy of the areas highlighted by the computer system as representing erythema.

Once again however, the trend was different for wet necrotic tissue. The difference between the clinician and the computer system was not statistically different. Although not as high as expected the level of agreement indicated by clinicians when examining areas selected by the computer system as being wet necrotic tissue (6.27 out of 10) was higher than erythema. The findings support the assertion made above that the contrast between wet necrotic tissue and surrounding tissue types facilitates easier recognition and hence provides a more valid criteria for the computer system to use as a criterion.

It could therefore be argued that the hue range identified as wet necrotic tissue by participating clinicians is a closer representation of the criteria being used by clinicians when assessing venous leg ulcers, than that identified for erythema. It could also be suggested that the identification of this manifestation is easier for clinicians to make than that of erythema because of the contrasts between the yellows and browns of wet necrotic tissue and the pinks and reds of the surrounding wound bed and skin hues.

6.3.5. Conclusions drawn

In summary the aims of this project have been partially met. The original intent was to develop an objective measure for assessing the colours manifested by venous leg ulcers. The intent was based on the assumptions that slow to heal or chronic wounds were locked in a cycle of inflammation, and that inflammation was manifested as erythema and wet necrotic tissue. To achieve the aim three objectives needed to be met: the development of a

reliable system for recording the colour manifested; the establishment of a hue range that represented the two manifestations of erythema and wet necrotic tissue; and the construction of a computer system that used the hue range to select and highlight areas within a digital image of a venous leg ulcer.

The method used in the first phase of this project to record the colours exhibited by a venous leg ulcer would appear to be reliable both within an episode of care or across episodes of care, and for images taken by one or more clinicians. The hue range derived in phase two from the opinions of experienced clinicians provides new insights into the criteria being used for the visual observation of venous ulcers. The findings have demonstrated that higher levels of agreement are reached between experienced clinicians when assessing wet necrotic tissue than when assessing erythema. The data has provided a further refinement of hues used for leg ulcer assessment beyond the crude colour criteria of Red-Yellow-Black-Pink that has predominated published literature.

However, the hue range identified would appear to have limited validity when used as a criterion for a computer system to select areas within an image that represents each manifestation. The surface area selected to represent erythema was statistical different from that selected by participating clinicians, as was the level of agreement indicated by clinicians when assessing the areas selected by the computer system to represent this manifestation. Although the difference of the surface area selected as wet

necrotic tissue by the computer system was not statistically different from areas selected by participating clinicians there was a difference and the level of agreement indicated by clinicians when assessing the areas selected by the computer system to represent this manifestation was lower than acceptable.

It has been postulated that the reason for these findings is related to the level of contrast between the yellow hues manifested by wet necrotic tissue and the red hues of the surrounding wound bed or skin. In other words it is easier to distinguish yellow from surrounding red than it is to distinguish varying shades of red from surrounding reds. The degree to which the difference in perception can be attributed to the physical properties of the light reflected from the ulcer or the psychological process of the clinician making the assessment can not be determined from the findings of this project. As discussed in Chapter Three, the exact mechanisms of colour perception is still to be determined.

It has been further postulated that even if the aim of the project had been completely met the propensity of clinicians to accept the colour perception of a computer system may be limited. If the assumptions of reactance theory are correct attempts to quantify the clinical observations being made by clinicians assessing venous leg ulcers may be seen as a threat to their freedom to choose. Thus further development of this computer system will have to be made with this in mind.

6.3.6. Recommendations for further research

Underling any of the above assertions are the limitations of this study. Although the sample has demonstrated similar characteristics of patients suffering from venous leg ulcers it is not a representative sample. Equally, the number of clinicians used to capture the initial images and the number of experienced clinicians used to establish and evaluate the hue range for each manifestation is small. Although controls have been used to standardise for variances in the image capture, printing, scanning and storing of colour data, the methods used may have introduced a degree of bias that has influenced the results and conclusions found. It is therefore recommended that the following research be undertaken:

1. Further replication studies using a representative sample of venous leg ulcer patients and the clinicians that care for this client cohort be undertaken to determine if the reliability of the method used in this study to record colour, magnification and orientation continues to be demonstrated.
2. Further replication studies using a larger international cohort of experienced clinicians be undertaken to determine the validity of the hue range identified for erythema and wet necrotic tissue in this study.
3. A series of studies be undertaken varying the hue tolerance used by a computer system to select areas within a digital image of venous leg ulcer. This study has demonstrated that a tolerance of one standard

deviation was insufficient to be accurate but two standard deviations were not selective enough.

4. Studies be undertaken to explore the propensity of wound care clinicians to accept automated systems of visual wound assessment.

The perception of colour remains subjective. How clinicians use these subjective criteria to assess the progress of a wound is still unknown. As the incidence and cost of chronic wounds, in particular venous leg ulceration escalates, more defined assessment methods will be required. The findings from this project suggest that the method developed to record a digital image of a venous leg ulcer provides a reliable colour measurement, magnification and orientation using technology that could be used in a clinical setting with minimal disruption and cost.

The findings provide insights into the range of colour that experienced clinicians perceive as either erythema or wet necrotic tissue, demonstrating that wet necrotic tissue is easier to identify than erythema. These findings may be of benefit to future developers of diagnostic technologies and providers of wound management education.

The validity of the colour range established for each manifestation as a criterion for a computer system to select areas within a digital photograph has not been established. Further research is needed to refine this hue range until it is perceived as a valid representation by experienced clinicians. Such

studies will need to explore the impact of smaller variations in the tolerance set for the computer system using the above hue range.

As technologies improve the ability to accurately measure colours exhibited by venous leg ulcers and then use that data to recommend treatments may become commonplace. This project provides one piece in the large jigsaw that makes up this area of research. It is hoped that it provides insights that will help reduce the time patients spend with venous ulceration. Whilst the condition may not threaten life or limb it severely impacts the quality of life experienced by these patients and the pain and costs they endure. Therefore any future research aimed at limiting the impost of this condition on the members of our society should be enthusiastically explored.

