SETTING PRIORITIES AND REDUCING UNCERTAINTIES FOR THE TREATMENT OF VITILIGO

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ABSTRACT

Vitiligo is the most common skin disorder resulting in depigmentation, but high-quality research is lacking. A Cochrane review of interventions for vitiligo published in 2010 highlighted methodological limitations with existing trials; which have generally been too small and heterogeneous to inform clinical recommendations.

The objective of this thesis was to improve the evidence base for the treatment of vitiligo.

This PhD was funded by the National Institute for Health Research, as part of the research programme called "Setting Priorities and Reducing Uncertainties for people with Skin Diseases". It includes the following: 1) identifying the most important research priorities for patients and clinicians, thereby informing the research agenda; 2) conducting a systematic review of outcome measures used in vitiligo trials and a survey of the most desirable outcomes for patients and clinicians; and 3) conducting a pilot double blind, randomised controlled trial (RCT) on home hand-held phototherapy in preparation of the first national multi-centre RCT for the treatment of vitiligo.

For the prioritisation exercise, a total of 660 treatment uncertainties were submitted by 460 patients and clinicians. The identified priority areas included interventions such as combination of topical agents and phototherapy. The systematic review on outcome measures identified 25 different domains that had been used in previous trials. Although percentage repigmentation was measured in 96%; 48 different scales had been used. In contrast, patients and clinicians favoured the use of "cosmetically acceptable" repigmentation. Finally, a 4-month pilot trial recruited 29 participants and tested the logistics of running a future RCT.

This work resulted in a commissioned call and funding of a national RCT on vitiligo (topical corticosteroids in combination with home hand-held phototherapy); the initiation of an international consensus exercise on core outcome measures for use in vitiligo trials; and informed the design and conduct of a future national RCT.

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V. Eleftheriadou

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LIST OF ABREVIATIONS

BAD - British Association of Dermatologists

BB-UVB - Broad Band Ultra Violet light B

BDNG - British Dermatological Nursing Group

BSA - Body surface area

CDLQI – Children Dermatology Life Quality Index

CEBD - Centre of Evidence Based Dermatology

CLRN – Comprehensive Local Research Network

COMET – Core Outcome Measures in Effectiveness Trials

DLQI – Dermatology Life Quality Index

JLA - James Lind Alliance

IFRCS – International Federation of Pigment Cell Societies

LRI – Leicester Royal Infirmary

MED – Minimal Erythema Dose

MET – Maximum Exposure Time

NB-UVB - Narrow Band Ultra-Violet light B

NIHR HTA - National Institute for Health Research Health Technology Assessment

NRES – National Research Ethics Service

NSV – non-segmental vitiligo

PBI – Patient Benefit Index

PBQ – Patient's Benefit Questionnaire

PCDS - Primary Care Dermatology Society

PCRN – Primary Care Research Network

PNQ – Patient's Need Questionnaire

PSP - Priority Setting Partnership

QA – Quality Assessment

QES - Questionnaire on Experience with Skin Complaints

QMC – Queen's Medical Centre

RCT - Randomised controlled trial

SCORAD – Severity Scoring for Atopic Dermatitis

SPRUSD – Setting Priorities and Reducing Uncertainties for people with skin diseases

SV – Segmental vitiligo

TC – Treatment Centre

TCS – Topical Corticosteroids

UV – Ultra Violet light

UVA - Ultra Violet light A

UVB - Ultra Violet light B

UK DCTN - UK Dermatology Clinical Trials Network

VASI – Vitiligo Areas Scoring Index

VIDA – Vitiligo Disease Activity Score

VETF - Vitiligo European Task Force

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INTRODUCTION

Why did I choose to undertake this PhD?

Throughout my studies in medical school I have come to realise that clinical practice should be accompanied by the principles of evidence based medicine. My university introduction to dermatology made me wish to pursue a career in this area. During my specialty training in Acute and General Medicine, I realised that the ability to diagnose inflammatory skin diseases and tumors, the satisfaction of diagnosis, investigation and treatment, surgical and histopathological expertise with understanding of the complex relationship between the skin and internal organs, put cutaneus physicians in a unique position of a clinician combining medical and surgical skills. Since then I have actively sought every opportunity to be involved in dermatology academic activities in order to contribute and to improve current clinical practice.

The Centre of Evidence based Dermatology (CEBD) at the University of Nottingham is well recognised as a centre of excellence and has an international reputation for skin research and evidence-based practice. I strongly believe that my PhD project "Setting priorities and reducing uncertainties for the treatment of vitiligo", in the Centre of Evidence based Dermatology will be crucial and extremely fruitful for my educational progression and career development towards the

achievement of my goal of becoming a Professor and Consultant Dermatologist. It will enable me to build on my attitude towards clinical excellence, develop a scientific critical approach and ethics and equip me with robust experience in order to continue my career in Academic Dermatology and ultimately help me to incorporate clinical research outcomes in clinical practice.

Why do research on vitiligo?

Skin diseases are very common, affecting over a quarter of the population in England and Wales. Although usually not life-threatening, skin diseases have a significant impact on the quality of life of patients and cause considerable psychological distress.

My proposed research study focuses on vitiligo, a condition which results in the loss of pigment from the skin. This can have a devastating impact on a patient's quality of life, especially for people with darker skin. Around 0.5 % of the world population has vitiligo and a variety of methods for repigmenting the skin of people with vitiligo have been tried in various parts of the world. There is some evidence from individual trials to support short term benefit from topical steroids, various forms of ultraviolet light with topical

preparations, and other therapies including skin grafting and ginkgo biloba, but long-term benefits and safety have been poorly reported. There is therefore, a great need for an extensive and well planned programme of research to find effective ways of managing this condition.

What were the sources of funding for this research?

This thesis is part of the wider research programme called "Setting Priorities and Reducing Uncertainties for people with Skin Disease" (SPRUSD), which is funded by the National Institute of Health Research (NIHR). The "SPRUSD" programme includes 4 work-streams: eczema prevention, eczema treatment, squamous cell carcinoma and vitiligo. Each of the work-streams consists of the following key activities:

1. Systematic review of the existing evidence base for available treatments
2. Definition and prioritisation of the most important research questions regarding treatment
3. Outcomes work to establish which outcomes are most important for patients and clinicians
4. Pilot work, with a view to submitting a funding application for multicentre efficacy trial

5. Generation of patient information and dissemination of findings.

My thesis describes the work conducted for the vitiligo work-stream of the SPRUDS programme.

What my research is about and what role have I played in it?

My thesis comprises a mixture of projects including a priority setting partnership, a full systematic review of outcomes for vitiligo, a survey on outcomes amongst patients and clinicians and a multi-centre pilot, randomised, controlled double-blind trial. Each one has a very different methodology and represents a significant research project in its own right. Each one of the projects was performed in collaboration with my supervisors and colleagues from various disciplines to ensure diversity of opinions and views and validity of the results. I played a key role in each one of the projects, generated ideas, co-ordinated and undertook the vast majority of the work myself. Each chapter in this thesis refers to each one of the projects mentioned above and they are all written in a similar fashion with a brief abstract at the beginning to assist navigation through the entire manuscript, introduction,

methods, results and discussion sections. In the methods section of each chapter, I have outlined in detail what part of work was undertaken by me and which ideas were mine.

My thesis comprises of the following:

- *Chapter 1: Literature review.*

There is very limited information available in the textbooks on vitiligo and therefore my first chapter is an up-to-date literature overview of the disease including definition, classification, aetiology, histopathology, prognosis, assessment and treatment. By doing this, I have attempted to gather and summarise existing evidence, hypotheses and suggestions, and also to identify some of the research gaps into various aspects of this neglected disease.

- *Chapter 2: Identifying the most important treatment uncertainties that need to be answered by research*.

The Centre of Evidence Based Dermatology (CEBD) worked in collaboration with the James Lind Alliance (JLA), in organising a Priority Setting Partnership (PSP) to identify the Top 10 most important uncertainties about the treatment for vitiligo for patients and clinicians. The vitiligo PSP had 5 stages: initiation,

consultation, collation, ranking exercise and a final prioritisation workshop.

- *Chapter 3: Establishing the most appropriate outcomes to use*.

A systematic review of outcome measures used in clinical trials for vitiligo was conducted. Also, a survey of the most desirable outcomes for patients and clinicians was conducted. The results of the above were crucial in order to inform the best choice of outcome measures to be used in the subsequent trial.

- *Chapter 4: Multicentre, pilot, randomised, double blind control trial*.

Based on the identified Top 10 priorities, a pilot trial was conducted to identify the strategic issues that need to be considered in developing a full randomised controlled trial (RCT). The pilot trial assessed issues such as the numbers of participants required for the main RCT, the ability to blind outcome assessment, and willingness of participants to be randomised. In addition, a face-to-face training programme on home hand-held phototherapy was developed and tested in this pilot trial.

- *Chapter 5: Impact of my research.*

Reflection on the implications of my research for future

vitiligo trials and in particular on the national multi-centre randomised trial involving home hand-held phototherapy. This chapter also includes details of transferable skills and competencies that I learned, academic achievements and opportunities which arose during this PhD and which contributed towards my development as an academic clinician.

Output from this research

During my PhD, I have published five peer-reviewed papers in leading dermatological journals both as a first author and as a co-author with significant contribution to major publications. I have also written two book chapters:

1) **Eleftheriadou V**, Thomas KS, Whitton ME*,* Batchelor JM, Ravenscroft JC*.* Which outcomes should we measure in vitiligo? Results of a systematic review and a survey amongst patients and clinicians on outcomes in vitiligo trials. **British Journal of Dermatology** 2012; 167: 804-814.

2) **Eleftheriadou V**, Whitton ME, Gawkrodger D, Batchelor JM, Corne J, Lamb B, Ersser S, Ravenscroft JC, Thomas KS and on behalf of the vitiligo priority setting partnership.

Future research into the treatment of vitiligo: where should our priorities lie? Results of the vitiligo priority setting partnership. **British Journal of Dermatology** 2011; 164: 530–536.

3) **Eleftheriadou V**. Implications for research after Cochrane Systematic review "Interventions for vitiligo" 2010. Current situation and future directions focusing on Western Europe. **British Journal of Dermatology** 2013 (accepted for publication).

4) **Eleftheriadou V**, Thomas K, Batchelor J *et al.* Core outcomes in vitiligo trials: progress and challenges. Editorial. **Clinical Investigation** 2013; 3: 417-419.

5) Gonzalez U, Whitton ME, **Eleftheriadou V** Pinart M, Batchelor J, Leonardi-Bee J. Guidelines for designing and reporting clinical trials in vitiligo. **Archives of Dermatology** 2011; 147: 1428-36.

6) Taieb A, Alomar A, Böhm M, Dell'Anna ML, De Pase A, **Eleftheriadou V**, Ezzedine K, Gauthier Y, Gawkrodger DJ, Jouary T, Leone G, Moretti S, Nieuweboer-Krobotova L, Olsson MJ, Parsad D, Passeron T, Tanew A, van der Veen W, van Geel N, Whitton M, Wolkerstorfer A, Picardo M and the writing group of the Vitiligo European Task Force (VETF) in cooperation with the European Academy of Dermatology

and Venereology (EADV) and the Union Européenne des Médecins Spécialistes (UEMS) (2012), Guidelines for the management of vitiligo: the European Dermatology Forum consensus. **British Journal of Dermatology** 2013; 168: 5-19.

7) Teovska Mitrevska N, **Eleftheriadou V**, Guarneri F. Quality of life in vitiligo patients. **Dermatologic Therapy** 2012; 25: S28–S31

Book chapters:

a. Dadzie O, Petit A, Alexis A.(Editors) Ethnic Dermatology, 2013, Wiley-Blackwell (Chapter "Vitiligo: Clinical Presentation and Management" by V. Eleftheriadou).

b. Lotti T, Hercogova J, Schwartz R (Editors) Vitiligo: What's new, what's true?, 2013, Wiley-Blackwell.(Chapter "Research into vitiligo: current situation and future directions focusing on Western Europe" by V. Eleftheriadou).

The following two papers are currently in preparation:

1) Eleftheriadou V, Thomas K, Ravenscroft J *et al.* Pilot, double-blind, placebo controlled randomised, multi-centre trial on home hand-held phototherapy in vitiligo

(Hi-Light trial). **Pigment Cell and Melanoma Research** (under-peer review).

2) Eleftheriadou V and Farley R. Hand-held NB-UVB phototherapy devices: output variations pre and post pilot double blind randomised, controlled, trial for the treatment of vitiligo trial. **Photodermatology, Photoimmunology, Photomedicine** (draft).

Finally, I have presented my work at the following meetings:

1) 8-11 May 2013, **International Investigative Dermatology** Conference, Edinburgh, Scotland. Poster presentation: Pilot double blind multi-centre randomised controlled trial on hand-held NB-UVB home phototherapy for focal or early vitiligo.

2) 7-8 June 2012, **3rd International Conference for Ethnic Skin and Hair**, London, UK (Invited speaker and faculty member). Oral presentation: Research update on vitiligo and clinical implications.

3) 2-5 November 2011, **The International School of vitiligo and pigmentary disorders**, Barcelona, Spain. Oral presentation: Evidence-based Centre of Dermatology. Vitiligo Work-stream.

4) 20-24 September 2011, **International Pigment Cell Conference**, Bordeaux, France (Selected speaker). Eleftheriadou V, XXIst International Pigment Cell Conference, Bordeaux, France. Pigment Cell & Melanoma Research 2011; 24; 4: 742-663 (abstract only).

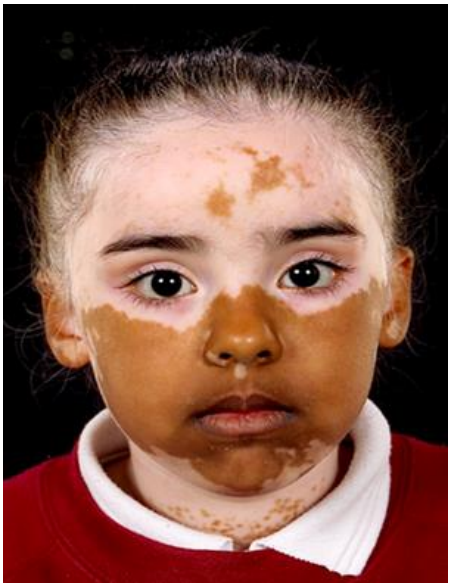
5) 23-25 September 2010, **1st Vitiligo World Congress**, Milan, Italy (Invited speaker, phototherapy session chair and member of the faculty). Oral presentation: Evidence-based management of vitiligo: How to define priorities for clinical research

6) 4-7 September 2010, **16th meeting of the European Society of Pigment Cell Research,** Cambridge, UK (Selected speaker). Eleftheriadou V, 16th Meeting of the European Society for Pigment Cell Research, Wellcome Trust Genome Campus, Hinxton, Cambridge, UK. Pigment Cell & Melanoma Research 2010; 23; 4: e1–e40 (abstract only).

Picture 1. Two children with vitiligo (Picture provided by the Vitiligo Society UK- a patients' support group).

CHAPTER 1: BACKGROUND

Vitiligo is an acquired, chronic depigmenting disorder of the skin. It causes loss of pigment on the affected areas of the skin and/or mucosae and is characterised by milky white, non-scaly macules with distinct margins. The hairs on the vitiliginous skin initially remain pigmented and after prolonged time, leucotrichia (whiteness of the hair) or poliosis could occur. Rarely, the eyes can be affected too. Vitiligo is sometimes referred to as leucoderma (-leu·co·der·ma) from the Greek words "leuco" meaning white and "derma" meaning skin. It is characterised by depigmented lesions on the skin that results from loss or damage of melanocytes (Picardo, 2010).



Picture 1.1 Patient with vitiligo and leucotrichia (Courtesy of Dr Jane Ravenscroft)

1.1 Historical perspective of vitiligo

Celsus was the first to use the name vitiligo in his Latin medical classic "De Medicina" at the second century B.C (Nair, 1978; Picardo et al., 2010). It is believed that the name derived from Latin "vitium" meaning defect or blemish (Rosenblum, 1968), rather than "vitellus" meaning calf (Panda, 2005; Picardo et a.l, 2010).

The disease, which "causes white spots" was recognised in ancient times. Descriptions of vitiligo are found in Indian ancient sacred books, such as Atharva Veda (1400BC) and the Buddhist sacred book Vinay Pitak (224-544 B.C) (Picardoet al., 2010). Also, it is believed that vitiligo like lesions were depicted in a Korean portrait painting of a Korean court scholar around mid-18th century (Lee, 1982)(Picture 1.2).