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Appendix A: Journal article

Developing an accurate system of measuring colour in a venous leg ulcer in order to assess healing

- **Objective:** To develop a standardised method of assessing venous ulceration, based on the colour of an ulcer bed and the surrounding skin.
- **Method:** This pilot study involved taking three sequential digital photographs during an episode of care and measuring the colour using image analysis software. Ten episodes of care were used for data collection.
- **Results:** Based on previous research, a threshold of ≤3° of colour and 3% of saturation was selected to indicate the reliability of the system. The mean of the colour measurements was inside the reliability threshold when measuring an ulcer bed, but outside the threshold for measuring the surrounding skin.
- **Conclusion:** The results indicate that the system provides consistent visual representation of a venous leg ulcer.
- **Declaration of interest:** None.

venous leg ulcers; colour measurement; assessment; wound healing

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Venous leg ulceration is not only debilitating for patients, but also difficult and expensive to manage. The reported prevalence varies from 1.1 per 1000 population to 6.4 per 1000 of population.[1-4] In North America, estimates put the costs of managing leg ulcers at between $25 million (£13 million) in 1985 to $1 billion in 1996.[5,6]

Management is aimed at reducing venous hypertension and providing a local wound environment conducive to healing.[5,7-13] To monitor the local environment, regular assessment is recommended. Assessment of an ulcer environment relies heavily on the observations of a clinician, in particular, the clinician's ability to recognise various tissue types in the base of an ulcer.[5,9,13-20] Expert opinion is that the predominance of a given tissue type is indicative of the ulcer healing process. A high percentage of wet necrotic tissue or slough in the ulcer bed indicates that an ulcer is undergoing destructive changes, while a predominance of granular tissue may be indicative of tissue proliferation or healing.[19,21-23]

Colour

A key element to assessing the local environment of a venous ulcer is the ability to recognise the various tissue patterns in the ulcer base and surrounding skin. Colour is often used to describe the predominant tissue in an ulcer bed.

- A yellow wound predominantly consists of wet necrotic tissue or slough
- A red wound is indicative of granulating tissue
- A green wound is representative of an infected ulcer.[19,21,23]

While this classification system offers a broad rule of thumb, in reality most wounds exhibit subtle colour differences. In our experience, it is these difference that clinicians use to assess wounds. But interpretation of colour within a wound is a subjective measure and can result in differences of opinion.

Human colour perception is influenced by a number of physical and psychological variables including room lighting, visual acuity, previous experience with colour and the person's current mood. Although studies have shown that a consensus of colour perception can be achieved when judging major colour groups, these findings are not supported when subjects are asked to discriminate between subtle hues of one colour. Colour discrimination thresholds for the same colour can change by a factor of 10 between subjects.[24]

Clinicians' differing perceptions can result in varying plans of treatment. As a result, patients with chronic wounds who are managed by a number of clinicians may be subjected to a range of local treatments and associated costs. As the cost of wound products escalate, so too does the need to develop systems that accurately measure a wound's progress. The literature suggests that the ability to recognise wound colours is an integral component of assessing wound healing,[19,21,23] so having a system that records measurements accurately and consistently is key. Such a system would assist the collection of data on a wound, based on colour patterns, over time, which could provide a non-invasive method for determining wound-bed tissue type.

When the pattern for each wound is collated for several wounds of the same type — for example,

venous leg ulcers — normative patterns of colour may be discernable. A library of patterns against which to compare a similar type of wound may provide early recognition of wounds that vary from the 'normal' pattern. For example, a wound that continues to produce wet necrotic tissue may be indicative of chronic inflammation or bacterial colonisation. Until such research is conducted, the potential of this data type is yet to be fully explored.

Previous systems to measure wound colour

Technological developments in the 1980s and a desire to move beyond the crude red-yellow-green-black colour measurement of wounds prompted research into systematic wound colour measurements. Technology designed to measure an erythema index following radiation treatment of the skin provided researchers with the first in a series of tools with which to measure wound colour, the spectrometer. However, this only measured colour over a very small area. In the 1990s advances in digital technology and computer image analysis — resulting principally from the measurement of skin lesion colour, specifically melanomas[25-34] — offered the possibility to measure colour over a large surface area and to store the data digitally.

However, attempts to apply computer analysis to wound images threw up confounding variables — differing light sources, unwanted reflections and variations in colours displayed by different types of wounds — that required controls when taking or capturing the image.[35] Once an image was captured, another group of variables came into play, including the algorithm used to measure the colour and differences in human colour perception. Various controls have been used to eliminate each variable.[35-37]

To help control for different lights sources, researchers have adopted the use of an in-shot reference. MAVIS (Measurement of Area and Volume Instrument), developed by Jones and Plassmann,[38] is a tool that principally measures wound volume. However, the researchers attempted to use it to segment an image into three tissue types: healthy skin, wound tissue and epithelial tissue. A magnesium oxide chip was placed in shot to act as a white reference. Prior to colours being measured, they were adjusted to accommodate for the amount of light reaching the white reference.

A similar system, involving the placement of a white disc in the shot to act as a colour reference, was used by Herbin et al.,[39] who were attempting to develop a colour index by assessing healing in blisters.

Unwanted glare or reflection created by wound exudate or shiny oedematous skin diluted the colour recorded in an image in a number of studies. Attempts to eliminate unwanted reflected light centred on either fixing the camera angle or filtering light reaching the camera. Arqvist et al.[37] captured a wound image via a camera mounted at 30° to the wound plane, the rationale being that light reflected from the wound would be reflected to the side of the camera lens. Mekkes and Westerhof[40] used two polarised filters to reduce unwanted reflections to enable a more accurate recording of wound colour.

Different wound types exhibit different colours. The colours recorded in the study by Herbin et al.[39] of blisters differed markedly from those exhibited by other wound types, such as pressure ulcers or traumatic wounds. To control for type, researchers turned to artificially created wounds[39] — blisters were created on the forearms of eight volunteers using heat. Hansen et al.[41] examined pressure injuries artificially created on the backs of pigs in an attempt to use colour analysis to predict the severity of pressure-related injury. By artificially creating wounds, researchers were able to control for size, shape, depth and location, all of which are variables that influence the amount of light entering the wound and hence the colour reflected.

Once the image was captured, researchers needed to select the most appropriate method to measure wound colour. Three mathematical equations or 'colour spaces' were available — red-green-blue (RGB), as used in computer monitors to replicate colour; cyan-magenta-yellow-key (CMYK) (key represents black), as used by printers to reproduce colour in clothing or printed material; and hue-saturation-brightness (HSB), said to be representative of human colour perception. While CMYK colour space has not been used in wound-colour research, both RGB and HSB have been tested.

Researchers using the RGB colour space reached the conclusion that the algorithm was not sensitive enough to detect differences in the subtle colour changes seen in wounds. Jones and Plassmann[38] concluded that this level of measurement was unable to distinguish between wound and skin, and wound and connective tissue. Mekkes and Westerhof[40] came to a similar conclusion. Unlike Jones and Plassmann, Mekkes and Westerhof used a three-dimensional RGB histogram to analyse the colour. They found that simple RGB thresholds were unable to distinguish between tissue types — in particular, the colour differences between granulation tissue, surrounding skin and newly formed epithelium.

To date, research using the HSB has been limited, but the evidence is more encouraging. Hansen et al.[41] claimed the model they developed provided colour analysis closely representative of the 'intuitive notions of human perception'. Their findings showed that if the ulcer duration was known, colour could be used to distinguish the severity of the pressure injury in a controlled laboratory setting.

The need to retain human colour perception in the data analysis was recognised by a number of researchers, including those who used the RGB

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colour space. Mekkes and Westerhof[40] used a clinician's knowledge of colours in ulcers healing by secondary intention to establish a frame of reference for their system. Arqvist et al.[37] used an 'operator' to map the base of an ulcer displayed in a digital colour photograph. Once the area of interest had been highlighted, the operator had to classify the ulcer by selecting one of 16 wound classifications.

An examination of the above studies indicates that a 'gold standard' for measuring colour represented in digital wound images is yet to be determined. The reliability of any one system has not been fully established. Studies have principally been based on artificial wounds, using a variety of controls and colour-measurement algorithms. Equally, systems that have a degree of inbuilt controls are either hard to replicate or unsuitable for the clinical setting.

Aim of the study

The aim of this pilot study was to test the reliability of a system in providing measurements of colour in digital images of venous leg ulcers. A reliable system was defined as one that provides a consistent colour measurement of a venous leg ulcer from three sequential digital images taken within three to five seconds of each other. Based on previous studies of human colour perception,[24] a consistent measurement of colour was defined as a range of less than or equal to 3° of hue and less than or equal to 3% of saturation between a defined area in three sequential images of the ulcer.

Study design

A prospective exploratory design was used to examine a set of three photographs of a participant's ulcer during a routine outpatient visit.

Ethics approval was obtained from relevant university and health networks.

Method

Sample

Data were collected from a convenience sample of a total of 10 episodes of care provided to three patients — two men and one woman with an age range of 48 to 76 years (mean: 64) — attending a vascular outpatient department. The ulcers had been present from one to three years and were located principally on the left medial aspects of the lower leg.

A total of seven ulcers were photographed, with one ulcer photographed on two separate episodes. Ulcer size ranged from 1.5cm to 8.7cm in length and 1.5cm to 4.6cm in width. All ulcers consisted primarily of granular tissue, with surrounding skin displaying various degrees of erythema.

Data-collection tool

Three sequential digital photographs were taken of each patient's venous leg ulcer. Images were captured using a purpose-built frame that enabled the angle of the patient's foot, the angle of the camera and the height of the camera to remain constant between photographs (Fig 1). The frame was constructed from clear acrylic to prevent visual obstruction and provide a surface that could be easily cleaned between patients to eliminate the risk of cross-infection.

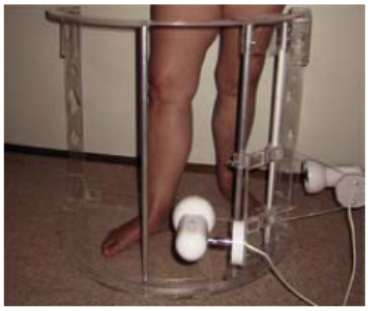

Fig 1. Capture frame

To reduce unwanted glare from wound exudate or oedematous skin, the frame housed two light sources set at 30° to the ulcer plane. In accordance with the original HSB research, the light source used daylights globes matched to the International Commission on Illumination Standard for Illumination, CIE illuminate C.[42]

One Cannon PowerShot A50 digital camera was used to photograph all wounds. Its 1.3 megapixel capacity provides a maximum resolution of 1280 x 960 pixels. All photographs were stored as JPEG files.

The colour of the ulcer was measured using commercial software — the Adelaide Skin Colour Program. This automatically adjusts colours to reflect the light conditions under which an image is taken, and quantifies the hue, saturation and brightness of pixels within a user-defined area of the image. The program uses an in-shot colour reference swatch containing cyan, yellow and magenta from the non-reflective Pantone colour specifier 1.3U (Fig 2). This colour swatch enables colours within a photograph to be adjusted for light conditions. This removes the need for the strict 'laboratory' conditions required by previous systems,[39,41] thus increasing its potential for clinical application.

Once imported into the program, the user highlights a section of the yellow, cyan and magenta colour strips from the in-shot reference swatch. Colour in the defined area is used by the software to calibrate the hues for the image. Once calibrated, the user selects an area within the base of the ulcer and an area of surrounding skin. The software then uses this to calculate the average hue and saturation of pixels within the defined areas.

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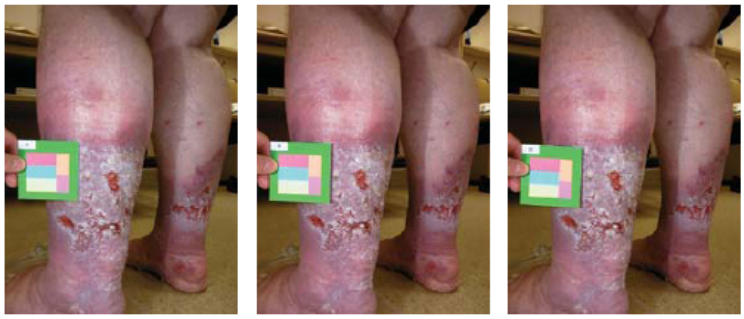


Fig 2. A series of three sequential photographs

Data-collection methods

Patients were asked to stand in the capture frame. The colour swatch and identification label containing a ruler were placed in shot. The patient was asked to remain as still as possible while three sequential images were taken of the ulcer. The time between each image was determined by the camera storage time, about three seconds between shots. Images were downloaded to a computer with a 17 inch monitor set to a resolution of 1024 x 768 pixels.