Picture 1.2 Korean portrait painting illustrating vitiligo like lesions on the left side and the lower part of the men's face (Courtesy of Dr Jeffrey Corne)

However, vitiligo was not differentiated from leprosy. Hippocrates included lichen, leprosy and vitiligo under the

same category. In the Bible, the Old Testament, five broad categories of diseases that cause white spots are mentioned: (1) white spots per se, (2) white spots associated with regrowth of hair which turn white, (3) white spots associated with inflammation, (4) white spots with scaling and (5) white spots with atrophy. The first two categories are believed to be referring to vitiligo. Also, in the Koran, Arabic names used to describe vitiligo were translated as leprosy in many languages (Nair, 1978; Panda, 2005; Goldman et al., 1966; Picardo et al, 2010).

The confusion with leprosy is an important cause for the social stigma attached to the white spots of the skin. Since ancient times, men and women with white patches of the skin, were not respected in society, were disqualified from marriage, or if white spots occurred during the marriage, it provided reason for divorce (Picardo et al., 2010; Nair, 1978).

1.2 Vitiligo European Task Force

Vitiligo European Task force (VETF) is a group of dermatologists with a strong interest in vitiligo. The group originates from the European Society of Pigment Cell Research (ESPCR). ESPCR is part of the International Federation of Pigment Cell Research Societies (IFPCS), consisting of four

regional scientific societies devoted to the study of various aspects of pigment cells. The four Pigment Cell Societies are: Asian Society for Pigment Cell Research (ASPCR), European Society for Pigment Cell Research (ESPCR), Japanese Society for Pigment Cell Research (JSPCR) and Pan-American Society for Pigment Cell Research (PASPCR)(Societies). Through IFPSCR, VEFT members work closely with international groups and individuals who hold strong interest into vitiligo research. They convene consensus conferences on issues of global importance for vitiligo clinical research, such as the consensus definition and classification of vitiligo (Taieb and Picardo, 2007; Ezzedine et al. 2012). Since 2010, I have been an active member, collaborated and initiated various international projects (see chapter 5) of the VEFT.

1.3 Definition and types of vitiligo

1.3.1 Definition of vitiligo

There is a current lack of consensus in the definition and methods of assessment of this disorder, which makes it difficult to compare the outcomes of different studies of the same treatment (Whitton et al., 2010).

In 2007, the Vitiligo European Task Force (VEFT) published a consensus paper which proposed the following consensus definition and classification of vitiligo (Table 1.1).

Vitiligo vulgaris/ Non-segmental vitiligo (NSV) is an acquired, chronic pigmentation disorder characterised by white patches, often symmetrical, which usually increase in size with time, corresponding to a substantial loss of functioning epidermal and sometimes hair follicle melanocytes (Taieb and Picardo, 2007).

Segmental vitiligo (SV) is defined as for NSV, except for a unilateral distribution that may totally or partially match a dermatome, but not necessarily (Taieb and Picardo, 2007). Dermatome is defined as the area of the skin that is supplied by a single nerve, originating from a single spinal nerve root.

Mixed vitiligo is characterised by presence of both non-segmental and segmental macules in the same patient.

Table 1.1 Types of vitiligo (Taieb and Picardo, 2007)

Type of vitiligo	Subtypes
Non-segmental (NSV)	Focal, mucosal, acrofacial, generalised, universal
Segmental (SV)	Focal, mucosal, unisegmental, bi or plurisegmental
Mixed (NSV+SV)	According to severity of SV
Unclassified	Focal at onset, multifocal, asymmetrical non segmental, mucosal (one site)

During the 2011 International Pigment Cell Conference (IPCC) several topics including revised classification, nomenclature and definition of stable vitiligo were discussed in seven working groups representing different geographical regions. A consensus emerged that segmental vitiligo should be classified separately from all other forms of vitiligo and that the term 'vitiligo' may be used as an umbrella term for all non-segmental forms of vitiligo (Table 1.2).

Table 1.2 Revised classification of vitiligo (Ezzedine et al., 2012)

Type of vitiligo	Subtypes
Vitiligo (NSV)	Mucosal (more than one mucosal site), acrofacial, generalised, universal, mixed (associated with SV), rare variants
Segmental (SV)	Unisegmental, bi or plurisegmental
Undetermined/unclassified	Focal, mucosal (one site in isolation)

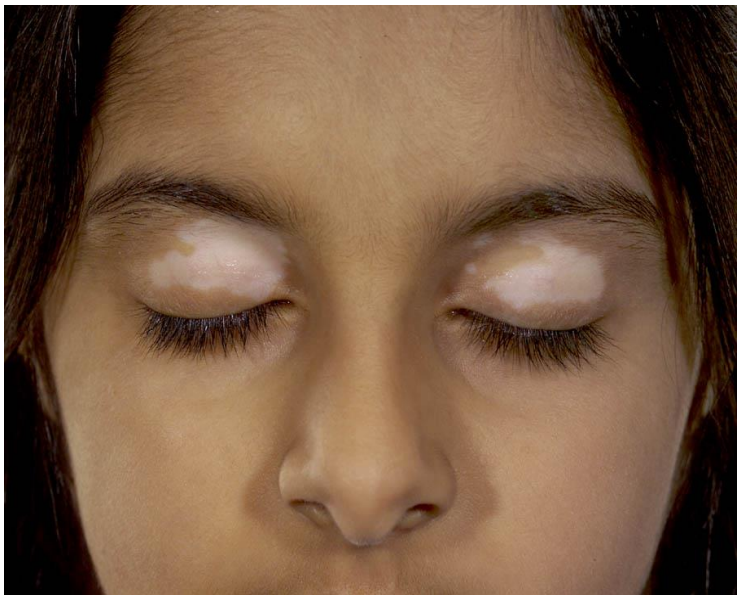
In this thesis, I am using the 2007 Vitiligo European Task Force's proposed classification (Table 1.1) for the following reasons:

- The new classification was published in June 2012 when all the protocols and projects for this thesis were in their final stage.
- The old classification is still widely used by research groups and clinicians worldwide and it will take some time to adopt the new classification.
- The old classification was used in previously published literature e.g. epidemiological studies used in this thesis.

Various other terms are also currently used in the literature to *clinically* describe the condition of vitiligo such as acrofacial, generalised, focal, universal and mucosal. Vitiligo may evolve and progress over time with the result that patients shift from one subtype to another (Liu et al., 2005).

1.3.2 Clinical subtypes of vitiligo

Focal vitiligo is characterised by one or few macules on a localised, non dermatomal distribution (Picture 1.3) (Picardo et al., 2010).



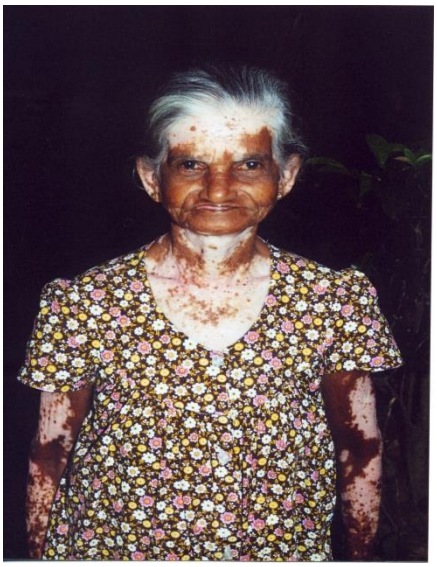
Picture 1.3 A teenage girl with focal, symmetrical lesions of non-segmental vitiligo on both eyes (Courtesy of Dr Jane Ravenscroft).

Acrofacial vitiligo affects periorificial facial areas and distal extremities. Periorificial vitiligo involves skin around the eyes, nose, ears, mouth and anus (Picardo et al., 2010).

Mucosal vitiligo affects the oral or/and genital mucosae. It can present as part of non-segmental vitiligo or as the only feature of vitiligo (Picardo et al., 2010).

Generalised vitiligo is referring to the non-segmental vitiligo (Picardo et al., 2010).

Vitiligo universalis is characterised by complete or almost complete depigmentation with possible small perifollicular pigmented areas on the sun exposed areas of the skin. It is the most severe form of non-segmental vitiligo (Picture 1.4) (Picardo et al., 2010).



Picture 1.4 A Shri-Lankan woman with extensive generalised vitiligo all over her body, with only a few pigmented areas left on her face and extremities. Scalp poliosis is also present (Courtesy of Dr Bernard Lamb).

Trichrome or **multichrome vitiligo** is mostly seen in darker skin phototypes. Within a vitiligo lesion, areas of depigmentation coexist with hypopigmented areas and with normal colour as in surrounding skin (Picardo et al., 2010).

Inflammatory vitiligo refers to lesions with raised red borders. Mild pruritis might be associated (Picardo et al., 2010).

Blue vitiligo refers to a blue discoloration of vitiligo patches reported after inflammatory vitiligo (Picardo et al., 2010).

Classification of segmental vitiligo of the face and neck was proposed by Gauthier in order to clinically describe the spreading pattern of the disease (Gauthier Y., 2006). The following 5 topographic patterns were proposed based on the ophthalmic (V1), maxillary (V2) and mandibular (V3) branches of trigeminal dermatome: Type I corresponding to the V1 partial or total involvement, Type II corresponding to V2 partial or total involvement, Type III corresponding to V3 partial or total involvement, Type IV corresponding to mixed distribution and Type V corresponding to cervico-facial one (Gauthier Y., 2006).

1.4 Prevalence of vitiligo and presentation

1.4.1 Prevalence

Vitiligo is the most common depigmenting disorder affecting around 0.5% of the world's population. The largest

epidemiological study was performed in 1977 on the island of Bornholm in Denmark, where vitiligo affected 0.38% of the population (Howitz et al., 1977). The majority of papers refer to an estimate of 0.5% to 1% prevalence worldwide. However, it is difficult to estimate the exact prevalence of vitiligo. Numbers, as high as 8.8%, have been reported in India (Behl, 1972). This may be due to inclusion of cases with chemically induced depigmentation (Sehgal and Srivastava, 2007). On the other hand, an attempt to estimate the prevalence of vitiligo in the black populations has been done in French West Indies, which concluded that the prevalence of vitiligo in black populations is comparable, or slightly less than, with the currently accepted data in white people (Boisseau-Garsaud et al., 2000). Overall, the highest incident rates have been recorded in India, followed by Mexico and Japan. The disparity between prevalence data and incidence figures may be due to a higher reporting of vitiligo, where attached social and cultural stigma may force patients to seek early consultation and/or the lesions are more prominent due to the darker skin colour of the population (Sehgal and Srivastava, 2007).

1.4.2 Sex

Adults and children of both sexes are equally affected although females often present for treatment more frequently,

probably due to the greater social consequences to women and girls affected by this condition (Singh et al., 1985; Fitzpatrick, 1964).

1.4.3 Age

Vitiligo develops at all ages but usually occurs in young people between the age of 10 and 30 (Singh et al., 1985; Fitzpatrick, 1964; Das et al., 1985; Howitz et al., 1977; Sehgal and Srivastava, 2007). However one epidemiological study showed that almost 50% of people develop vitiligo after the age of 40 (Howitz et al., 1977). It is estimated that almost half of patients present before the age of 20 years, and nearly 70-80% before the age of 30 years (Sehgal and Srivastava, 2007). A recent paper suggested that childhood onset vitiligo (before the age of 12) is common and affects 32% of patients (Nicolaidou et al., 2012) compared to previously reported 25% (Halder et al., 1987; Hu et al., 2006). Also, the same study confirmed that the majority of patients (89%) had a disease onset after the age of 4 (Nicolaidou et al., 2012).

Non-segmental vitiligo can occur at any age whereas segmental vitiligo tends to occur at a young age (Nicolaidou et al., 2012) before the age of 30 in 87% of cases, and before the age of 10 in 41.3%. Segmental vitiligo accounts for 5% to 16% of overall vitiligo cases (Hann and Lee, 1996).

Finally, a study in Jordan showed that vitiligo prevalence increases with age (0.45 %< 1 year old; 1% aged 1-5 years old, 2.1% aged 5-12 years old) (Al-Refu, 2012).

1.4.4 Clinical presentation

The most commonly affected initial sites in non-segmental vitiligo are usually the face, followed by anterior trunk, neck and posterior trunk (Hann et al., 1997b). It has been reported that generalised vitiligo can start at any site of the body but sun-exposed areas such as fingers, hands and face are commonly the initial sites reported by patients (Picardo et al., 2010). Interphalangeal joints, elbows and knees are the frequently affected extensor surfaces. For patients with vitiligo on the hands, vitiligo often progresses to the face. This explains the frequency of acrofacial vitiligo in these patients (Chun and Hann, 1997).

In segmental vitiligo the most commonly involved areas are face (51.1%), anterior trunk (21.5%) and extremities (10.8%) (Hann and Lee, 1996). The same study showed that the most common dermatomal distribution of vitiliginous lesions is trigeminal, thoracic and cervical with 52.1%, 22.8% and 17.4% respectively. Trigeminal dermatomal distribution affects the skin of the face, thoracic refers to the skin of the trunk and cervical dermatomal distribution affects the skull,

neck and upper extremities. (See definition of dermatome in the *definition and types of vitiligo*, page 18)

1.4.5 Hair involvement in vitiligo

Scalp poliosis (Picture 1.4) is the most frequent manifestation of hair involvement in vitiligo followed by eyebrows, pubic hair and axilla as reported in one study (Song, 1994).

1.4.6 Eye and ear involvement in vitiligo

Hypopigmented lesions on the iris are found in 20-50 % of patients with vitiligo according to several studies. However, no ophthalmic involvement has been reported in a small group of black patients with vitiligo (Albert et al., 1983; Albert et al., 1979; Biswas et al., 2003; Bulbul Baskan et al., 2006; Rosenbaum et al., 1979; Ayotunde and Olakunle, 2005). Loss of otic melanocytes may also occur in some patients with vitiligo. Hearing disorders have also been reported in vitiligo patients (Dereymaeker et al., 1989; Nikiforidis et al., 1993; Orecchia et al., 1989; Tosti et al., 1987).

1.5 Differential diagnoses

The aetiology of the disease is still unknown and therefore the definition and classification of vitiligo are purely descriptive. Where vitiligo is classical, the diagnosis is straight forward and can be made in primary care; however challenging cases require assessment by a dermatologist (Gawkrodger et al., 2008).

The following depigmenting or hypopigmenting disorders should be considered in the differential diagnosis of vitiligo (Tables 1.3 and 1.4) (Gawkrodger et al., 2008; Taieb and Picardo, 2007; Picardo et al., 2010).

Table 1.3 Differential diagnoses for non-segmental vitiligo

Disorders to be excluded from the definition of non-segmental vitiligo		**Clinical presentation**
Inherited or genetic induced hypomelanoses	Piebaldism	Midline body depigmentation, white forelock, bilateral shin depigmentation.
Hypopigmented lesions are present at birth, however in low phototypes are usually discovered after the first sun exposure.	Tuberus sclerosis	Ash-leaf white spots, seizures, angiofibromas, mental retardation.
	Hypomelanosis of Ito	Blascholinear distribution, uni or bilateral hypopigmented streaks.
	Albinism	To be considered for vitiligo universalis in case when the onset or the history of the disease is unknown. Classic oculocutaneous albinism associated with nystagmus and hair depigmentation is not a consideration, but milder syndromic albinisms should be considered (e.g. Hermanski-Pudlak syndrome, Griscelli syndrome).
	Waanderburg's syndrome	White forelock, hypertelorism (increased distance between to organs or two body parts), deafness, retinal pigment abnormalities.
Post inflammatory hypomelanoses	Psoriasis	
	Atopic eczema	Diagnosis is usually made on clinical ground of primary skin inflammatory disease.
	Lichen sclerosis	
Para-malignant hypomelanoses	*Mycosis fungoides*	In dark-skinned individuals, T-cell lymphoma can present as hypopigmented lesions.
	Melanoma associated depigmentation	Characterised by depigmentation around a cutaneous melanoma and associated with spontaneous or vaccine-induced regression of primary melanoma.
Occupational and drug induced depigmentation	Occupational vitiligo	Caused by exposure to depigmentation agents e.g. phenols.
	Drug induced depigmentation	Caused by drugs such as recently reported depigmentation following treatment with imatinib, imiquimod, potent topical corticosteroids.
Melasma	Common hypermelanotic disorder	Also known as "mask of pregnancy". Normal but hypochromic looking skin could be misleading when associated with hyperchromic lesions.
Post traumatic leucoderma	Deep burns or scars	Lesions could be unusual shape, however may be difficult to distinguish from true vitiligo lesions when scaring is not obvious as in case of toxic epidermal necrolysis.
	Toxic epidermal necrolysis	
Para-infectious hypopigmentation	Tinea versicolor	Skin mycosis which cause hypopigmented lesions with scaling.