Data analysis

To assess the reliability of the system, the difference between colour hues exhibited in predefined areas of the three images was calculated by subtracting the smallest from the largest hue measurement. The mean difference was then calculated and the variance examined. Colour saturation was examined in the same manner.

Results

Visual examination of each set of images demonstrated that the frame maintained a consistent angle of leg rotation and magnification for each photograph (Fig 2) and over subsequent episodes (Fig 3). Overlaying of the images revealed small changes in location for each limb indicative of a small movement by the patient. Unwanted reflection was present in three sets of photographs, resulting from oedematous skin surrounding the ulcer. Crucially, the ulcer bed was not affected by unwanted reflections in any of the images (Fig 4).

As expected, the colours exhibited by the ulcer bed were at the red end of the spectrum, with colour ranging from a hue of 341° to 359° and a mean hue of 350.3°. Small differences in the ulcer bed colour were evident between the three photographs in a set. The differences in hue measurements within each photographic set ranged from 2° to 4° of hue, with a mean difference of 2.5° (Table 1). As expected, the colour of the surrounding skin showed greater variation, ranging from 292° to 365° of hue. The difference between each photograph in a set of three photographs for the surrounding skin hue ranged from 1° to 15°, with a mean of 4.1° (Table 1).

Colour saturation of the ulcer bed demonstrated greater variation than hue. Saturation ranged from 44.9% to 74.3%, with a mean of 59.1%. The difference in saturation measurements within each set of three photographs ranged from 1% to 6.8%, with a mean of 3.57% (Table 2). Colour saturation for the skin surrounding the ulcer ranged from 19.2% to 41.4%, with a mean of 29%. The difference in saturation measurements for each set of images ranged from 1.3% to 8.1%, with a mean of 3.24% (Table 2).

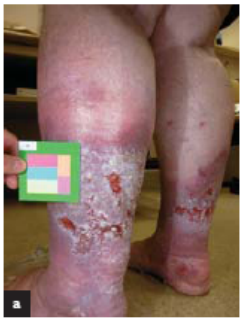
Discussion

It was expected that the colours displayed would be at the red end of the spectrum as all ulcer beds in the study contained primarily granular tissue. This was confirmed by the mean hue of 350.3° of colour. Equally, it was expected that the colour of the sur-

Table 1. Difference in hue measurements (°)

Episode number	Ulcer bed	Surrounding skin
1	3	2
2	1	2
3	1	2
4	2	2
5	2	1
6	3	4
7	4	3
8	3	3
9	3	15
10	3	7
Mean	2.5	4.1

RYB color code. Am J Nurs 1988; 88: 10, 1342-1346.
22 Haas, A. Wound healing. Dermatol Nurs 1995; 7: 1, 28-34, 74.
23 Moriarty, M.B. How color can clarify wound care. RN 1988; 51: 9, 49-54.
24 Krauskopf, J., Gegenfurtner, K. Color discrimination and adaptation. Vision Res 1992; 32: 11, 2165-2175.
25 Zhang, J., Chang, C.I., Millar, S.J., Kang, K.A. A feasibility study of multispectral image analysis of skin tumors. Biomed Instrum Technol 2000; 34: 4, 275-282.
26 Seidenari, S., Pellacani, G., Giannetti, A. Digital videomicroscopy and image analysis with automatic classification for detection of thin melanomas. Melanoma Res 1999; 9: 2, 163-171.
27 Landau, M., Matz, H., Tur, E. et al. Computerized system to enhance the clinical diagnosis of pigmented cutaneous malignancies. Int J Dermatol 1999; 38: 6, 443-446.
28 Sober, A.J., Burstein, J.M. Computerized digital image analysis: an aid for melanoma diagnosis — preliminary investigations and brief review. J Dermatol 1994; 21: 11, 885-990.
29 Green, A., Martin, N., Pfitzner, J. et al. Computer image analysis in the diagnosis of melanoma. J Am Acad Dermatol 1994; 31: 6, 958-964.
30 Schindewolf, T., Stolz, W., Albert, R. et al. Classification of melanocytic lesions with color and texture analysis using digital image processing. Anal Quant Cytol Histol 1993; 15: 1, 1-11.
31 Stoecker, W.V., Moss, R.



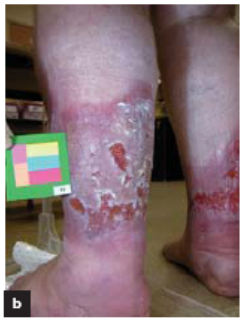


Fig 3. Images of the same ulcer taken at different episodes: (a) episode 1; (b) episode 2

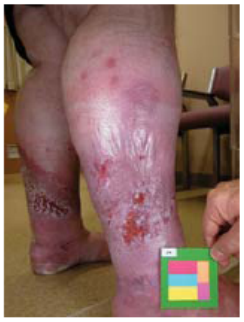


Fig 4. Unwanted reflection from oedematous skin

rounding skin would be closer to the blue end of the spectrum. This was again confirmed by a mean hue of 313.7° for the skin surrounding the ulcer.

The hue measurements obtained when using this system are consistent with those from previous studies.[36,38] But the results differ from previous studies in that there is a clear difference between the colours of the ulcer bed and the surrounding skin. Where Jones and Plassmann[38] were unable to differentiate the colour of skin from wound-bed colour, our results provide hues that are consistently different by a mean of 37°. Use of HSB in preference to the RGB colour space used by Jones and Plassmann[38] may account for the differences. Equally important, patients recruited for the pilot were Caucasian. Further research examining the difference between ulcer bed and colours or other skin types would be needed to support this finding.

While the colour measurements matched the spectral expectations for varying tissue types, the inconsistent hue measurements within each photographic set suggest that the method of capture is not totally reliable. While, on average, the hue difference for the ulcer bed was equal to or less than the criteria established for reliability (3° of hue), one set of photographs demonstrated a difference of 4° of hue. The reliability of the system is further called into question when colour measurements of the surrounding skin are taken into account. A mean of 4.1° of difference is outside the criteria established for reliability, and in one instance the differences within a photographic set were as high as 15° of hue. The larger variation in saturation measurements across the three photographs in each set (mean range of 3.57%) similarly raises further concerns about the system's reliability.

Larger than expected differences between hue may have resulted from the method used to select the image area for measurement. Small colour variations may have resulted because the pixel areas selected varied between images, so were subject to small differences of one or two pixels. Equally, a small movement of the patient between shots may have changed the amount of light falling on either the patient's leg and/or the in-shot colour key. Small changes in the reflected light could result in the 1–3° of difference within the photographic sets.

It would appear that to improve the reliability of the system, a technique enabling the user to select the same pixel area for each image is necessary. Most studies have relied on an user-selected area for image analysis.[35,37,39,40] This may account for the limited success demonstrated by such systems, including this pilot. In an effort to eliminate this inconsistency, magnification down to the pixel level may enable users to select the same area for each photograph.

To eliminate minor movement of the patient's leg, techniques used for radiographic procedures such as computerised tomography could be

Table 2. Difference in measurements of saturation (%)

Episode number	Ulcer bed	Surrounding skin
1	4.4	1.3
2	6.9	1.9
3	1.9	1.7
4	1.0	2.3
5	2.2	3.0
6	2.3	2.0
7	5.6	2.6
8	1.5	2.6
9	6.8	8.1
10	3.1	6.9
Mean	3.5	3.2

H. Digital imaging in dermatology. Comput Med Imaging Graph 1992; 16: 3, 145-150.
32 Claridge, E., Hall, P.N., Keefe, M., Allen, J.P. Shape analysis for classification of malignant melanoma. J Biomed Eng 1992; 14: 3, 229-234.
33 Green, A., Martin, N., McKenzie, G. et al. Computer image analysis of pigmented skin lesions. Melanoma Res 1991; 1: 4, 231-236.
34 Cascinelli, N., Ferrario, M., Tonelli, T., Leo, E.. A possible new tool for clinical diagnosis of melanoma: the computer. J Am Acad Dermatol 1987; 16: (2 Pt 1), 361-367.
35 Herbin, M., Venot, A., Devaux, J.Y., Piette, C. Color quantitation through image processing in dermatology. IEEE Trans Med Imaging 1990; 9: 3, 262-269.
36 Plassmann, P., Jones, T. MAVIS: a non-invasive instrument to measure area and volume of wounds. Measurement of area and volume instrument system. Med Eng Phys 1998; 20: 5, 332-338.
37 Arqvist, J., Hallgren, L., Vincent, J. Semiautomatic classification of secondary healing ulcers in multispectral images. In: Paper presented at the 9th International Conference on Pattern Recognition, Rome, 1988.
38 Jones, B.F., Plassmann, P. An instrument to measure the dimensions of skin wounds. IEEE Trans Biomed Eng 1995; 42: 5, 464-470.
39 Herbin, M., Bon, F.X., Venot, A. et al. Assessment of healing kinetics through true color image processing. IEEE Trans Med Imaging 1993; 12: 1, 39-43.
40 Mekkes, J.R., Westerhof, W. Image processing in the study of wound healing. Clin Dermatol 1995; 13: 4, 401-407.
41 Hansen, G., G.L., Sparrow, E.M., Kokate, J.Y

et al. Wound status evaluation using color image processing. IEEE Trans Med Imaging 1997; 16: 1, 78-86.
42. MacAdam, D. The physical basis of color specification. In: Byrne, A., Hilbert, D.R. (eds) Readings on Color: Volume 2: The Science of Color. Cambridge, MA: MIT Press, 1997

employed. A review of these examinations reveals that, in most instances, the patient is either supine or, if vertical, entirely supported. Changing the orientation of the frame used to capture the images from a vertical to a horizontal orientation will allow patients to lie down. This may, in turn, reduce the amount of leg movement between photographs.

Visual examination of the image sets indicated that the position of the in-shot colour key, which was hand-held, varied between photographs in the same set. In some instances, it was close enough to the light source to appear washed out. This would have led to a different colour balance being applied to the image before the colour was measured, resulting in hue and saturation differences.

Placing the in-shot colour reference at a set distance to the light source may help reduce variations in hue. If, as suggested above, the capture frame was used horizontally, this would be easier to achieve as the reference swatch could be placed on the back of the frame adjacent to the patient's leg.

A more encouraging outcome of the study was the apparent consistency between the visual appearance of the three sequential photographs. Although the reliability required for consistent measurement of colour has yet to be achieved, the frame used in the study has the potential to ensure a photograph that is consistent for rotation and magnification. Although similar consistency can be achieved with systems such as MAVIS,[36] this system may provide similar opportunities at a fraction of the cost and be easier to use in the clinical setting and therefore be more widely available. The frame can be collapsed and carried in a case similar in size to a briefcase and can be set up in less than three minutes.

Conclusion and recommendations

Hues recorded in this study demonstrated differences in colour between the ulcer bed and surrounding skin. The hue and saturation measurements obtained are consistent with those expected for the tissue type examined.[37] Equally, the photographs taken illustrate a consistent angle of rotation and degree of magnification, both during an episode and across episodes.

However, the study did not demonstrate the ability of the system to record accurately the colour of an ulcer bed and the surrounding skin. While the average hue for an ulcer bed fell within the definition used to determine reliability, the range of difference (0–15°) reduces confidence in the findings.

The study is further limited by its small sample size and the exclusion of patients with darker skin colours.