	Leprosis	Characterised by hypochromic lesions. Usually associated with loss of sensitivity and should be suspected in individuals living in endemic areas.

Table 1.4 Differential diagnoses for segmental vitiligo

Disorders to be excluded from the definition of non-segmental vitiligo	**Clinical presentation**
Naevus depigmentosus	Congenital or detectable in the first year of life and stable in size and proportions to the child growth.
Segmental or hemicorporeal hypomelanosis of Ito	Characterised of narrow depigmented streaks following Blascho's lines could be difficult to distinguish in cases of multisegmental vitiligo.

1.6 Quality of life in vitiligo patients

Porter *et al* reported that the cosmetic disfigurement of this seemingly inconsequential skin disease has a major impact on the quality of life of patients and negatively affect sexual relationships (Porter et al., 1979; Parsad et al., 2003a; Sukan and Maner, 2007). Many people are frightened and embarrassed by vitiligo. They experience discrimination from others and believe that they do not receive adequate support from their doctors (Porter et al., 1987; Sukan and Maner, 2007). A recent survey conducted by the Vitiligo Society UK amongst their members showed that over half (56.6%) of respondents indicated that vitiligo moderately or severely

affects their quality of life (QOL) (Talsania et al., 2010). Finding a cure or effective lasting treatment was the main priority for most affected respondents. Disappointingly, most respondents obtain information about their disease from non-medical sources: 431 (83%) from the Vitiligo Society and 129 (25%) from the internet, compared with 61 (12.5%) from dermatologist (Talsania et al., 2010).

Also, patients with vitiligo may receive limited or ambivalent support from friends and family, and experience a number of psychological problems such as shame, depression and anxiety, which can lead to low self-esteem and social isolation (Porter et al., 1978). Majority of patients with vitiligo on exposed areas complain of unpleasant emotions compared (88%) to 20% of those with lesions in unexposed areas (Nogueira et al., 2009). The most frequently cited emotions were fear, specifically spreading of vitiliginous lesions (71%), shame (57%), insecurity (55%), sadness (55%) and inhibition (53%) (Nogueira et al., 2009). Self-image of vitiligo patients is also considerably decreased. Mood disturbances are common, particularly in teenagers. Vitiligo that begins in childhood can be associated with significant psychological trauma that may have a long lasting effect on personal self-esteem. Children with vitiligo usually avoid or restrict sport activities and often lose vital days in school (Parsad et al., 2003a). A study in the

Netherlands on the impact of childhood vitiligo on adult life showed that psychosexual development of young adults with childhood vitiligo appears to be comparable with that of healthy controls. However, patients reporting negative experiences of their vitiligo during childhood reported significantly more problems in social development (Linthorst Homan et al., 2008). In addition, a small study suggested that female Muslim patients in Iran experience greater quality of life impairment than males (Parsad et al., 2003a).

Finally, a study examined the extent of stigmatisation experienced by vitiligo patients considering the visibility of their lesions. Perhaps unsurprisingly, this study showed that patients with visible lesions experienced a higher level of stigmatisation (Schmid-Ott et al., 2007).

At present, there is limited research done into the psychological impact of the disease and the efficacy of psychological therapy on patients with vitiligo is not fully understood (Picardo et al., 2010; Papadopoulos et al., 1999). Papadopoulos *et al* (1999) provided preliminary evidence that cognitive behaviour therapy could provide benefit in terms of coping and living with vitiligo and that psychological therapy itself may have a positive effect on progression of the disease.

1.6 Aetiology and pathogenesis

The aetiology of vitiligo is poorly understood and has been disputed for decades. It is still not clear whether the melanocytes in vitiligo lesions have disappeared or are simply not functioning properly and why this is happening. Several theories have been developed to explain the pathogenesis of this proposed multifactorial disease (Dell'anna and Picardo, 2006; Denman et al., 2008; Le Poole et al., 1993; Le Poole et al., 2004; Schallreuter et al., 2008; Taieb, 2000). The immunological and the genetic theories seem to provide the most robust evidence to date.

The autoimmune aetiology of vitiligo has been considered strongly based on reports of its frequent association with other autoimmune disorders such as thyroiditis. Also, studies showed that the frequency of vitiligo and other autoimmune diseases was increased in relatives of vitiligo patients, supporting a genetic component to vitiligo.

A large epidemiological survey of 374 Caucasian patients with generalised vitiligo (most with sporadic occurrence of the disease) and their families, 133 multiplex vitiligo families; were analysed in the UK and North America, showed that 19.4% of vitiligo patients aged ≥ 20 years old, reported clinical history of autoimmune thyroid disease compared to

2.39% of the overall Caucasian population of the same age. Hyperthyroid was the most frequent of the reported forms. The same study reported significantly elevated frequency of pernicious anaemia (1.9%) with a 13-fold increase in frequency over the general population aged over 20 years old, Addison's Disease (0.38%) with a 76-fold increase in frequency over the general population aged over 20 years old, systemic lupus erythematosus (0.19%) with an 8-fold increase in frequency over the general population aged over 20 years old, irritable bowel disease frequency (0.67%) was elevated two-fold over the general population over 20 years old. The frequency of the above disorders was also elevated in their first degree relatives. No significant increase was observed in the frequencies of other autoimmune diseases such as alopecia areata, type 1 diabetes mellitus, psoriasis, rheumatoid arthritis, scleroderma and Sjogren's syndrome. Around 30% of the patients with generalised vitiligo were affected with at least one additional autoimmune disorder (Alkhateeb et al., 2003). Another study in familial generalised vitiligo in Caucasian families reported that relatives of families with multiple affected members have higher frequencies of thyroid disease, rheumatoid arthritis, psoriasis, adult onset diabetes mellitus and Addison's disease. It was also suggested that familial generalised vitiligo is characterised by earlier

disease onset and a broader repertoire of associated autoimmune disorders than vitiligo with sporadic occurrence (Laberge et al., 2005). A large retrospective study in China, did not confirm the above reported associations with thyroid disease and the most frequently reported autoimmune diseases were rheumatoid arthritis (0.32%), chronic urticaria (0.45%), ichthyosis (0.27%) and alopecia areata (0.32%). This difference is believed to result mainly from the different ages of the studied populations, as most of the patients studied were under the peak-onset age of commonly associated diseases (Liu et al., 2005).

Several smaller studies confirmed associations of vitiligo with thyroid disorders (Schallreuter et al., 1994; Dogra et al., 2005; Birlea et al., 2008), type 1 diabetes mellitus (Dogra et al., 2005; Birlea et al., 2008) and rheumatoid arthritis (Birlea et al., 2008; Dogra et al., 2005).

These findings also suggest that pathologic variants in specific genes predispose to vitiligo and the above mentioned autoimmune diseases. Several of these susceptibility genes have now been identified such as loci in the MHC (major histocompatability complex) (Majumder et al., 1988; Liu et al., 2007), PTPN22 (LaBerge et al., 2008; Le Poole et al., 2001), and NALP1 (Jin et al., 2007).

In addition, according to immunological studies, T-cell infiltrates, particularly CD8+ has been found in vitiliginous skin (Van den Wijngaard et al., 2000; Le Poole et al., 1996). An increased number of CD8+ cytotoxic lymphocytes reactive to MELAN A/Mart 1, which is a melanoma antigen recognised by T-cells, and tyrosinase has been reported. Antibodies to melanocytes in the sera of vitiligo patients have been found. These antibodies are also present in the sera of healthy individuals, but their prevalence is much lower (Cui et al., 1992; Cui et al., 1995; Farrokhi et al., 2005; Hann et al., 1996; Harning et al., 1991; Naughton et al., 1983a; Naughton et al., 1983b). Correlations have been described between the incidence and level of melanocytes antibodies and disease activity, showing that circulating pigment cell antibodies are found in individuals with active disease as well as suggesting that antibodies are detected in patients with greater extend of depigmentation (Harning et al., 1991). So far a wide variety of pigment cells antigens have been identified as targets for vitiligo associated antibodies, such as tyrosinase, a melanogenic enzyme; however the exact role of these autoantibodies in the development of the disease still remains unclear (Cui et al., 1992; Cui et al., 1995; Farrokhi et al., 2005; Hann et al., 1996; Harning et al., 1991; Naughton et al., 1983a; Naughton et al., 1983b; Kemp et al., 1997).

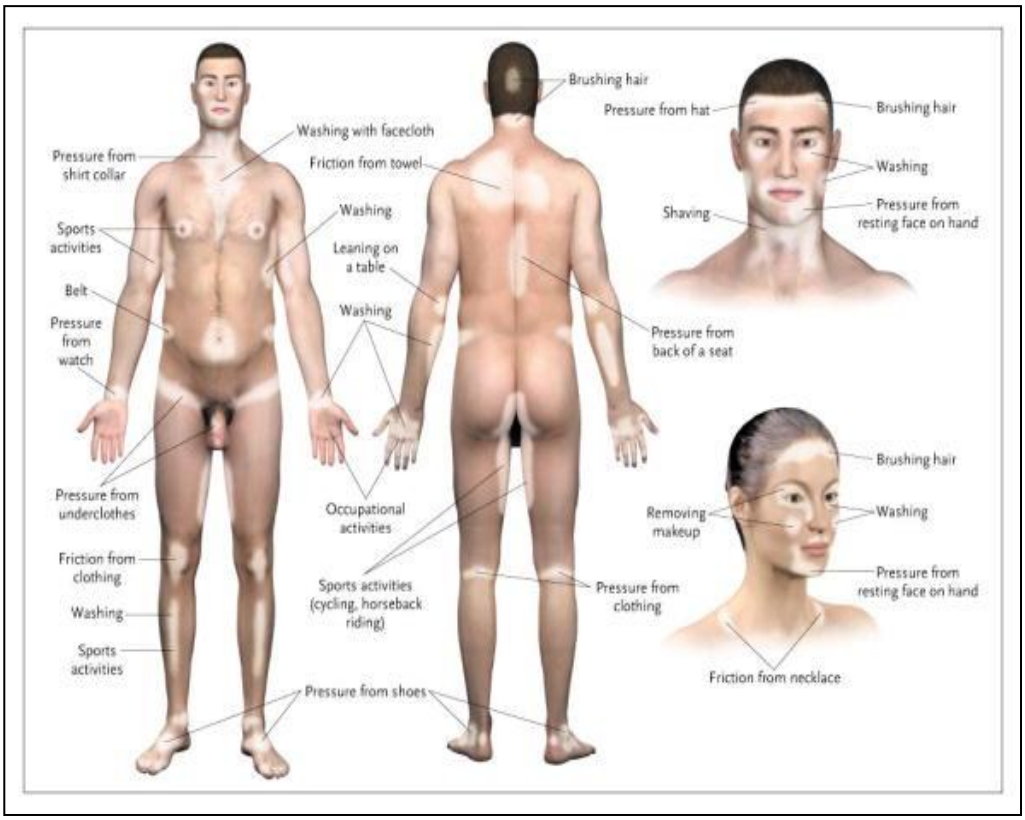
Indeed, the above results show that vitiligo is associated with other autoimmune diseases, such as thyroiditis, and suggest that there is a genetic predisposition in vitiligo. However a large epidemiological study to verify these possible associations is still lacking (Picardo et al., 2010).

Other theories such as oxidative stress theory, Koebner's phenomenon theory, cytokines theory, neuronal theory have also been suggested amongst others.

According to the *oxidative stress theory*, it has been suggested that melanocytes degeneration is caused by free radicals and other toxins produced intra or extracellularly. In vitiliginous skin, the melanocytes are damaged by the increased ROS (reactive oxygen species) levels generation of free radicals and toxic metabolites or due to a defective antioxidant pathway (Boissy and Manga, 2004; Jimbow et al., 2001; Le Poole et al., 1993; Schallreuter et al., 2008; Taieb, 2000). Also, cultured vitiliginous melanocytes show decreased levels of the catalase, the principle enzyme that is involved in the H_2O_2 removal and are more susceptible to the toxic effects of hyproperoxide and UV (Dell'Anna et al., 2007b; Jimbow et al., 2001; Kroll et al., 2005; Maresca et al., 1997).

On the other hand, vitiligo lesions have been described at sites of repeated trauma such as repeated friction or

pressure and scars, burns, wounds and other types of abrasions (Eyre and Krueger, 1982; Gauthier and Surleve-Bazeille, 1992; Gauthier et al., 2003; Hatchome et al., 1990; Levai, 1958b; Levai, 1958; Mulekar et al., 2007; Sweet, 1978). The Koebner's phenomenon, named after German dermatologist in 1877, refers to the appearance of new psoriatic lesions on lines of trauma. Later in 1890, Kaposi was the first to connect the Koebner's phenomenon with the appearance of new vitiligo lesions (Picardo et al., 2010). Consequently, it has been hypothesised that many lesions of non-segmental vitiligo could be related to repeated frictions occurring during washing, dressing, personal care, sports and other activities (Eyre and Krueger, 1982; Gauthier and Surleve-Bazeille, 1992; Gauthier et al., 2003; Hatchome et al., 1990; Levai, 1958b; Levai, 1958a; Mulekar et al., 2007; Sweet, 1978) (Picture 1.5).



Picture 1.5 Koebner's Phenomenon (Taieb and Picardo, 2009).

In Koebner's phenomenon, vitiligo patches develop in an isomorphic response to the friction or pressure resulting from such common activities as brushing hair, drying skin with a towel, and wearing a belt or watch.

Based on the Koebner's phenomenon, so called koebnerisation could occur at the site of melanocytes and grafts transplantation and therefore it is important to evaluate the risk of inducing new lesions prior to surgical or cosmetic procedures in vitiligo patients (Hatchome et al., 1990; Mulekar et al., 2007).

Also, studies have shown that human epidermal melanin unit, represents the symbiotic relationship in which one

melanocyte transports pigment-containing melanosomes through its dendrites to approximately 36 keranocytes (Fitzpatrick, 1964; Fitzpatrick and Breathnach, 1963). Moreover, data suggest that melanogenesis is regulated via specific melanogenic cytokines produced and released by keratinocytes and that fibroblasts derived growth factors can contribute to the regulation of melanocytes activities and skin pigmentation as well. Finally, vitiliginous skin, exhibits an impaired expression of keratynocyte-derived cytokines and growth factors affecting melanocytes activities and survival. Such an imbalance possibly plays a role in melanocytes disappearance, according to the cytokines and growth factors theory (Cario-Andre et al., 2006; Norris et al., 1996; Valyi-Nagy et al., 1990).

And finally, distribution of depigmentation in segmental vitiligo similar to the herpes zoster dermatomal distribution has been observed, as discussed in the definition and types of vitiligo section. It has been proposed that segmental vitiligo could result from the dysfunction of sympathetic nerves in the affected area (Koga, 1977; Koga and Tango, 1988). According to the neurogenic theory, an abnormal effect of neurohormones and neuropeptides has been suggested to cause the melanocyte loss or damage in segmental vitiligo

(Al'Abadie et al., 1994; McGuire, 1970; Chanco-Turner and Lerner, 1965).

In conclusion, various theories have been suggested to explain the pathogenesis of vitiligo. Together, the available data suggest that vitiligo is multifactorial and may be a syndrome rather than a single disease (Wolff, 2007; Le Poole et al., 1993). No single theory fully explains the pathoaetiology of vitiligo(Picardo et al., 2010).

1.7 Histopathology

The diagnosis of vitiligo can be made on clinical grounds, however in difficult cases, a skin biopsy can be performed to differentiate vitiligo from other pigmentary disorders (Tables 1.3 and 1.4) (Picardo et al., 2010).

The main histopathological finding in vitiliginous skin is the lack of melanocytes in the basal layer of the lesion and loss of melanin pigment from the epidermis. Otherwise skin appears to be normal in all other aspects. Occasionally, reduced number of melanocytes characterised by degenerative changes can be present in vitiligo lesions as well (Maize, 1998; Elder, 2005; Hann et al., 2000).

When performing a biopsy of hypopigmneted lesions, the inclusion of normal skin in the specimen is advised (Picardo et al., 2010). It is also important to indicate on the specimen if the disease is active or stable, as it has been shown that the histopathological findings differ according to the 3 phases of the disease: early stages, established lesions and long standing lesions (Hann et al., 2000). Established vitiligo lesions and long-standing lesions show absence of melanin in the epidermal layer and otherwise normal skin. In addition, in the long-standing vitiligo lesions, degenerative changes in cutaneous nerves and adnexal structures (skin appendages such as hair, skin muscles and glands) have been reported (Elder, 2005). In contrast, in early stage lesions, there may be lymphocytic inflammation infiltrates at the margin of vitiliginous lesion. The inflammation is usually lichenoid with little if any epidermal damage. Also, few melanocytes are present and melanin in the epidermal basal layer can be either reduced or not (Elder, 2005; Maize, 1998; Wolf, 2007; Picardo et al., 2010).

In conclusion, the previous histopathological changes are referring to non-segmental vitiligo only, as the data for segmental lesions is insufficient to reach a conclusion (Attili and Attili, 2008). Therefore research into the histopathology of early stage non-segmental lesions and segmental vitiligo

lesions would perhaps contribute to our understanding of the aetiology of vitiligo.

1.8 Natural history and prognosis

Despite being a common condition, which may have a major negative impact on its patients, there are no studies on the natural history of vitiligo. Therefore, evidence and recommendation are based on consensus view (Gawkrodger et al., 2008).

Dermatology text books fail to comment on the natural history of the disease and despite some reports of spontaneous repigmentation, this is unlikely. The British Association of Dermatologist guidelines for diagnosis and management of vitiligo suggest that vitiligo is a chronic and persistent disorder characterised by active, inactive and stasis periods (Gawkrodger et al., 2008).

Currently, there is lack of agreement on the definition and assessment of stability and activity of vitiligo. Several authors define stable vitiligo as a period when the condition does not progress from 4 months to 3 years (Parsad and Gupta, 2008; Njoo et al., 1998; Gupta, 2009).

A set of objective criteria, the vitiligo disease activity score (VIDA) has been suggested by Njoo et al (1999) to follow the course of vitiligo lesions, but it has limitations. This is a 6-point scale evaluating the disease activity by the appearance of new lesions or enlargement of pre-existing vitiligo lesions during a period from 6 weeks to a year. Reduction in VIDA score indicates better control of the vitiligo (Njoo et al., 1999) (Figure 1.1).

Figure 1.1 Vitiligo Disease Activity Score (Njoo et al., 1999)

Vitiligo Disease Activity score on a 6-pont scale

Vitiligo Activity Time	Period VIDA Score
Active 6 weeks or less	+4
Active 6 weeks to 3 months	+3
Active 3 - 6 months	+2
Active 6 - 12 months	+1
Stable 1 year or more	0
Stable with spontaneous repigmentation 1 year or more	-1

Njoo et al 1999

Few prognostic features of vitiligo have been identified mainly from epidemiological studies. Leukotrichia has been referred to as a feature of poor prognosis for repigmentation,

with the assumption that there are no melanocytes left within the depigmented area (Parsad et al., 2004). Family history, associated autoimmune diseases and the presence of mucosal involvement have also been suggested as poor prognostic indicators (Dave et al., 2002; Harning et al., 1991). According to one study, when the trunk and hands were the initial site affected by vitiligo, there was more widespread progression and when the initial sites were face and hands, the progression of the disease seemed to be less aggressive (Hann et al., 1997a).

The progression of segmental vitiligo differs from the non-segmental type and is usually limited to months or a few years (Hann and Lee, 1996; Koga and Tango, 1988). Also, segmental vitiligo does not usually cross the midline and spreads along the initially affected unilateral dermatome (Koga, 1977; Hann and Lee, 1996; Hann et al., 1997b). In conclusion, defining the prognosis of the disease is of great importance to patients in allowing them to adjust to their disease. It is also important in choosing a treatment option and predicting the effectiveness of therapy and therefore, a longitudinal epidemiological study is needed to define the natural history of vitiligo (Picardo et al., 2010; Gawkrodger et al., 2008).

1.9 Evaluation and assessment

The updated Cochrane systematic review "Interventions for vitiligo 2010" concluded that the majority of studies differ greatly in the ways in which vitiligo is measured and in the myriad combination of interventions assessed (see page 53 for information on Cochrane Systematic reviews and Cochrane collaboration). Despite the fact that the majority of the studies scored the percentage repigmentation, no two studies used exactly the same method of scoring; therefore the outcomes were pre-specified by the authors of the review. Only 9% (5/57) of studies addressed patient-rated quality of life. Cessation of spread of vitiligo or stabilisation of the disease was only reported in 9% (5/57) of the studies also. As a result, with the exception of one meta-analysis, it was not possible to pool data (Whitton et al., 2010).

Hamzavi et al. (2004) have introduced a quantitative parametric score, named Vitiligo Area Scoring Index (VASI). The total body VASI is calculated using a formula that includes contributions from all body regions (possible range, 0–100) (Figure 1.2).

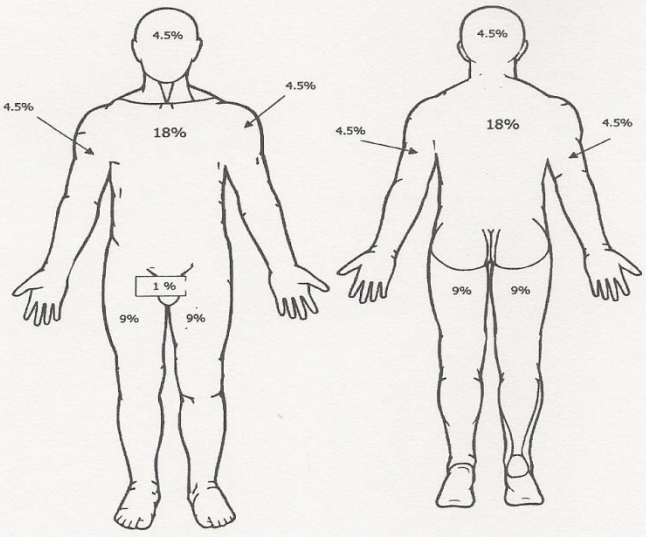
Figure 1.2 VASI score formula by Hamzavi et al (2004).

VASI*=All Body Sites [Hand Units]× Residual Depigmentation.*

One hand unit, which encompasses the palm plus the volar surface of all the digits, is approximately 1% of the total body surface area and is used as a guide to estimate the baseline percentage of vitiligo involvement in each body area (Hamzavi et al., 2004).

As previously mentioned, the Vitiligo European Task Force was established with one of its aims to create a consensus scoring system (Taieb and Picardo, 2007). VEFT produced an evaluation check list for non-segmental vitiligo (Table 1.5) and the following scoring system (Figure 1.3).

Figure 1.3 VEFT recommendations for scoring extend, stage and spread of vitiligo provided by Taieb et al. on behalf of the other VEFT members (Taieb and Picardo, 2007).



The patient palm including digits averages 1% of BSA (body surface area)
Please draw the patches and mark the evaluated patches on figure

area	% area	Staging (0-3) largest patch in each area	Spreading (-1 +1) largest patch in each area
Head and neck	0-9%		
Trunk	0-36%		
Arms (inc. hands)	0-18%		
Legs (inc. feet)	0-36%		
Hands and feet			
Totals	0-100%	0-15	(-5 +5)

Child under 5: changes for head and neck total 18% (9% front and back); legs 13,5% each (6, 75 % front and back); no change in other parts

STAGING SCORE

0	normal pigmentation (no depigmentation)
1	incomplete depigmentation (incl spotty depigmentation, trichrome and homogeneous lighter pigmentation)
2	complete depigmentation (may include hair whitening in a minority of hairs, less than 30%)
3	complete depigmentation plus significant hair whitening (more than 30%)

SPREADING SCORE

-1	regressive vitiligo	ongoing subclinical repigmentation
0	similar limits	
+1	progressive vitiligo	ongoing subclinical depigmentation

During clinical examination, it is necessary to take enough time for the first visit, for up to 30 minutes. For fair-skinned patients, a dark room and examination with Wood lamp might be necessary as vitiligo is less visible to the naked eye in these patients. Skin biopsy is usually not required, except when other diagnoses cannot be ruled out (Picardo et al., 2010).

The following check list (Table 1.5) provides guidance on information necessary for clinical evaluation of the disease as well as for research purposes. Although, the referred check list has been designed for non-segmental vitiligo, it is applicable for both segmental vitiligo and unclassified forms (Picardo et al., 2010).

The Vitiligo European Task Force scoring system is a clinical assessment tool, which combines analysis of the extent, grading of depigmentation and progression. For the evaluation of the extent of depigmentation, the "rule of nine" has been adopted from the already used SCORAD (Severity Scoring for Atopic Dermatitis) index for atopic eczema. The "rule of nine" is used to calculate the affected area as a percentage of the whole body, by estimating the face and neck, and the upper limbs, as 9% of the whole body surface each, 18% for the lower limbs and anterior trunk each and 1%

each for genitals, each palm and the back of each hand. To determine extent, the sites affected by vitiligo are shaded on a drawing of a body (European Task Force,1993) (Figure 1.3).

Table 1.5 Evaluation check list for non-segmental vitiligo (Taieb and Picardo, 2007; Picardo et al., 2010)

Patient's features	**Disease features**	**Family history**	**Interventions**
Phototype (Fitzpatrick's skin type) Ethnic origin Age of onset Occupation Stress/anxiety levels Halo nevus History of autoimmune disease Global Quality of life assessment "how vitiligo does affects your everyday life?" (10-point analogue scale)	Duration Activity (Progressive, regressive, stable over the last 12 months) Episodes of repigmentation Koebner's phenomenon Itch before flares Thyroid disease Vitiligo on genitalia Clinical photographs	Premature hair greying Vitiligo Autoimmune disease in family	Type and duration of previous treatments including opinion if effective/useful. Other diseases

The proposed evaluation of the stage of the disease is based on the repigmentation pattern as following:

- Stage 0 – normal pigmentation
- Stage 1- incomplete depigmentation
- Stage 2- complete depigmentation and may include hair whitening in the minority of hairs, less than 30%
- Stage 3- complete depigmentation with hair whitening more than 30%

Finally, the spreading of the disease is evaluated as:

- 0 - stable disease
- -1 - observed on-going repigmentation
- +1 - additional depigmentation patches in a given area

In addition, the Vitiligo European Task Force commented during the Rome workshop, that in order to test and evaluate the described scoring system, it was felt that patients' opinion should be used in the grading evaluation (Taieb and Picardo, 2007). Also, as vitiligo is a psychologically devastating disease (see *Quality of life in vitiligo patients*), inclusion of a more

detailed questionnaire, to fully evaluate the severity and the psychological impact of the disease, in the standard clinical assessment would be useful. Ideally, development of a specific vitiligo Quality of life scale would probably be helpful (Picardo et al., 2010).

Recently, during the 2011 International Pigment Cell Conference (IPCC), it was recommended that the overall stability may best be assessed based on the stability of individual lesions rather than the overall stability of the disease as the latter is very difficult to define reliably and precisely (Ezzedine et al., 2012). It is not uncommon for individual lesions in a patient to follow different courses: some regress, some stay stable and some progressing simultaneously. The VEFT tool and the VASI score both allow such regional follow-up (Ezzedine et al., 2012; Taieb and Picardo, 2007; Hamzavi et al., 2004). Ideally stability should be assessed using a combination of a clinical scoring tool, patient's own history and digital photographs of specific lesions over at least 12 months (Ezzedine et al., 2012).

Only recently, an attempt was made to develop and validate a patient-defined benefit questionnaire for the treatment of vitiligo. The patient's benefit index (PBI) for vitiligo was validated based on data of 1023 vitiligo patients in

Germany and showed high correlation with prior selected parameters of therapeutic success, such as Dermatology Quality of Life Index (DLQI) and 5-Dimentional European Quality of Life Questionnaire (EQ-5). The PBI is calculated on the basis of two questionnaires: a patient's defined need questionnaire completed prior to starting a treatment and a patient's benefit questionnaire completed after therapy. Global value PBI is calculated using the following algorithm, where the importance of each treatment goal is divided by the sum of all importance value and multiplied by the goal attainment value. Specifically, the PBI is the arithmetic mean of all rated benefits (PBQ items) weighted by the relative importance of each corresponding need item (PNQ) for each patient (Figure 1.4) (Augustin et al., 2008).

Figure 1.4 Patient benefit index (PBI) with k preference items (PNQ range 0–4) and benefit items (PBQ range 0–4)

$$PBI = \sum_{i=1}^{k} \frac{PNQ_i}{\sum_{i=1}^{k} PNQ_i} PBQ_i$$

Finally, the index of potential repigmentation was recently proposed (Benzekri et al., 2012). All vitiliginous lesions in a given patient are examined and classified according to the following classification: Type A-hypochromic lesions, Type B-achromic with dark hairs and Type C-achromic lesions with white hair. The index is calculated by dividing the addition of (percentage of Type A lesions + percentage of Type B lesions) by the addition of (percentage of Type D lesions + percentage of Type B lesions). The index is a scale from zero to nine. Values superior to five predict good response to treatment. On the other hand, values inferior to five predict refractory to treatment vitiligo (Benzekri et al., 2012).

In conclusion, there is lack of consensus on the scales and scores used in clinical trials for vitiligo. Standardised methodologies for classifying vitiligo and for assessing the effect of interventions need to be developed and all researchers should adopt the same standards so that the data from future trials can be more easily pooled. Patient-centred outcomes should be incorporated into the design of all future studies (Whitton et al., 2010).

1.10 Management overview

The Cochrane Collaboration is an international network of more than 28,000 dedicated people from over 100 countries. They work together to help healthcare practitioners, policy-makers, patients and carers, make well-informed decisions about health care, by preparing, updating, and promoting the accessibility of Cochrane Reviews. Over 5,000 Cochrane Reviews are published so far and they are available online in the Cochrane Database of Systematic Reviews, part of The Cochrane Library.

Cochrane systematic review is a meta-analysis of trials. There are three types of Cochrane Review: intervention reviews, diagnostic test accuracy reviews and methodology reviews address issues relevant to how systematic reviews and clinical trials are conducted and reported. Cochrane Reviews base their findings on the results of trials which meet certain, strict quality criteria, such as double-blind randomised controlled trials; therefore Cochrane reviews are internationally recognised as being the benchmark for high quality information about the effectiveness of health care (Cochrane collaboration http://www.cochrane.org/).

The first Cochrane systematic review "Interventions for vitiligo" was conducted in 2006. This review was updated in

2010 (Whitton et al., 2010). The aim of this review was to assess all interventions used in the management of vitiligo. The updated Cochrane systematic review 2010 "Interventions for vitiligo" concluded that no cure and no way of limiting the spread of the disease has been found to date. The above review identified 38 randomised controlled studies that had been published between 2006 and 2009, resulting in 57 studies overall with 3139 participants. However, until the aetiology of the disease is clear, treatments will continue to be based on the many theories that exist for this disease (Whitton et al., 2010).

In 2008, a detailed guideline for the diagnosis and management of vitiligo was published in the UK (Gawkrodger et al., 2008). This user-friendly guideline was based on evidence from the first Cochrane systematic review 2006 and expert consensus taking into account patient choice and clinical expertise (Gawkrodger et al., 2008). Current British Association of Dermatologists (BAD) clinical guidelines for the diagnosis and management of vitiligo, recommend NB-UVB, tacrolimus and topical steroids (Gawkrodger et al., 2008).

Recently, a new guideline on vitiligo was developed by the Guideline Subcommittee "Vitiligo" of the European Dermatology Forum and brought several changes into the

previously proposed management of vitiligo (Taieb et al., 2013) (Table 1.6). This guideline suggests early treatment of small lesions of recent onset and childhood vitiligo with combination of phototherapy and topical agents (Taieb et al., 2013). This new European Guideline aims to bring clarity into the treatment options available for various types of vitiligo and provide expert advice based on the best available evidence and specialist consensus (Taieb et al., 2013).

Table 1.6 Summary of new European guideline for the management of vitiligo (Taieb et al., 2013)

Type of vitiligo	Level	Usual management
SV or limited NSV(<2-3% of BSA)	First line	Avoidance of triggering factors, topical therapies (corticosteroids, calcineurin inhibitors)
	Second line	Localised NB-UVB therapy, especially excimer monochromatic lamp or laser
	Third line	Consider surgical techniques if repigmentation cosmetically unsatisfactory on visible areas
NSV	First line	Avoidance of triggering / aggravating factors. Stabilisation with NB-UVB therapy, at least 3 months. Optimal duration at least 9 months, if response. Combination with systemic/topical therapies, including reinforcement with localised UVB therapy.
	Second line	Systemic steroids (e.g. 3–4-month mini-pulse therapy) or immunosuppressants if rapidly progressing disease or absence of stabilisation under NB-UVB
	Third line	Graft in non-responding areas especially with high cosmetic impact. However, Koebner phenomenon limits the persistence of grafts. Relative contraindication in areas such as dorsum of hands
	Fourth line	Depigmentation techniques (hydroquinone monobenzyl-ether or 4-methoxyphenol alone or associated with Q-switched ruby laser) in non-responding widespread (>

50%) or highly visible recalcitrant facial /hands vitiligo

A no treatment option (zero line) can be considered in patients with a fair complexion after discussion. For children, phototherapy is limited by feasibility in the younger age group and surgical techniques are rarely proposed before pre-pubertal age. There is no current recommendation applicable to the case of rapidly progressive vitiligo, not stabilized by ultraviolet (UV) therapy. For all subtypes of disease or lines of treatment, psychological support and counselling, including access to camouflage instructors is needed.