We propose making refinements to eliminate the inconsistencies found in our results: these include using a consistent method for defining the area of an image to be measured, changing the orientation of the capture frame to horizontal and placing the in-shot reference at a set distance from the light source. Further research incorporating the above refinements and a larger sample size is currently being planned. ■

Disclaimer

In the February 2005 issue of *Journal of Wound Care*, we published the results of a pilot study by Eccles and Hollinworth entitled: A pilot study to determine whether a static magnetic device can promote chronic leg ulcer healing.[1]

One of the authors of this article, Dr N. Eccles, has been distributing to practitioners across the UK a copy of a reprint of this article with an accompanying letter. *Journal of Wound Care* would like to make the following disclaimer:

In a letter accompanying a copy of a *Journal of Wound Care* reprint, Dr N. Eccles states that this work was part of a larger study that ran to 'some 50 pages' and infers that the editing process condensed all the information into four pages.

This is not so. *Journal of Wound Care* received only an article slightly longer than four pages, which was edited. The pilot study presented to *Journal of Wound Care* was discrete, although it may well have been part of a larger study, and was based on an earlier telephone survey of 160 users of the device.

Journal of Wound Care refutes the inference that it edited a much larger piece of work and in no way supports or endorses the use of the study product.

Correction

Due to an editorial error, the title of the letter published in the April issue of *Journal of Wound Care* was left out. The title is: Regeneration of postoperative wounds in surgical patients. The name of the leading author, Dr Anna Kircheva, was also excluded. Apologies for any confusion caused.

Dr A.B. Kircheva can be contacted at: Department of Hospital Epidemiology, 'St. Anna' University Hospital of Varna, 100 Tzar Osvoboditel Street, Varna, Bulgaria.
Tel: +359/52/2136-572;
fax: +359/52/237-115.
Email: anna_kir4eva@yahoo.com

Reference
1 Eccles, N.K., Hollinworth, H. A pilot study to determine what her a static magentic device can promote chronic leg ulcer healing. J Wound Care 2005; 14: 2, 64-67.

Appendix B: Data collected at the time of recruitment

Demographics

Participant number

Age: …….

Country of origin ……..

Baseline data

1. Does the patient currently suffer from, or has suffered from, any of the following conditions?

☐ Diabetes ☐ Rheumatoid arthritis ☐ Deep vein thrombosis

2. When was the venous ulcer first diagnosed? …/…./….

3. Ankle Brachial Pressure Index ……

4. Ulcer dimensions:

Length of the ulcer ….. cm
Width of the ulcer ….. cm
Area of the ulcer ….. cm^2

5. Current dressing products used

☐ Hydrocolloid ☐ Zinc bandage ☐ Hydrogel

☐ Other ……

6. Type of compression

a. ☐ Mild ☐ Medium ☐ Strong

b. ☐ Stocking ☐ Bandage ☐ Other ……

Camera ……./……

Foot ……./……

Camera Ht …….cm (R) side of camera support

Comments

Appendix C: Data collected on subsequent episodes

Participant number ……

Visit number ……..

1. Ulcer dimensions:

Length of the ulcer ….. cm
Width of the ulcer ….. cm
Area of the ulcer ….. cm^2

2. Current dressing products used:

☐ Hydrocolloid ☐ Zinc bandage ☐ Hydrogel

☐ Other ……

3. Type of compression

a. ☐ Mild ☐ Medium ☐ Strong

b. ☐ Stocking ☐ Bandage ☐ Other ……

Camera ……./……

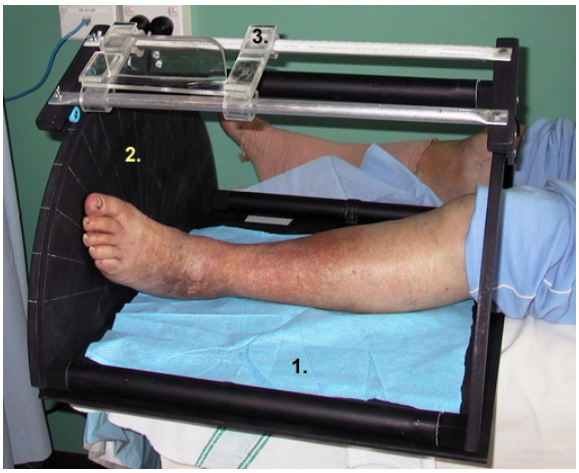
Foot ……./……

Camera Ht …….cm (R) side of camera support

Comments:

Appendix D: Instructions to Clinicians for recording a photograph

Instructions for taking a wound photograph using the Ulcer-cam 2 system



1. Base
2. Foot protractor and frame
3. Camera housing

1. Place the Ulcer-cam 2 frame on the trolley with foot protractor and frame (no. 2) in the open position.
2. Cover the base (no. 1) with a clean, disposable, non-reflective blue sheet.
3. Ask the patient to place his / her leg on the base and close the foot protractor and frame over the leg.
4. If using the system to record a first image:
    a. Place the foot against the foot protractor (no. 2) and rotate the leg until the ulcer is visible.
    b. Record the number of degrees against which that the patient's great toe aligns.
    c. Rotate the camera housing (no. 3) until the camera is at approximately 30 degrees to the ulcer and lock in place.
    d. Record the number of degrees that the camera housing indicator aligns with.
    e. Move the camera housing along the horizontal slider until the ulcer is visible in the camera viewing screen and lock the camera mount.
    f. Record the number of centimetres that the camera housing indicators align with on the horizontal slider.
    g. Record the patient's participant number, episode number and date on the patient label supplied, and place on the base, ensuring that it can be seen in the camera viewing screen.
    h. Place the 'in-shot' reference on the base of the frame ensuring that it can be seen in the camera viewing screen.
    i. Take three sequential image of the ulcer approximately one second apart.
    j. Open the frame and ask patient to remove his / her leg.

5. If using the system to record images at subsequent episode:
    a. Repeat steps a-j but…
    b. Align the patient's great toe with the mark that coincides with the degrees recorded at the initial visit.
    c. Rotate the camera housing to the degree recorded at the initial visit
    d. Move the camera along the horizontal guides until the camera housing indicator is aligned with the number of centimetres recorded at the initial visit.

Appendix E: Invitation to expert clinicians

Adresss

Dear XXXX,

You have been identified as a clinician that frequently observes venous leg ulceration. For this reason I would like to invite you to participate in a research study entitled:

“Developing a reliable method for measuring wet necrotic tissue and erythema manifested by venous leg ulcers”

As you will be aware, there is evidence to suggest that chronic venous leg ulcers are “locked” in the inflammatory phase of the wound healing cycle. There is an abundance of literature that describes the visual manifestations of the inflammatory phase as an intense or bright area of erythema surrounding the ulcer, with yellow slough or wet necrotic tissue evident in the ulcer bed. The aim of this project is to develop a reliable method for measuring these visual manifestations with a view to providing clinicians with an additional tool for assessing the progression, or non-progression of a venous leg ulcer.

To achieve this aim I need to establish a consensus about the range of colour that experienced clinicians, such as yourself, believe represents the following:

- erythema surrounding an ulcer that is indicative of inflammation
- slough or wet necrotic tissue evident in an ulcer bed.

This data will be used as the criteria for image analysis software that will determine the percentage of each tissue type displayed within a given photograph.

If you agree to be involved, I will send you a set of twenty coloured photographs of venous leg ulcers. You will be asked to draw around areas on the photographs that you believe represent the above tissue types and mail the photographs back in the return envelope. Our trials indicate that this should take approximately 30–45 minutes.

Once I receive the photographs, I will measure the colour range inside the areas you have defined using computer image analysis software. This will provide a range of colour that represents each of the above tissue types. The colour range will be used to develop software that scans a photograph of an ulcer and identifies areas of colour that fall within the parameters established from the above colour range.

To test that the software is mapping accurately I will send a second set of twenty photographs to you and ask you to repeat the exercise conducted on the first set of images. The areas you identify will be compared to those mapped by the software and the amount of difference analysed.

If you would like to participate please complete the expression of interest below and forward it to me in the envelope provided.

Thank you for taking the time to consider this proposal.

Yours truly,

Bill McGuiness

Deputy Head of School

School of Nursing and Midwifery

La Trobe University

✂_____

I ……. would like to participate in the study described above. I understand that at no time will my name be used in any data sets or manuscripts and that I am free to withdraw at any time.

Signature …… Date …/…/…

Please detach and return in the pre-paid envelope provided.

Appendix F: Instructions to expert clinicians

Name
Address

Dear Name,

Thank you for agreeing to participate in the study entitled:

“Developing a reliable method for measuring wet necrotic tissue and erythema manifested by venous leg ulcers”

Enclosed is a set of twenty coloured photographs of venous leg ulcers. Using the pens supplied, please outline areas in each photograph that represents the following:

1. Erythema surrounding the ulcer
    a. Please use the red pen
2. Yellow slough or wet necrotic tissue evident in the ulcer bed
    a. Please use the blue pen

You may outline more than one area for each tissue type.

When complete, please return the photographs in the reply paid envelope included with this package by **XXXX.**

When I receive the photographs, I will measure the colour range inside the areas you have defined using computer image analysis software.

To test that the software is mapping accurately I will send a second set of twenty photographs in the near future and ask you to repeat the exercise conducted on the first set of images. The areas you identify will be compared to those mapped by the software and the amount of difference analysed.

If you would like any further information please contact me on

XXXXXXX

Yours truly,

Bill McGuiness

Appendix G: Visual analogue scale data sheet

Please indicate the level to which you agree or disagree with the area highlighted in each **image** for each **tissue type.**

Please note both tissue types are not displayed in every image.

Example

Image	Tissue	Opinion	Comments
1 **No slough displayed**	Erythema **Outlined in blue**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	
2	Erythema **Outlined in blue**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	
	Wet necrotic (Slough) **Outlined in yellow**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	

Image	Tissue	Opinion	Comments
3	Erythema **Outlined in blue**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	
	Wet necrotic (Slough) **Outlined in yellow**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	

Image	Tissue	Opinion	Comments
4	Erythema **Outlined in blue**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	
	Wet necrotic (Slough) **Outlined in yellow**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	
5	Erythema **Outlined in blue**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	
	Wet necrotic (Slough) **Outlined in yellow**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	
6	Erythema **Outlined in blue**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	
	Wet necrotic (Slough) **Outlined in yellow**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	

Image	Tissue	Opinion	Comments
7	Erythema **Outlined in blue**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	
	Wet necrotic (Slough) **Outlined in yellow**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	
8	Erythema **Outlined in blue**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	
	Wet necrotic (Slough) **Outlined in yellow**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	
9	Erythema **Outlined in blue**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	
	Wet necrotic (Slough) **Outlined in yellow**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	

Image	Tissue	Opinion	Comments
10	Erythema **Outlined in blue**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	
	Wet necrotic (Slough) **Outlined in yellow**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	
11	Erythema **Outlined in blue**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	
	Wet necrotic (Slough) **Outlined in yellow**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	
12 **No erythema displayed**	Wet necrotic (Slough) **Outlined in yellow**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	

Image	Tissue	Opinion	Comments
13	Erythema **Outlined in blue**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	
	Wet necrotic (Slough) **Outlined in yellow**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	
14 **No slough displayed**	Erythema **Outlined in blue**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	
15 **No slough displayed**	Erythema **Outlined in blue**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	

Image	Tissue	Opinion	Comments
16 **No slough displayed**	Erythema **Outlined in blue**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	
17 **No slough displayed**	Erythema **Outlined in blue**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	
18	Erythema **Outlined in blue**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	
	Wet necrotic (Slough) **Outlined in yellow**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	

Image	Tissue	Opinion	Comments
19	Erythema **Outlined in blue**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	
	Wet necrotic (Slough) **Outlined in yellow**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	
20	Erythema **Outlined in blue**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	
	Wet necrotic (Slough) **Outlined in yellow**	Strongly Disagree — Place an X on the line to indicate your level of agreement or disagreement — Strongly Agree	

Do you have additional comments?

……
……
……

Thank you for completing this project.