The following table summarises the existing evidence from the updated Cochrane systematic review, the new European Dermatology Forum guideline on vitiligo, the British Associations of Dermatologist guidelines for diagnosis and management of vitiligo, and the Indian Association of Dermatologists, Venereologists and Leprologists standard guidelines of care for vitiligo surgery (Gawkrodger et al., 2008; Whitton et al., 2010; Parsad and Gupta, 2008; Taieb et al., 2013) (Table 1.7). This table aims to provide an overview of various treatment modalities tested for vitiligo over decades and provide a concise summary of clinical recommendations for each modality. I believe that it is helpful, in light of such a large heterogeneity of interventions, to summarise our existing knowledge for each intervention from several sources in one table and its applicability for clinical practice.

Interventions in this table are classified into one of the following categories: topical treatments, phototherapy, complementary treatments, systemic treatments, psychological treatments, depigmentation or cosmetic camouflage. This classification was adopted from the Cochrane Systematic review 2010 (Whitton et al., 2010). Several interventions, which were not mentioned in the Cochrane Systematic review but were mentioned in the clinical guidelines (as above), were also added to one of the above mentioned categories such as skin grafts, self-tanning products, p-benzyloxy-phenol, hair grafts, micropigmentation.

In addition, I have also included interventions that are still in an early investigative stage; trials are currently on-going or not yet published (Table 1.8).

Table 1.7 Summary of interventions for vitiligo

Broad category	Intervention	Agents/Techniques	Randomised controlled trial/ Cochrane systematic review 2012	Comments and recommendations
1.Topical treatments ***(monotherapies and combination with light therapies)***	*1.1 Topical corticosteroids*	Betamethasone; Clobetasol; Clobetasol plus UVB; Fluticasone with UVA; Fluticasone alone	(Kandil, 1974);(Khalid et al., 1995);(Sanclemente et al., 2008); (Kumaran et al., 2006); (Lepe et al., 2003); (Lim-Ong et al., 2005); (Westerhof et al., 1999)	The use of highly potent or potent topical corticosteroids (TCS) is recommended for generalised symmetrical vitiligo in both children and adults (Gawkrodger et al., 2008).Once-daily application of potent TCS is advisable for patients with limited, extra-facial involvement for a period no longer than 3 months, according to a continuous treatment scheme or, better, to a discontinuous scheme (15 days per month for 6 months) (Taieb et al., 2013). As potent TCS appear to be at least as effective as very potent TCS, the first category should be the first and safest choice. The combination of corticosteroids with UVA light is reported to be more effective than topical corticosteroids alone (Whitton et al., 2010). Anti-inflammatory properties of the steroids may act on the immune /inflammatory component, mainly in recent and active lesions, lowering the total amount of administered UV radiation. Although prospective studies are still lacking, the combination of TCS and UVB sources (NB-UVB and

				308 nm excimer lasers or lamps) may be promising for difficult to-treat areas, e.g. over bony prominences. Potent topical steroids applied once a day (3 weeks out of 4) can be used on vitiligo lesions for the first 3 months of phototherapy (Taieb et al., 2013).
	1.2 Calcineurin inhibitors (CI)	Pimecrolimus; Pimecrolimus plus NB-UVB; Tacrolimus plus Xenon Chloride Eximer Laser (XCEL); Tacrolimus alone; Tacrolimus plus NB-UVB	(Cestari et al., 2001); (Dawid et al, 2006); (Esfandiarpour et al., 2009); (Kawalek et al., 2004); (Lepe et al., 2003); (Mehrabi and Pandya, 2006)	In adults and children topical pimecrolimus should be considered as an alternative to the use of topical steroid. The side effects profile of pimecrolimus and others CI is better than that of a highly potent topical steroid (Gawkrodger et al., 2008; Taieb et al., 2013). Topical CI should considered in adults and children with vitiligo as an alternative to topical steroids for new, actively spreading, lesions on thin skin. The use of topical CI should be restricted to selected areas, in particular the head and neck region. Twice-daily applications are recommended. The treatment should be prescribed initially for 6 months. During this period of treatment, moderate but daily sun exposure should be recommended. If effective, prolonged treatment (e.g. longer than 12 months) may be proposed (Taieb et al., 2013). The combinations of calcineurin inhibitors with excimer laser or NB-UVB has been tested and showed promising results, however these should be treated with caution as long term data carginogenicity is still lacking (Whitton et.al.,

				2010; Taieb et al., 2013).
	1.3 Vitamin D analogues	Calcipotriol; Calcipotriol plus PUVA; Calipotriol plus excimer laser; Calcipotriol plus NB-UVB; Tacalcitol; Tacalcitol plus NB-UVB; Tacalcitol plus monochromatic excimer light (MEL)	(Kumaran et al., 2006); (Akhyani et al., 2005); (Ermis et al., 2001); (Goldinger et al., 2007); (Arca et al., 2006); (Rodriguez-Martin et al., 2009); (Leone et al., 2006); (Lu-yan et al., 2006)	The use of topical calcipotriol as monotherapy and in combination with phototherapy is not recommended (Gawkrodger et al., 2008; Taieb et al., 2013).
	1.4 Khellin	Topical Khellin plus UVA (KUVA)	(Procaccini et al., 1995)	Although khellin appears to be less phototoxic in comparison with psoralens, there is currently insufficient evidence to recommend khellin with UV for the treatment of vitiligo (Whitton et al., 2010; Gawkrodger et al., 2008).
	1.5 Pseudocatalase	Dead sea climatotherapy plus psedocatalase	(Schallreuter et al., 2002); (Bakis-Petsoglou et al., 2009)	This combination treatment has shown promising results in a pilot non randomised controlled trial. However 1 subsequent study failed to confirm these data (Bakis-Petsoglou et al., 2009; Taieb et al., 2013).
	1.6 Melagenina	Melagenina plus infra-red light	(Souto et al., 1997)	This intervention derived from human placental extract is used topically in conjunction with light to treat vitiligo. The study didn't examine any outcomes of interest. Burning with infra-red light was reported (Whitton et al., 2010).
	1.7 Intralesional steroid injections	Triamcinolone acetonide suspension	(Vasistha and Singh, 1979)	This intervention is not used in practice. One study showed that intralesional steroid injections are no better than placebo (Gawkrodger et al.,

				2008). This study also showed adverse effects such as telangiectasia, infection, skin atrophy and intradermal haemorrhage (Whitton et al., 2010).
	1.8 Catalase/dismutase superoxide	Catalase/dismutase superoxide C/DSO with brief sun exposure	(Sanclemente et al., 2008)	Catalase/dismutase superoxide is plant based topical treatment with antioxidant properties. The study didn't examine any outcomes of interest. Self-limiting erythematous popular rash was reported (Whitton et al., 2010).
	1.9 Lactic acid	Topical 15% lactic acid; Topical 15% lactic acid plus UVA	(Sharquie, 2005)	One study examined the effectives of topical lactic acid alone and in conjunction with UVA. The results were not reliable due to 63% dropouts with no reason given (Whitton et al., 2010).
	1.10 Antioxidant mitochondrial stimulating cream	Antioxidant and mitochondrial stimulating cream; Antioxidant mitochondrial stimulating cream plus oral antioxidants and phenylalanine	(Rojas-Urdaneta, 2007)	Only one small trial examined the effectiveness of antioxidant and mitochondrial stimulating cream alone and in combination with oral antioxidant and/or phenylalanine. The only side effects reported were mild acne and pruritis (Whitton et al., 2010).
2.Phototherapy	*2.1 PUVA*(psoralen and UVA) *and PUVAsol* (psoralen and sunlight)	Topical PUVA (Trimethylpsoralen or 8-methoxypsoralen); Oral PUVA; Topical PUVAsol; Oral PUVAsol; Oral PUVAsol plus calcipotriol	(Bhatnagar et al., 2007); (Ruiz Maldonado and Tamayo , 1975); (Khalid et al., 1995); (Pathak et al., 1984); (Akhyani et al., 2005); (Cestari et al., 2001); (Ermis et al., 2001); (Parsad et al., 1998); (Farah et al., 1967)	In most patients NB-UVB should be used in preference to PUVA. PUVA is not recommended in children. The recommended treatment regimen should not exceed 150 PUVA treatments (Gawkrodger et al., 2008). PUVA is claimed to be particularly effective in darker skinned individuals, however, evidence is lacking (Gawkrodger et al., 2008; Whitton et al., 2010). There is an uncertainty regarding the risk of skin cancer in

				patients with vitiligo and therefore clinicians should be caution in prescribing PUVA (Gawkrodger et al., 2008). Side effects of oral PUVA and PUVAsol such as nausea, pruritis, dizziness, headaches, eye discomfort and vague gastrointestinal symptoms were reported (Whitton et al., 2010).
	2.2 UVA	UVA	(El-Mofty et al., 2006); (Procaccini et al., 1995); (Sharquie, 2005)	Conclusions cannot be drawn if UVA is more effective in comparison with other phototherapies as there is no such a study (also see PUVA) (Whitton et al., 2010).
	2.3 UVB	BB-UVB (broad band UVB); NB UVB (narrow band UVB); NB-UVB plus Er-YAG laser ablation plus 5 Fluorouracil	(Asawanonda et al., 2008); (Arca et al., 2006); (Bhatnagar et al., 2007); (Hamzavi et al., 2004); (Yones et al., 2007); (Anbar et al., 2008); (Casacci et al., 2007); (Lim-Ong et al., 2005); (Mehrabi and Pandya, 2006)	NB-UVB is indicated for generalized NSV. Total body treatment is suggested for lesions involving more than 15–20% of the body area. Total NB-UVB has also been proposed as treatment for active spreading vitiligo, however only limited supportive data are available. Targeted phototherapies (laser and non-laser) are indicated for localized vitiligo and in particular for small lesions of recent onset and childhood vitiligo, to avoid side-effects due to total body irradiation with UVB, and in all cases where contraindications exist for total body irradiation (risk for melanoma or non-melanoma skin cancer, photo-aggravated disease, etc.). The BAD guidelines suggest that treatment regimen for patients with skin types I-III should not exceed 200 UVB treatments; however there is as yet no consensus as to the optimum treatment duration of NBUVB or targeted

			phototherapy. Many therapists tend to stop irradiation if no repigmentation occurs within the first 3 months of treatment or in case of unsatisfactory response (< 25% repigmentation) after 6 months of treatment. Phototherapy is usually continued as long as there is on-going repigmentation or over a maximum period of 1 or 2 years. Maintenance irradiation is not recommended, but regular follow-up examinations are suggested for detecting relapse (Gawkrodger et al., 2008; Taieb et al., 2013). Combination topical therapies with NB-UVB showed to be more effective than NB-UVB monotherapy. Erythema, itching, burning and blistering has been reported. BB-UVB is not properly evaluated (Whitton et al., 2010).
	Home NB-UVB phototherapy	(Wind et al., 2010)	Only one study evaluated the effectiveness of home versus hospital NB-UVB therapy. Although the results showed that both treatments are comparable, with similar repigmentation and occurrence of side-effects, satisfaction with the result was significantly lower in the home group. It is suggested that home NB-UVB therapy is a valuable alternative to outpatient light therapy for vitiligo (Wind et al., 2010).

	2.4 Lasers	Xenon-chloride excimer laser (XCEL); Xenon Chloride excimer (XCEL) laser plus tacrolimus; 308nm excimer laser; 308nm excimer plus topical hydrocortisole	(Goldinger et al., 2007); (Hofer et al., 2005); (Passeron et al., 2004); (Sassi et al., 2008); (Kawalek et al., 2004); (Casacci et al., 2007); (Lu-yan et al., 2006)	Excimer laser delivers a condensed beam of UVB light to the skin. It is commonly used in conjunction with topical therapies. The combinations of light therapies with topical tacrolimus or calcipotriol are reported to be more effective in repigmenting vitiligo lesions. Reported side effects include burning, stinging, erythema, oedema, hyperpigmentation (Whitton et al., 2010). One study claims that 308nm MEL therapy is more effective than NB-UVB for treatment of vitiligo (Casacci et al., 2007, Whitton et al., 2010).
	2.5 Other light sources	308nm Monochromatic excimer light (MEL); MEL plus Tacalcitol		
3.Complementary and alternative therapies	*3.1 Zengse pills*	Zengse pills and cobamamide tablets; Zengse pills alone	(Shi et al., 2008)	Only one study evaluated the effectiveness of Zengse pills with or without cobamamide and psoralea tincture. Although the design of study was unclear the authors reported positive results. Side effects such as redness, itching and constipation were reported (Shi et al., 2008; Whitton et al., 2010).
	3.2 Gingko biloba	Gingko biloba	(Parsad et al., 2003b)	Oral Gingko biloba is a herb with immunomodulatory and antioxidant properties. One study has reported that Gingko biloba pills has significantly improved repigmentation and stopped the disease spreading. Nausea was the only observed side effect (Parsad et al., 2003b; Whitton et al., 2010). The use of oral Gingko biloba cannot be recommended unless further studies confirm the above effects (Gawkrodger et

				al., 2008).
4. Oral treatments (monotherapies and combination with light therapies)	*4.1 Polypodium leucotomos*	Polypodium leucotomos plus NB-UVB; Polypodium leucotomos plus PUVA	(Middelkamp-Hup et al., 2007); (Reyes et al., 2006)	Polypodium leucotomos is a type of fern with photoprotective and immunomodulatory properties. It has been reported that Polypodium leucotomos plus PUVA is more effective than PUVA in repigmenting vitiligo lesions (Reyes et al., 2006). However combination of Polypodium leucotomos plus NB-UVB does not improve patients' quality of life (Middelkamp-Hup et al., 2007). Currently there is no convincing evidence that this treatment has a role in the treatment of vitiligo (Gawkrodger et al., 2008).
	4.2 Levamisole	Oral levamisole plus momethasone furoate cream	(Agarwal et al., 2005)	One study has shown no statistically significant difference in repigmentation between the oral levamisole plus momethasone furoate cream group and the topical mometasone plus placebo group (Whitton et al., 2010).
	4.3 Oral corticosteroids	Oral Minipulses (OMP) of bethamethasone plus PUVA; OMP plus NB-UVB OMP plus BB-UVB; OMP alone; oral dexamethasone	(Rath et al., 2008); (Radakovic-Fijan et al., 2001)	OMP plus NB-UVB showed better repigmentation compared to OMP alone, in contrary with OMP plus PUVA or BB-UVB compared to OMP alone (Whitton et al., 2010, Rath et al., 2008). Dexamethasone has been reported to stop the spreading of the disease (Radakovic-Fijan et al., 2001). OMP therapy is not considered useful for repigmenting stable vitiligo. The use of oral dexamethasone cannot be recommended due to the side effects such as weight gain, acne,

				menstrual irregularity and hypertrichosis (Gawkrodger et al., 2008, Taieb et al., 2013).
	4.4 Azathioprine	Azathioprine plus PUVA	(Radmanesh and Saedi, 2006)	No recommendation could be made based on one study only, however the combination of Azathioprine plus PUVA has shown an enhanced repigmentation compared with PUVA alone (Gawkrodger et al., 2008).
	4.5 L-phenylalanine	Oral L-Phenylalanine plus UVA	(Siddiqui et al., 1994)	There was no statistically significant difference between the Oral L-Phenylalanine plus UVA and the no treatment group (Whitton et al., 2010).
	4.6 Vitamin B12 and folic acid	Vitamin B12 and folic acid plus NB-UVB	(Tjioe et al., 2002)	Authors reported that the addition of Vitamin B12 and folic acid to the NB-UVB does not improve the outcome of treatment (Tjioe et al., 2002).
	4.7 Oral antioxidants	Antioxidants pool (AP) (alpha lipoic acid, Vitamin B and C, and polyunsaturated fatty acids) plus NB-UVB	(Dell'Anna et al., 2007a)	Although the authors reported that oral supplementation with AP containing a-lipoic acid before and during NB-UVB significantly improves the clinical effectiveness of NB-UVB, the Cochrane systematic review found no statistically significant difference between the treatment and the control group (Whitton et al., 2010; Dell'Anna et al., 2007a). Larger trials are needed to evaluate the effectiveness of this modality.
5. Surgical treatments ***(monotherapies and***	5.1 Skin grafts	Suction epidermal blister grafts; Punch grafts plus PUVA or topical corticosteroids; Minipunch grafting; Split skin grafts;	(Ozdemir et al., 2002); (Barman et al., 2004); (Khandpur et al., 2005); (Navarro, 2002); (McGovern et al., 1999); (Lahiri	Surgery is indicated for all types of stable vitiligo that do not respond to medical treatment. Test grafting may be performed in doubtful cases to detect stability. The choice of surgical intervention

combined with light therapies)		Autologous skin minigrafts plus 8-methoxypsoralen (8-MOP); Minigrafts alone; Flip-top grafting; Autologous cultured epithelial grafts	et al., 2004); (Hasegawa et al., 2007); (Pai et al., 2002); (Achauer et al., 1994); (Kahn and Cohen, 1998); (Ozdemir et al., 2002); (Guerra et al., 2003); (Pianigiani et al., 2005); (Toriyama et al., 2004)	should be individualised (Parsad and Gupta, 2008, Taieb et al., 2013). Punch grafts is the easiest and the least expensive method and may be used on all areas other than nipples and the angle of the mouth. Suction blister epidermal grafting has the advantage that the chances of scaring are minimal as the graft is epidermal. However these 2 methods are not suitable for large lesions. On the other hand, split skin grafts have the advantage of treating large areas in a short period of time but require skills and experience (Parsad and Gupta, 2008). Split skin grafting is recommended as the best option when a surgical treatment is required. Minigrafts are not recommended due to a high incidence of side effects and poor cosmetic results (Gawkrodger et al., 2008).
	5.2 Other tissue grafts	Hair grafts	(Malakar and Dhar, 1999); (Laxmisha et al., 2006); (Agrawal and Agrawal, 1995); (Na et al., 1998)	Hair follicle grafting has been performed by a few authors for treating small patches in hair bearing area and has been found useful in treating lesions with leukotrichia (Parsad and Gupta, 2008).
	5.3 Micropigmentation		No studies found (Whitton et al., 2010)	Micropigmentation is a form of semi-permanent tattooing. It has been used on areas resistant to treatment such as the lips and the tips of the fingers (Whitton et al., 2010).
	5.4 Melanocyte transplantation	Autologus epidermal cell suspension (non-cultures melanocytes grafting) transplantation; Cultured	(Czajkowski, 2004); (Van Geel et al., 2004); (Olsson and Juhlin, 1998); (Olsson and Juhlin, 2002); (Mulekar, 2003); (Olsson and	Autologous epidermal suspension applied to a laser abraded lesion followed by PUVA or NB-UVB is recommended as the optimal surgical

		autologous melanocytes transplantation; Suction blister transplantation; Autologous cellular suspension (melanocytes medium plus hyalouronic acid plus epidermal cells) plus NB-UVB or PUVA; Autologous transplant of epidermal suspension from skin graft	Juhlin, 1995); (Czajkowski et al., 2007); (Chen et al., 2004); (Tegta et al., 2006)	transplantation (Gawkrodger et al., 2008). The major advantage of these procedures is they can treat large areas of vitiligo lesions, however do require a properly equipped laboratory and trained personnel (Parsad and Gupta, 2008). Phototherapy (NB-UVB or PUVA) should be used for 3 or 4 weeks after surgical procedures to enhance repigmentation (Taieb et al., 2013).
6. Depigmentation		p-(benzyloxy)phenol (monobenzyl ether of hydroquinone)	No RCT found (Whitton et al., 2010)	Depigmentation should be reserved for adults with extensive generalised vitiligo (more than 50% depigmentation) or who have extensive depigmentation on their face or hands (Gawkrodger et al., 2008; Taieb et al., 2013)
7. Psychological therapy		Group cognitive behaviour therapy; Person centred therapy	(Papadopoulos L, 2004)	Despite the small evidence base on CBT the psychological support and strategies to cope with the effects of disfigurement are an important part of the treatment of vitiligo. Psychological interventions should be offered as a way of improving coping mechanisms in patients with vitiligo. Parents of affected children should be offered psychological counselling (Gawkrodger et al., 2008; Taieb at al., 2012).
8. Cosmetic camouflage		Self-tanning products; Cover products	No RCT found (Whitton et al., 2010)	There is wide choice of cosmetic agents. Specialist camouflage services are available (Gawkrodger et al., 2008; Taieb et al., 2013).

Table 1.8 Treatments for vitiligo that are still in an early investigative stage, trials are on-going or not yet published.

Broad category	Intervention	Reference	Comments
a. Topical treatments	Piperine	(Faas et al., 2008)	Combination of piperine and UV showed induced marked pigmentation response in mice, which support its potential use in treating vitiligo (Faas et al., 2008).
b.Phototherapy	*Helium neon Laser; Helium neon Laser plus tacrolimus*	(Wu et al., 2008)	Helium laser is a gas laser, which operates in the red spectrum and is the latest invention for treating vitiligo combined with topical treatments such as tacrolimus (Wu et al., 2008, Whitton et al., 2010).
	PUVB	(Mofty et al., 2001)	One study, non-randomised (Whitton et al., 2010), suggested that the use of psoralen plus broadband UVB is as effective as PUVA in the treatment of vitiligo. However, the long-term side effects of psoralen plus UVB are unknown (Mofty et al., 2001).
c. Oral treatment	Oral Ginkgo Biloba plus NB-UVB; Vitamin E plus NB-UVB	Alghamdi 2009 (on-going study: ClinicalTrials.gov NCT01006421; (Elgoweini and El Din, 2009)	It has been suggested that oral vitamin E may represent a valuable adjuvant therapy to NB-UVB (Elgoweini and El Din, 2009).

It is clear from the above tables that over the years, a large number of procedures and interventions have been tried. It total, 82 interventions have been studied over a period of 43 years (1967-2010). To summarise, there is a tendency towards exploring combinations of interventions and invention of new techniques, without properly exploring the currently used interventions such as topical corticosteroids, tacrolimus and NB-UVB. Current clinical recommendations for vitiligo that is limited to only a few patches include treatment with topical agents such as corticosteroids and calcineurin inhibitors, and localised NB-UVB phototherapy such as excimer laser. For more extensive or spreading disease, whole body NB-UVB phototherapy is recommended. Surgical treatments are reserved for stable vitiligo and especially for vitiligo that is non-responsive to previous treatments areas. Surprisingly, the only licensed treatment for vitiligo at the moment is cosmetic camouflage (Gawkrodger et al. 2010).

In addition, a large national study of 1023 patients in Germany assessed the clinical features, treatment outcomes and satisfaction in patients with vitiligo. The study showed that most of the patients with vitiligo have already experienced a broad spectrum of interventions; however the most frequently prescribed treatments, such as topical corticosteroids and vitamin D analogues as well as surgical transplantation were

rated mostly negatively. Only a few therapies were considered to be beneficial from a patients' perspective. Surprisingly, the pseudocatalase with Dead Sea climatotherapy and cosmetic camouflage were the most valued interventions. The study concluded that there is a great need for beneficial options for the treatment of vitiligo and for continuing medical education of doctors, in prescribing appropriate treatment while supporting the psychological needs of their patients (Radtke et al., 2010).

Finally, the recently updated Cochrane systematic review 2010 revealed that no firm clinical recommendations for the treatment of vitiligo can be made. Fifty seven RCTs with 3,139 participants have been analysed, however most of the trials had fewer than 50 participants and few lasted longer than 6 months (Whitton et al., 2010). It was not possible to conduct meta-analysis of any of the included interventions due to heterogeneity of trial design (Whitton et al., 2010).

The "Implications for research" section of this Cochrane Review, comments on the issues around research into vitiligo and suggestions are made to overcome these in light of the evidence that has been summarised (Gonzalez and Williams, 2011).

The major issues around vitiligo trials have been identified as (Whitton et al., 2010):

1. Lack of consensus on the classification and definition of vitiligo

2. Lack of consensus on the methods of assessment and outcome measures of vitiligo

3. Large heterogeneity of interventions compared

4. Need for a large definitive trial on combination phototherapy treatments

In conclusion, my research addresses most of the above mentioned issues (Table 1.9). As mentioned at the beginning of this chapter, international efforts have been made to address the issue of classification of vitiligo.

Table 1.9 Summary of research described in this thesis, in light of issues identified by the Cochrane Systematic review 2010

Chapter	Title of chapter	Brief outline of chapter	Issue identified by the Cochrane review 2010
1	Introduction and Background	Literature review on vitiligo. Issues around vitiligo research	
2	Future research into the treatment of vitiligo: where should our priorities lie?	Priority Setting Partnership amongst patients and clinicians aiming to identify the Top 10 important uncertainties on the treatment of vitiligo	Large heterogeneity of interventions compared
3	Which outcomes should be measured in future vitiligo trials?	A systematic review of outcomes used in RCTs and a survey of patients' and clinicians' views	Lack of consensus on the outcome measures of vitiligo
4	Hi-light pilot trial for vitiligo	A pilot randomised controlled double blind multi-centre trial on home hand-held phototherapy for the treatment of vitiligo	Need for a large definitive trial on combination phototherapy treatments
5	Impact of my research	Reflection on the above and implications on future vitiligo trials such as application for a national multicentre RCT. Personal academic achievements and transferable skills learned	As above

In conclusion, there is a great need for international consensus on the future research agenda and core outcome measures for vitiligo. The former and the latter could be used in future trials in order to gather and steer the efforts of clinicians and researchers all over the world towards aspects important to both patients and clinicians. It is sad and disappointing that no large, well conducted trials have yet been conducted on any of the current available treatments for vitiligo.

Finally, the aetiology and pathogenesis of vitiligo remains unclear. It is still not understood what causes the destruction of melanocytes (Chapter 1.6, page 33). Also, uncertainties remain about the natural history and epidemiology of this disease (Chapter 1.8, page 43). If a cure for vitiligo is to be found, further research is required in understanding the aetiology, epidemiology and natural history of vitiligo. Current treatments help to alleviate symptoms i.e. temporary repigmentation of vitiliginous patches, but these do not cure the underlying disease.

CHAPTER 2: FUTURE RESEARCH INTO THE TREATMENT OF VITILIGO. WHERE SHOULD OUR PRIORITIES LIE?

Abstract

Background

A recently updated Cochrane systematic review "Interventions for vitiligo" showed that the research evidence for treatment of vitiligo is poor, making it difficult to make firm recommendations for clinical practice.

Objective

The aim of the vitiligo Priority Setting Partnership was to stimulate and steer future research in the field of vitiligo treatment, by identifying the ten most important research areas for patients and clinicians

Methods

The vitiligo Priority setting Partnership was established and included patients, healthcare professionals and researchers with an interest in vitiligo. Vitiligo treatment uncertainties were gathered from patients and clinicians, and then prioritised in a transparent process, using a methodology advocated by the James Lind Alliance.

Results

A total of 660 treatment uncertainties were submitted by 460 participants. These were reduced to a list of the 23 most

popular topics through an online / paper voting process. These 23 topics were then prioritised at a face-to-face workshop in London. The final list of the top ten treatment uncertainties, included interventions such as systemic immunosuppressants; topical treatments; light therapy; melanocyte-stimulating hormones (MSH) analogues; gene therapy; and the impact of psychological interventions on the quality of life of vitiligo patients.

Conclusions

The top ten research areas for the treatment of vitiligo provide guidance for researchers and funding bodies, to ensure that future research, answers questions that are important to both clinicians and patients.

2.1 Introduction

2.1.1 Why set priorities in vitiligo?

Eighty two interventions for vitiligo have been evaluated in clinical trials over the last 43 years. However, due to the small numbers of participants and heterogeneity of design of trials to date, it is difficult to make firm recommendations for clinical practice (Whitton et al., 2010). Indeed, in the face of so many treatment options and with so little information regarding their relative efficacy, it is difficult to identify which clinical trials are most important and timely.

In order to address this concern, the Vitiligo Priority Setting Partnership was established, with the aim of helping to identify:

i) Which interventions should be evaluated?

ii) What the most important topics are to patients and clinicians?

iii) Could these topics be answered by clinical research?

2.1.2 Why involve patients and doctors in clinical research?

It is increasingly recognised that patients and healthcare professionals have a key role to play in identifying important areas for research. The James Lind Alliance (JLA) is a

Department of Health and Medical Research Council funded initiative, which has been established to bring patients and clinicians together in 'Priority Setting Partnerships' to identify and prioritise the unanswered questions that they agree are most important (Chalmers, 2004). The pharmaceutical and medical technology industries and academia play an essential role in developing new treatments (James Lind Alliance, 2010). However, the priorities of industry and academics are not necessarily the same as those of patients and clinicians. For this reason many areas of potentially valuable research are neglected. Therefore, it is essential that researchers and funding bodies are aware of the needs of patients and clinicians (James Lind Alliance, 2010).

Vitiligo Priority Setting Partnership (PSP) was the first priority setting partnership in the field of dermatology and the third of its kind to have been convened by the JLA. Previous partnerships have been conducted in the fields of asthma (James Lind Alliance, 2010) and urinary incontinence (Buckley et al., 2010).

All the uncertainties identified by the priority setting partnerships are added to the Database of Uncertainties about the Effects of Treatments (DUETs) (http://www.library.nhs.uk/duets/), in order to provide reference for funding bodies and researchers. Research

funding bodies in the UK, systematically scan important research resources to identify evidence gaps and make recommendations for research. This includes Cochrane systematic reviews and more recently DUETs.

DUETs has been established in the UK to publish uncertainties about the effects of treatment which cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence. A treatment uncertainty exists when "no up-to-date systematic review exists, or up-to-date systematic reviews show that uncertainty continues" (Lloyd et al., 2006), i.e. more research needs to be done to establish the effectiveness and safety of an existing or innovative treatment modality.

2.2 Methods

The aim of the vitiligo PSP was to reduce the number of uncertainties surrounding the treatment of this condition and to steer future research to questions of importance to both people living with the disease and people treating the disease. The James Lind Alliance provided guidance and support in conducting this PSP and played a role of facilitator to ensure the transparency and fairness of the process. The vitiligo PSP had 5 stages and adopted the methods advocated by the JLA

(James Lind Alliance, 2010) (Figure 2.1). I coordinated the vitiligo PSP, refined and complemented their current guidelines to meet the needs of this particular PSP and provided an important insight into their methodology. Stakeholders included professional organisations and patient support groups as outlined below.

2.2.1 Stage 1: Initiation

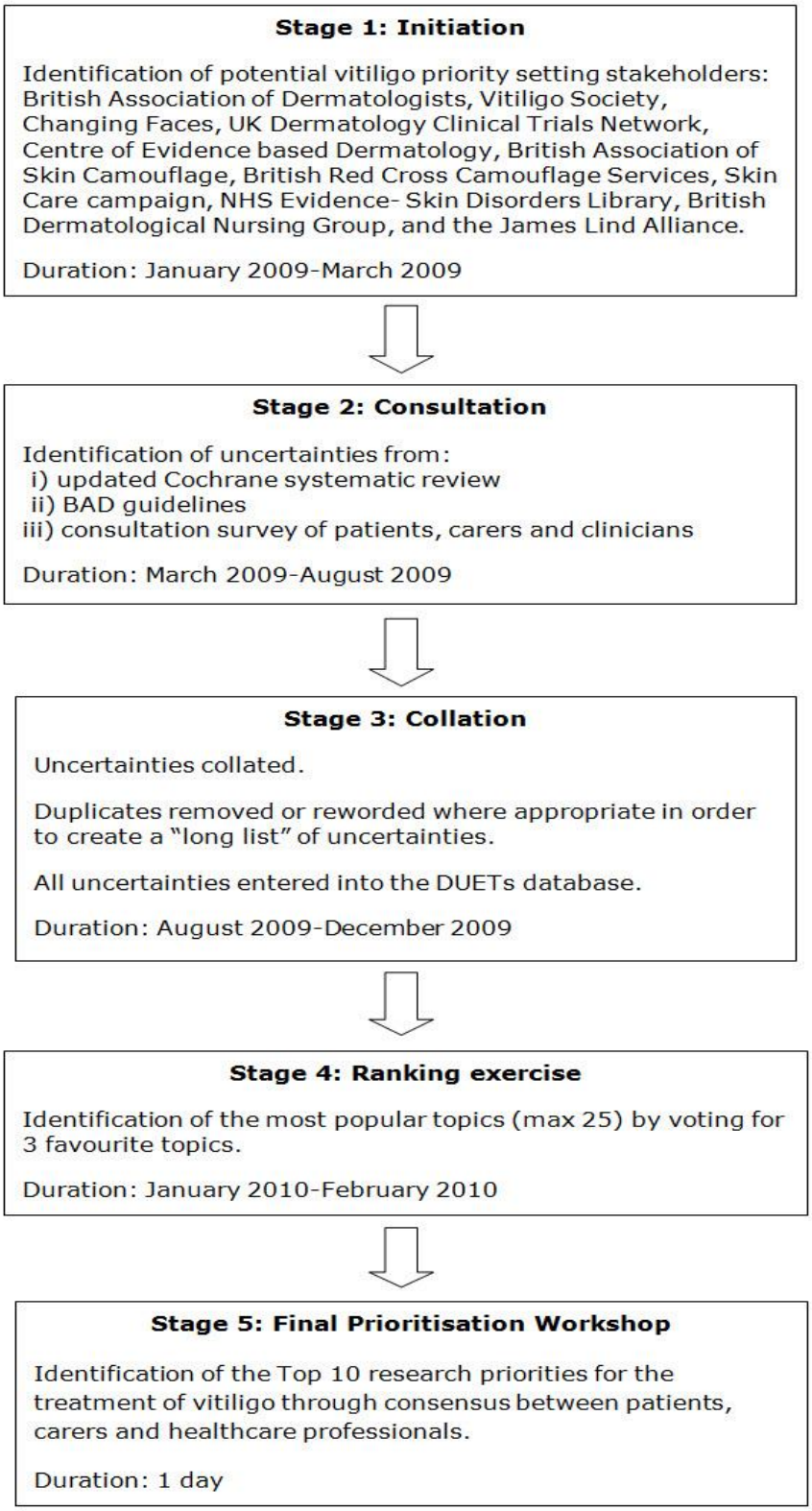
The aim of this stage was to establish the vitiligo PSP by raising awareness, identifying and engaging potential stakeholders.