Appendix H: Plain Language Statement and Consent Form

PLAIN LANGUAGE STATEMENT

Plain Language Statement
Version 1 Dated 13/9/02
Site Alfred

Full Project Title: Piloting a method for measuring the percentage of wet necrotic tissue and erythema manifested by venous leg ulcers over time

Principal Researcher: Bill McGuiness

Associate Researcher(s): Professor Sandra Dunn

This Plain Language Statement and Consent Form is # pages long. Please make sure you have all the pages.

1. Your Consent

You are invited to participate in a study being conducted by myself, Bill McGuiness. I am a PhD candidate, School of Nursing and Midwifery, Flinders University, and a lecturer in the Clinical School of Advanced Nursing Practice, La Trobe University. The study will be used to complete my PhD. This sheet will provide you with relevant information about the project. It is important that you take the time to read it carefully before deciding if you want to participate.

This Plain Language Statement contains detailed information about the research project. Its purpose is to explain to you as openly and clearly as possible all the procedures involved in this project before you decide whether or not to take part in it.

Please read this Plain Language Statement carefully. Feel free to ask questions about any information in the Statement.

Once you understand what the project is about and if you agree to take part in it, you will be asked to sign the Consent Form. By signing the Consent Form you indicate that you understand the information and that you give your consent to participate in the research project.

You will be given a copy of both the Consent Form and this Plain Language Statement to keep as a record.

2. Description of the Project

The purpose of this project is to test the reliability of a system developed for taking pictures of your leg ulcer.

A total of 30 people will participate in this project.

Previous experience has shown that when wounds heal they take on different visual appearances. In the early stages they may be red or inflamed. Later the inflammation decreases and the wound takes on a normal skin colour. If the wound is not healing properly it will show a number of alternate visual characteristics, for example yellow pus or black areas. Every time a nurse or doctor changes your dressing he/she looks at the wound to see if it is healing properly. Currently the nurse or doctor compares what he/she is seeing with what they remember about your wound or other similar wounds.

Recently a range of cameras that store an image on a computer disc rather than on film has become available. The format is called digital photography, and enables the image to be analysed by a computer. In particular this study will measure the colour of your leg ulcer by using a computer to analyse a digital image of it. I believe that by measuring colour we can determine the amount of yellow tissue (slough) in your ulcer, and the amount of inflamed area in the surrounding skin. These measurements may help nurses and doctors to assess how well your leg ulcer is healing You are invited to participate in this research project because *(state why the participant's involvement is sought/desirable)*.

Participation in this project will involve three digital photographs of your wound being recorded each time you come to the vascular outpatient clinic.

To take each photograph, I have to place a frame over your leg. This frame will enable me to record the angle of your foot and the location of the camera when the photograph is taken. This will ensure that the photographs are similar each time. The procedure will take an additional 1-2 minutes for each dressing change.

3. Possible Benefits

If the system for taking the photographs is proven to be reliable it may provide a system for detecting when leg ulcers are failing to heal properly.

4. Possible Risks

Possible risks, side effects and discomforts include a delay of approximately 2 minutes while the frame is placed over your leg and the photograph taken.

5. Alternatives to Participation

Your involvement in this study is entirely voluntary, and your non-participation will not affect your treatment at The Alfred in any way. Should you decide to withdraw from the study you may do this freely and without prejudice to any future treatment at The Alfred.

6. Confidentiality and Disclosure of Information

To ensure that information about you is kept confidential, the names of people participating in the project are replaced with a number. Access to the numbered information is restricted to myself. As prescribed by The National Health and Medical Research Council, all research information will be stored in a locked cupboard and kept for 7 years and then destroyed. When the findings of the project are published your name or any specific reference to you will *not* be mentioned.

7. New Information Arising During the Project

During the research project, new information about the risks and benefits of the project may become known to the researchers. If this occurs, you will be told about this new information. This new information may mean that you can no longer participate in this research. If this occurs, the person(s) supervising the research will stop your participation. In all cases, you will be offered all available care to suit your needs and medical condition.

8. Results of Project

On completion of the project you wil be sent a report detailing the findings of the project.

9. Further Information or Any Problems

If you require further information or if you have any problems concerning this project (for example, any side effects), you can contact the principal researcher Professor Sandra Dunn. The researchers responsible for this project are:

Mr Bill McGuiness 9276 3790

Professor Sandra Dunn (08) 8204 5543

10. Other Issues

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about your rights as a research participant, then you may contact

Name: Rowan Frew

Position: Secretary of the Human Ethics and Research Committee, The Alfred

Telephone: 9276 3848

You will need to tell Rowan the name of one of the researchers given in section 9 above.

11. Participation is Voluntary

Participation in any research project is voluntary. If you do not wish to take part you are not obliged to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with The Alfred.

Before you make your decision, a member of the research team will be available so that you can ask any questions you have about the research project. You can ask for any information you want. Only sign the Consent Form once you have had a chance to ask your questions and have received satisfactory answers.

Before deciding whether or not to take part, you may wish to discuss the project with a relative or friend or your local health worker. Feel free to do this.

If you decide to withdraw from this project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to inform you if there are any health risks or special requirements linked to withdrawing.

12. Ethical Guidelines

This project will be carried out according to the National Statement on Ethical Conduct in Research Involving Humans (June 1999) produced by the National Health and Medical Research Council of Australia. This statement has been developed to protect the interests of people who agree to participate in human research studies.

The ethical aspects of this research project have been approved by the Human Research Ethics Committee of this Institution.

CONSENT FORM

Consent Form
Version 1 Dated 13/9/02
Site The Alfred

Full Project Title : Piloting a method for measuring the percentage of wet necrotic tissue and erythema manifested by venous leg ulcers over time

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I have read, or have had read to me in my first language, and I understand the Plain Language Statement version 1 dated 13/9/02.

I freely agree to participate in this project according to the conditions in the Plain Language Statement.

I have a copy of the Plain Language Statement and the Consent Form to keep.

The researcher has agreed not to reveal my identity and personal details if information about this project is published or presented in any public form.

Participant's Name (printed) ……

Signature Date

Witness's Name (printed) ……..

Signature Date

Researcher's Name (printed) ……

Signature Date

Note: All parties signing the Consent Form must date their own signature.