To raise awareness and to build the PSP, relevant professional bodies and patient support groups were approached during this stage: British Association of Dermatologists (BAD); UK Dermatology Clinical Trials Network; NHS Evidence-Skin Disorders; Cochrane Skin Group; British Dermatological Nursing Group; Changing Faces; British Red Cross Camouflage Service; Skin Care Campaign; Primary Care Dermatology Society; Vitiligo European Task Force; British Association of Skin Camouflage and Vitiligo Society. Individual researchers, dermatologists, specialist nurses and psychologists with a special interest in vitiligo, were also informed. An invitation to participate was sent to the above relevant organisations and individuals. Representatives of interested organisations and

individual clinicians signed a response slip declaring their intention to take part in the process. The organisations were acting as advocates for their members; however it was essential that individuals with vitiligo (and their parents/carers), directly participated in the PSP process. In order to recruit these individuals, organisations advertised the PSP through various communication channels, such as articles in their newsletter (the Vitiligo Society UK) and adverts on their website (the Vitiligo Society UK and the Changing Faces). Information on the PSP was also available on the website (www.vitiligostudy.org.uk).

Organisations were excluded from participating if they were considered to have conflicts of interest that may affect their views (Buckley et al., 2007).

Figure 2.1 Summary of methods of the vitiligo Priority Setting Partnership



The vitiligo PSP Steering group was established and included 12 members with knowledge and interest in vitiligo and representatives of relevant organisations such as the British Association of Dermatologists, the UK Dermatology Clinical Trials Network, the Vitiligo Society, the NHS Evidence-Skin Disorders, the Cochrane Skin Group, the British Dermatological Nursing Group, Changing Faces, James Lind Alliance, and the Centre of Evidence Based Dermatology (CEBD) (see acknowledgment section). The role of the Steering Group was to oversee the overall development of the process, to advise on the direction and implementation of the research project, to ensure transparency and to resolve any disputes arising from differences of opinions, and generally to address any issue with major implications for the project. Initiation stage took place from August 2008 until February 2009.

2.2.2 Stage 2: Consultation

The aim of this stage was to collect treatment uncertainties. An online and paper survey was undertaken that encouraged patients and clinicians to submit their questions about the treatment of vitiligo (see appendix 1, vitiligo survey for the vitiligo Priority Setting Partnership).

Literacy skills were considered when developing this survey and consequently they were designed to be simple in reading ability. The information sheets were designed to be easy to understand and provided the names of the investigators. They also outlined the importance of the study, what the study involved, the voluntary nature of the study, the complaints procedure, the confidential and anonymous nature of the research (Oppenheim, 2000), when and where the results of the study will be published, the name of the organisation commissioning the study and the organisation undertaking the study.

Completing the survey was considered consenting to participate in the research and for allowing the uncertainties provided to be published on DUETs.

Basic demographics on participants such as age, sex, relation to the subject (patient, clinician, parent or carer of child with vitiligo) were also gathered. Participants were assured of anonymity.

All data were stored safely and securely. Electronic files were password protected and hard copies of data (e.g. surveys) were stored in a locked filing cabinet, with only the investigators directly involved in this study having access, in accordance with the Data Protection Act (1998).

Surveys were chosen as the data collection method rather than structured interviews or focus groups, because there was no potential for interview bias (Grey, 2004) or interview effects (Aldridge, 2001). Furthermore, because the researcher did not have to be present whilst the survey was completed, the sample could be drawn from a wide geographical area (Aldridge, 2001). For practical and ethical reasons, the parents of children with vitiligo were asked to complete the survey on their child's behalf.

It was anticipated that approximately 100 individuals would be recruited to take part in this study. Ideally, random selection of participants would have been used; however time constraints, budgets and the sample to be recruited, meant that this was not plausible. Consequently, the sample was recruited utilising a combination of sampling methods, including volunteer sampling, purposive sampling and convenience sampling. Volunteer sampling involved recruiting participants that responded to an advert in a newsletter or on a website of relevant organisations as above and volunteered to take part (Grey, 2004). Purposive sampling, involved selecting a sample with attributes of interest to this PSP (Aldridge, 2001). In other words, articles were placed in newsletters and on websites targeting the population of

interest i.e. patients with vitiligo and their carers and clinicians with interest in this disease.

Convenience sampling, consisted of deliberately targeting and selecting participants (Aldridge, 2001). Individuals with vitiligo who were in contact with the CEBD and the JLA previously, were directly contacted, informed of the study and asked if they would like to participate. These sampling methods were chosen in order to recruit as larger sample as possible from the population of interest.

Therefore, paper copies of the questionnaire and participant information leaflets with a stamped addressed envelope were sent to the Vitiligo Society (n = 1268) and to the British Association of Dermatologists (n = 835). Emails were sent to members of the UK Dermatology Clinical Trials Network (n = 500), and details of the project (with link to the online survey www.vitiligostudy.org.uk) were advertised on the websites and in the newsletters of the relevant organisations listed above.

Additional treatment uncertainties and research recommendations were identified from existing sources of current evidence: updated Cochrane systematic review 2010 " Interventions for vitiligo" (Whitton et al., 2010) and the BAD guidelines for diagnosis and management of vitiligo

(Gawkrodger et al., 2008). The consultation stage took place from March 2009 to the end of August 2009.

2.2.3 Stage 3: Collation

The aim of this stage was to create a "long-list" of uncertainties by collating, refining submitted uncertainties and rewording similar questions following the methodology below:

- Step 1: creation of taxonomy based on currently known interventions.

  Before going through each submitted question individually, a list of know existing treatment options i.e. treatment taxonomy was created. The vitiligo PSP taxonomy was based on the Cochrane systematic review 2010 "Interventions for vitiligo". The main categories of interventions were adopted from the "description of intervention" section of the review and included phototherapy, systemic (oral) treatments, topical treatments, complementary treatments, combination treatments and other treatment modalities. Other main categories included diet and lifestyle, vitamins and supplements and complementary/alternative treatments. After the main categories were created, subcategories were added to each one of these (Table 2.1).

Table 2.1 Examples of main categories and subcategories for vitiligo PSP.

Main category	Subcategories
Phototherapy (light therapy)	Narrow Band-UVB
	Broad Band-UVB
	UVA
	PUVA
	PUVAsol
	Excimer light
	Other light therapies
Psychological interventions	Cognitive Behavioural Therapy
	Group therapy
	One to one therapy
	Other psychological interventions
Diet and lifestyle	Diet
	Lifestyle
Other treatments	Gene therapy
	Stem cells
	Other treatments

- Step 2: allocation of originally submitted uncertainty to the created taxonomy.

  Each submitted uncertainty was allocated into at least one of the previously created categories.
- Step 3: confirmation that submitted question was an uncertainty.

All uncertainties were checked against the existing systematic review and the BAD guidelines to ensure that they had not been answered already.

- Step 4: exclusion of non-treatment uncertainties.
  Non-specific questions, statements and questions about prevention, aetiology or genetics of vitiligo were excluded (Table 2.2).
- Step 5: long list of indicative uncertainties
  An indicative uncertainty was defined as a refined and rephrased uncertainty which combined two or more of originally submitted uncertainties covering the same or similar topic. Each indicative uncertainty, represented a broad area for research, rather than focussing on a specific research question. This was necessary in order to reduce the list of uncertainties to a manageable number (Table 2.3). Duplicate submissions were combined, but their frequency and source was recorded.

Table 2.2 Examples of non-treatment uncertainties

Originally submitted uncertainty	Reference to
What is the cause of acquired vitiligo?	Aetiology
Which is the best method/treatment available to aid repigmentation?	Non-specific
Why patchy distribution?	Non-specific
The source of the disease: is it viral, genetic or environmental? Why is it only certain patterns occur in some areas of body?	Aetiology and distribution
What makes vitiligo become active after being stable for many years?	Triggering factors/Spreading
Can you diagnose the condition or the faulty gene in an unborn child?	Genetics
My personal opinion: stress appears to exaggerate depigmentation Is there any evidence of this and if stress relief eases the condition?	Aetiology/Triggering factors
GP/Dermatologists views on treatments available for vitiligo is usually negative.	Guidance needed
I have tried UVB light treatment for 4 years and went to Dead Sea in Jordan…… I had good improvement on the face but rest of the body still same (no change).	Statement

Table 2.3 Examples of formatting originally submitted questions into indicative uncertainties in vitiligo PSP.

	Originally submitted uncertainty	Indicative uncertainty 1	Indicative uncertainty 2	Comments
1	What foods/vitamins help?	What role does diet play in the management of vitiligo?	What role do vitamins and supplements play in the management of vitiligo?	Reference made to two interventions
2	Topical tacrolimus plus light	How effective is UVB light when combined with creams and ointments for the treatment of vitiligo?		Due to the large number of combinations of UVB and topicals, these were combined
3	Steroids plus NB-UVB			
4	Is long term tacrolimus ointment safe and effective for vitiligo treatment?	Are calcineurin inhibitors effective?	Are there any side effects associated with using topical calcineurin inhibitors for the treatment of vitiligo?	Reference made to effectiveness and safety
5	Do calcineurin inhibitors really work?			
6	How long should patient use tacrolimus to treat vitiligo?	What is the optimal duration and optimal timing for the treatment of vitiligo with tacrolimus?		
7	How often does (super) potent steroid or tacrolimus result in useful repigmentation?	Which treatment is more effective: steroid cream or tacrolimus/pimecrolimus?		Due to the large number of combinations of various strengths of topical steroids
8	How does tacrolimus			

	compared to steroid?		and calcineurin inhibitors, these were combined
9	Effectiveness or potent topical steroid or Protopic RCT: potent steroid vs. Protopic vs. placebo		
10	My grandmother had her thyroid removed and I have heard there may be a link between thyroid problems and vitiligo. Are there tests and treatments linked to this that could be further investigated? Is there any evidence that people with vitiligo who have also been treated for thyroid problems see any improvement in their skin?	Does the treatment of underlying autoimmune condition in patient with vitiligo is of any benefit?	Autoimmune conditions include thyroid problems, diabetes etc.
11	Is there link to other conditions such as thyroid, diabetes that prescribed medicines could help?		

- Step 6: Dealing with non-specific uncertainties.

  Non-specific uncertainties mainly referred to a group of interventions. Being too broad, they could not be translated into meaningful indicative uncertainties, they were counted. This information assisted during the final workshop (Table 2.4).

Table 2.4 Examples of non-specific treatment uncertainties and their count information.

Non-specific indicative uncertainties	Count	Source
Effectiveness of light therapy for the treatment of vitiligo	32	Systematic review, Vitiligo Society, British Association of Dermatologists
Surgical procedures for vitiligo	11	British Association of Dermatologists
Which is the most effective topical treatment?	10	Systematic review, British Association of Dermatologists
Optimal maintenance regime after light therapy	3	Systematic review, Vitiligo Society, British Association of Dermatologists
Safety of topical treatments	1	British Association of Dermatologists

Throughout the process, the Steering Group members conducted ten teleconferences in order to resolve disputable issues such as whether a submitted question should be excluded or which category it fits best. All indicative uncertainties i.e. "long list" were entered into a spread-sheet and into DUETs. Collation stage took place between August 2009 and December 2009.

2.2.4 Stage 4: Ranking exercise (Interim prioritisation exercise)

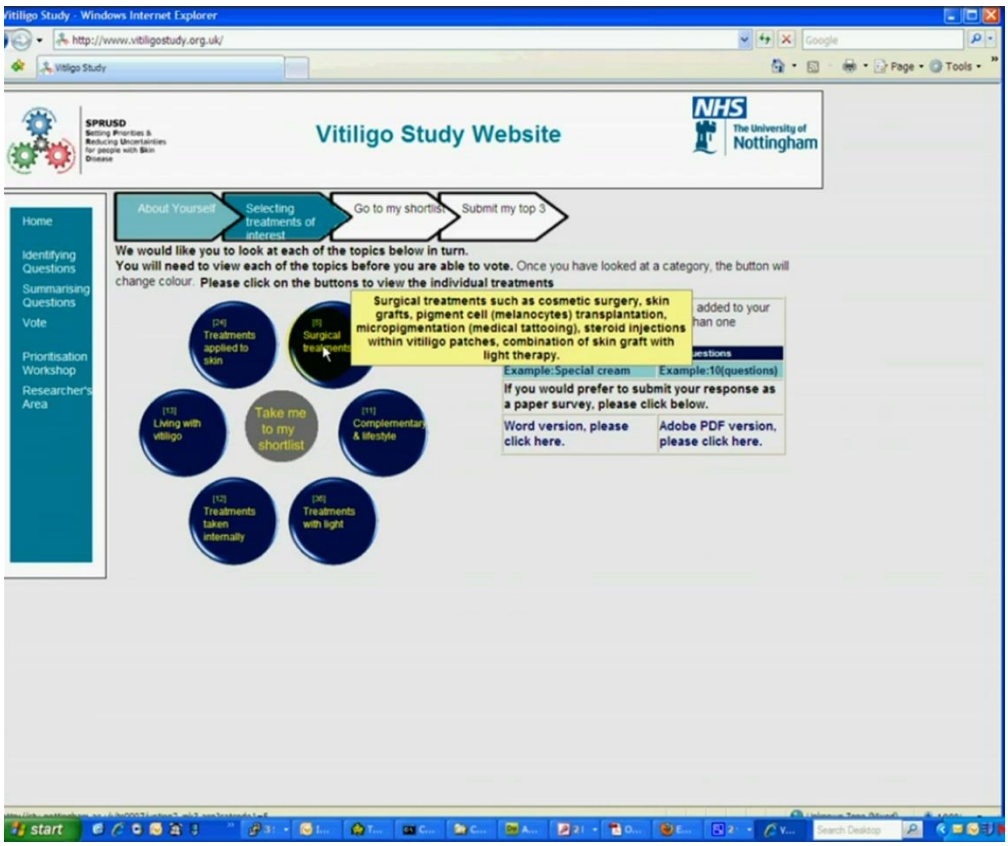
The aim of the ranking exercise was to create a "short-list" of uncertainties for the final prioritisation workshop and to reduce their number to no more than 23. As the majority of participants from the consultation stage expressed a

willingness to engage in the process further, a link to the website (www.vitiligostudy.org.uk) was sent via email to those people. The ranking exercise was also advertised on the websites and in the newsletters of relevant organisations, as per the consultation stage. In addition, advertisements and articles were placed in the Voice magazine for black and ethnic minorities, the British Dermatological Nursing Group magazine (Eleftheriadou et al., 2009) and the bulletin of the Primary Care Dermatology Society (Eleftheriadou, 2009) to target specific groups that had been under-represented during the consultation stage. Advertisements were also disseminated to attendees of the Royal Society of Medicine meeting "Medicine and Me: vitiligo".

2.2.4.1 Ranking website

During the ranking exercise, a specific study website was developed (www.vitiligostudy.org.uk) to allow participants to rank uncertainties online. An innovative voting system was conceived by myself and developed with IT support from the University of Nottingham. All the uncertainties for the ranking exercise were written in a patient-friendly format making them comprehensive for participants without clinical or scientific background. The voting system was piloted before going online.

All uncertainties from the "long list" were divided into 6 broad categories based on the taxonomy created during the collation stage. These broad categories were displayed in a circle on the first page of the website (Picture 2.1).

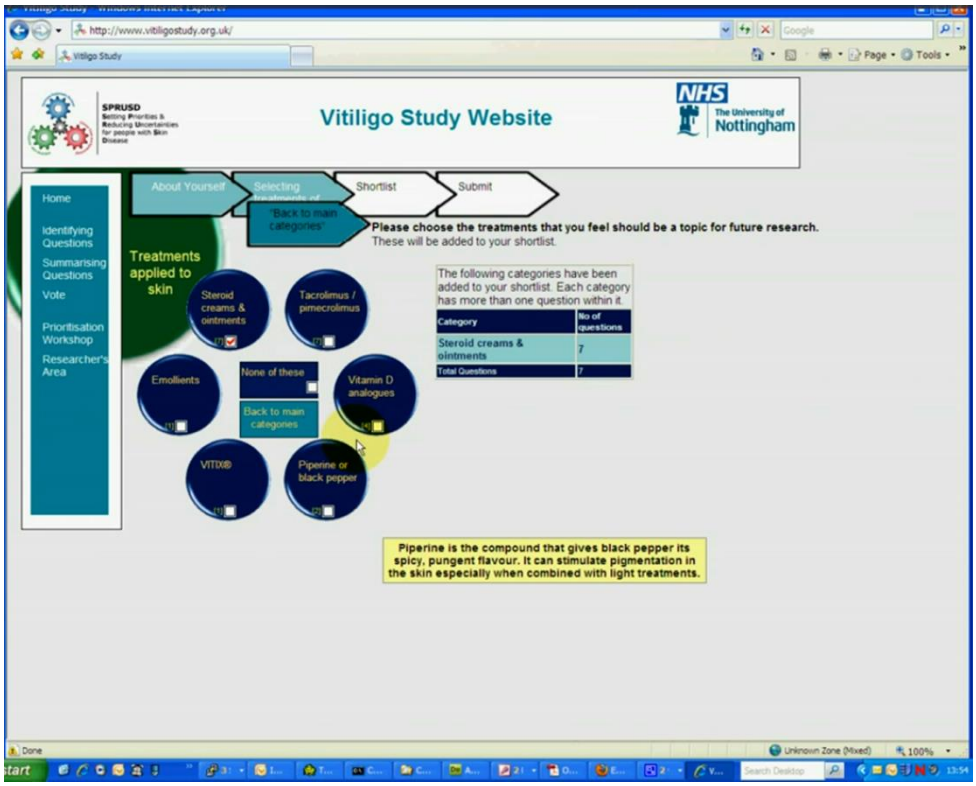


Picture 2.1 Ranking website: broad categories displayed in a circle. The mouse arrow is placed on the surgical treatments category and the yellow box contains the pop up help text on the same category.

Displaying categories in a circle was used to guard against selection bias, which might have been an issue if the broad categories were put into a list. The order in which the categories were displayed was random every time a new

participant entered the website. Instructions on how to vote and information on the vitiligo PSP was also available on the website. A demonstrating video (http://www.youtube.com/watch?v=VeWl6RPjYxU) was also available on the website.

Help text, with brief information on treatment modalities which were included in each broad category appeared by placing the mouse arrow on each category. By clicking on each broad category, participants were able to review all treatment modalities included in more details. These treatment modalities were also displayed into a randomly rotating format same as the broad categories (Picture 2.2).

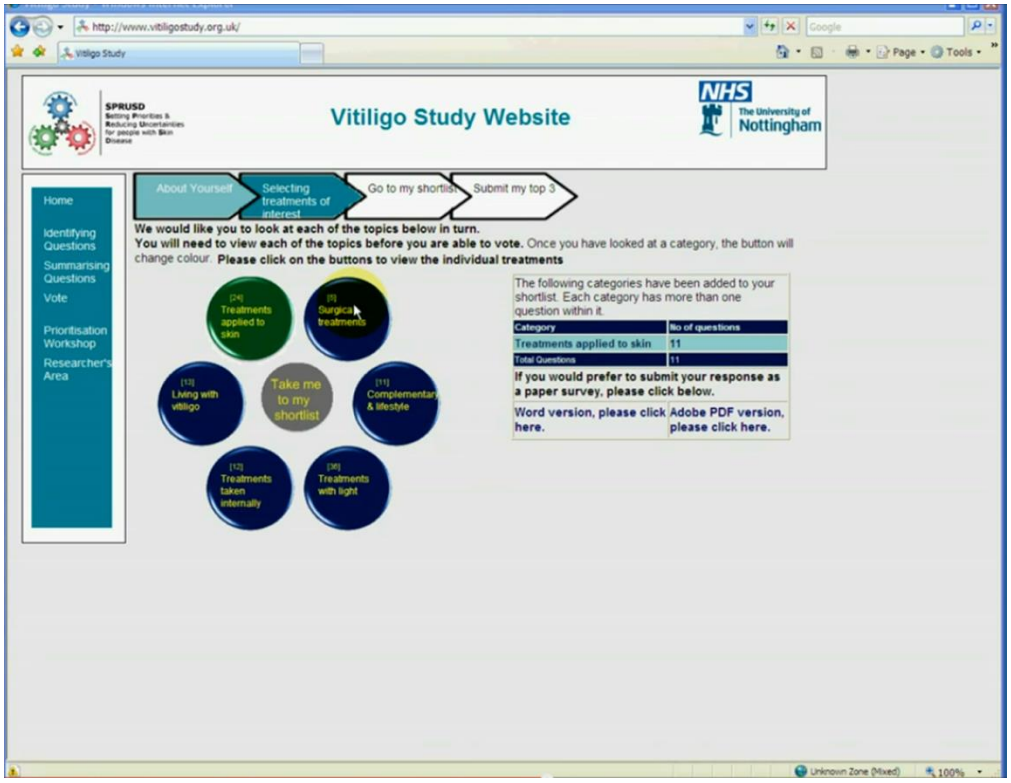


Picture 2.2 Ranking website: treatment modalities included in the topical treatments (treatments applied to skin) category. The mouse arrow is placed on the piperine/black pepper subcategory. The yellow box contains pop up help text on piperine.

Alongside popular and widely used treatment modalities such as topical corticosteroids, other less known interventions such as melagenina were also included in the long list; therefore it was important that participants were familiar with all of the proposed treatments before voting.

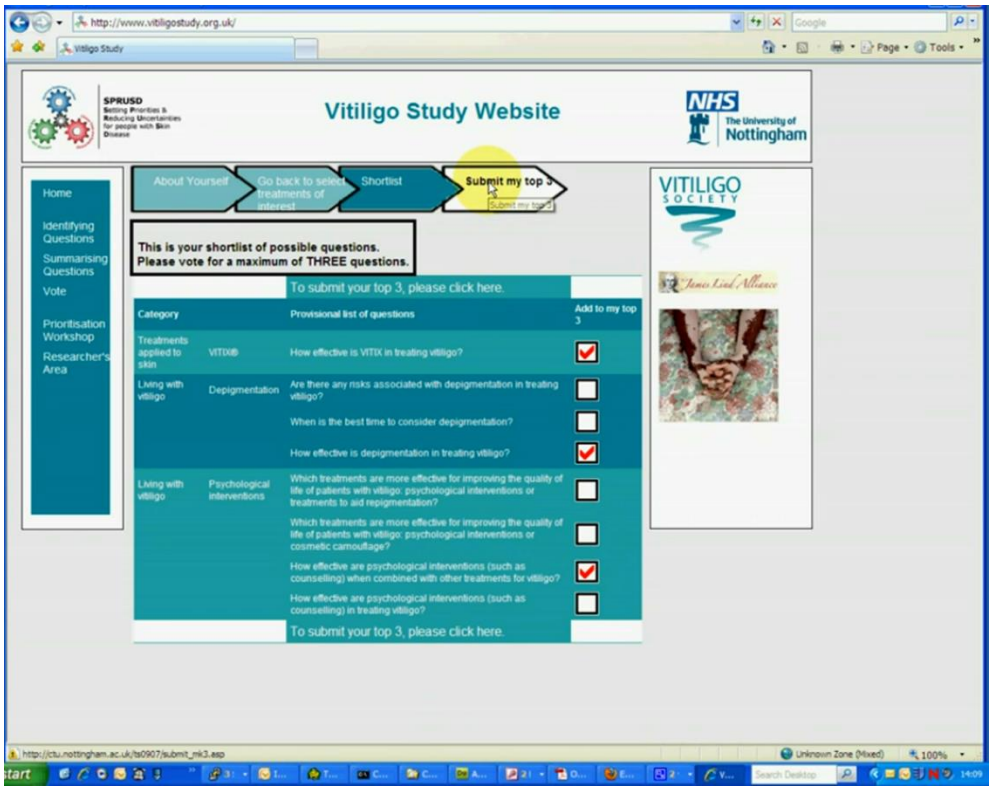
In order to ensure that and to avoid "targeted voting" i.e. viewing only one or two broad categories, which interested participants more or were more familiar to them and ignoring the rest of the categories, it was mandatory to view all six

broad categories (by clicking on them) before voting. In order to assist the participants in keeping track of which main categories they had already reviewed, the category button changed colour indicating that it was accessed (Picture2.3).



Picture 2.3 Ranking website: topical treatments (treatments applied to skin) broad category changed colours from blue to green indicating that this category was accessed.

After clicking on all 6 broad categories and choosing the intervention of their choice, participants were able to review specific uncertainties surrounded each intervention and vote for up to 3 selected uncertainties (Picture 2.4).



Picture 2.4 Ranking website: three uncertainties selected

Paper copies of the questionnaire were also available to download from the website, or by contacting the study team directly. The order in which uncertainties appeared on the paper survey was randomised in order to guard against response bias.

People responding to the survey were asked to complete their demographics details. The same demographic questions were recorded as per consultation stage of survey including age, sex, and relation to the subject (patient, clinician, parent or carer of child with vitiligo). The Steering Group recommended the inclusion of ethnicity question at this stage

as it was important to know the ethnic grouping of participants for this work, given the nature of the condition.

The online and paper votes were pooled together for the final meeting of the Steering group. The aim of the meeting was to review the results of the ranking exercise and "short list" the Top 23. In order to ensure that short listing for the final priority setting workshop was well balanced and representative of all groups, the list of Top 25 uncertainties for each representative group (healthcare professionals, patients and black and ethnic minorities) were also reviewed.

The ranking exercise was open for a period of one month, from January 2010 until February 2010.

2.2.5 Stage 5: Final Prioritisation Workshop

The aim of this workshop was to identify the top ten most important treatment uncertainties for vitiligo by creating consensus through a face-to-face meeting of healthcare professionals and patients. Members of the Steering Group and participants from the ranking exercise attended the final prioritisation workshop. A participant pack was prepared for each attendee and included: glossary of research terms, background information on vitiligo PSP including the aim of the Final Prioritisation Workshop and agenda of the day.

In preparation for the workshop, cards were made for each shortlisted uncertainty. Each card included detailed information on each of the 23 uncertainties: a list of original submitted uncertainties, which were later merged into this one uncertainly and whether the uncertainty was featured in the systematic review or guidelines for vitiligo or the top 25 for patients, clinicians, black and ethnic minorities groups.

Efforts were made to ensure that equal numbers of patients and healthcare professionals attended. The workshop was a full day event, held at the London offices of the British Association of Dermatologists on 25th March 2010 (Picture 2.5).

Consensus was reached by using a nominal group technique (James Lind Alliance Guidebook 2010). The participants were separated into four small groups comprising a mixture of healthcare professionals and patients. Initially, the groups shared their reflections on the shortlisted uncertainties and submitted their personal rankings.

The groups were then asked to place the uncertainties in order of priority. The ranked uncertainties from each group were reported to the facilitator and pooled to give an aggregated score for each uncertainty. The aggregate scores were then revealed to the groups and discussed again. Groups

were again asked to agree their top ten uncertainties, in light of the previous discussions, and these were pooled to achieve a revised and final list that was agreed by all participants (Picture 2.6).

Picture 2.5 Final prioritisation workshop at the British Association of Dermatologists House, London, UK

From left up to right down: Dr Viktoria Eleftheriadou; group of attendees; Mrs Sally Crowe-Independent JLA advisor and Chair of the Steering Group; Mrs Jennifer Viles-Chair of the Vitiligo Society UK (patient support group)

Picture 2.6 Fours groups of participants during the final prioritisation workshop at the British Association of Dermatologists House, London, UK

The above methods used during the vitiligo Priority Setting Partnership, as well as previous PSPs are outlined in the James Lind Alliance guidebook (http://www.jlaguidebook.org/).

2.2.6 Personal contribution

The initiation of the process was already in place when I commenced the post of Research Associate at the Centre of Evidence Based Dermatology (CEBD) (August 2009). Representatives of the JLA, as well as my predecessor had established the Steering group and contacted relevant organisations, as above. I took over the project since then,

amended the original protocol in light of submissions from the consultation stage. I undertook all the tasks from processing the uncertainties, creating the taxonomy and the step by step approach described above, to inputting the final "long list" into a spread-sheet, ready for uploading on DUETs database.

Also, I conceived and developed the innovative voting system, the text and the demonstration video for the vitiligo study website. I worked closely with IT support team to bring my idea and vision into practice and developed a user-friendly, easy to navigate website.

Finally, I analysed all the data from all stages of the PSP, organised and prepared the necessary material and played a role of organiser and facilitator during the Final Prioritisation workshop.

2.2.7 Ethics

This project was approved by the Medical School Research Ethics Committee, University of Nottingham, UK. Ethics Reference No: G/2/2009

2.2.8 Statistical methods

We aimed for a minimum of 100 participants in the consultation and the ranking exercise and for 20 participants

for the final prioritisation workshop. This sample size was estimated on the basis of previous JLA priority setting partnerships (Elwyn et al., 2009), and determined by the timeframe available for the vitiligo PSP. Data from all stages were stored and analysed in MS Access 2007.

2.3 Results

2.3.1 Stages 2 and 3: Consultation and collation

The response rate for members of the Vitiligo Society was 24% (307/1268) and for BAD/UKDCTN members was 14% (119/835). Sixty-six per cent of responses (302/461) were from patients, 31% (142/461) were from healthcare professionals, and 3% were from other sources. More women responded than men (53% women, 30% men, 17% did not specify), and the majority were aged 30-60 years old (8% were <30 years, 50% were 30-60 years, 25% were > 60 years, and 17% did not specify).

Of the 2,303 surveys circulated, 461 (20%) were returned. This resulted in 1,427 questions about vitiligo. Non-treatment questions (n = 767), about the natural history of vitiligo, its aetiology and prevention, were excluded. Overall, 660 uncertainties that specifically related to the treatment of vitiligo were gathered during the consultation stage. Thirty-

one per cent were from healthcare professionals (206/660), 48.5% were from patients (320/660) and 20.5% were unknown (134/660). An additional 58 treatment uncertainties were identified from the BAD guidelines and the updated Cochrane systematic review. The resulting 718 uncertainties were refined into a "long-list" of 93 treatment uncertainties, which were used for the ranking exercise.

2.3.2 Stage 4: Ranking exercise (Interim prioritisation exercise)

In total, 230 people (patients: 72%, health care professionals: 23%, did not specify: 5%) responded to the ranking exercise, submitting 638 individual votes. Each participant voted for up to three of their favourite uncertainties. Forty one per-cent of participants (95/230) submitted their vote by completing a paper copy questionnaire, 48% (111/230) opted for online ranking and 11% (24/230) submitted their votes by submitting an electronic copy of the questionnaire.

Twenty per-cent of paper (19/95) voters were excluded as they submitted more than three favourite topics. The number of votes per uncertainty ranged from 49 to 0 (median 5). The demographic characteristics of participants in the ranking exercise were broadly similar to those in the

consultation stage (63% were women, and 55% were aged between 30 and 60 years). Of those who specified their ethnicity (n = 127), 42% were white and 12.6% were from black and ethnic minorities. At the end of this stage, 23 indicative uncertainties were identified for use in the final prioritisation workshop (Table 2.5).

2.3.3 Stage 5: Final Prioritisation Workshop

The workshop was attended by 47 people: 21 were patients or patients' representatives, 16 were healthcare professionals (including dermatologists, specialist nurses, general practitioners with specialist interest in dermatology, researchers, camouflage practitioners, and a trichologist / psychologist). In addition, 7 JLA facilitators were present, and 2 observers (one from the National Institute of Health and Clinical Excellence (NICE), and one from the National Institute of Health Research National Evaluation, Trials and Studies Coordinating Centre (NIHR NETSCC, Internal Relations Directorate) (see vitiligo PSP acknowledgement section).

By the end of the workshop, a ranked list of the top ten treatment uncertainties had been collated and agreed by consensus. In addition, two treatment uncertainties were suggested as *"ones to watch"*, as these interventions were either still in an early investigative stage, or trials were

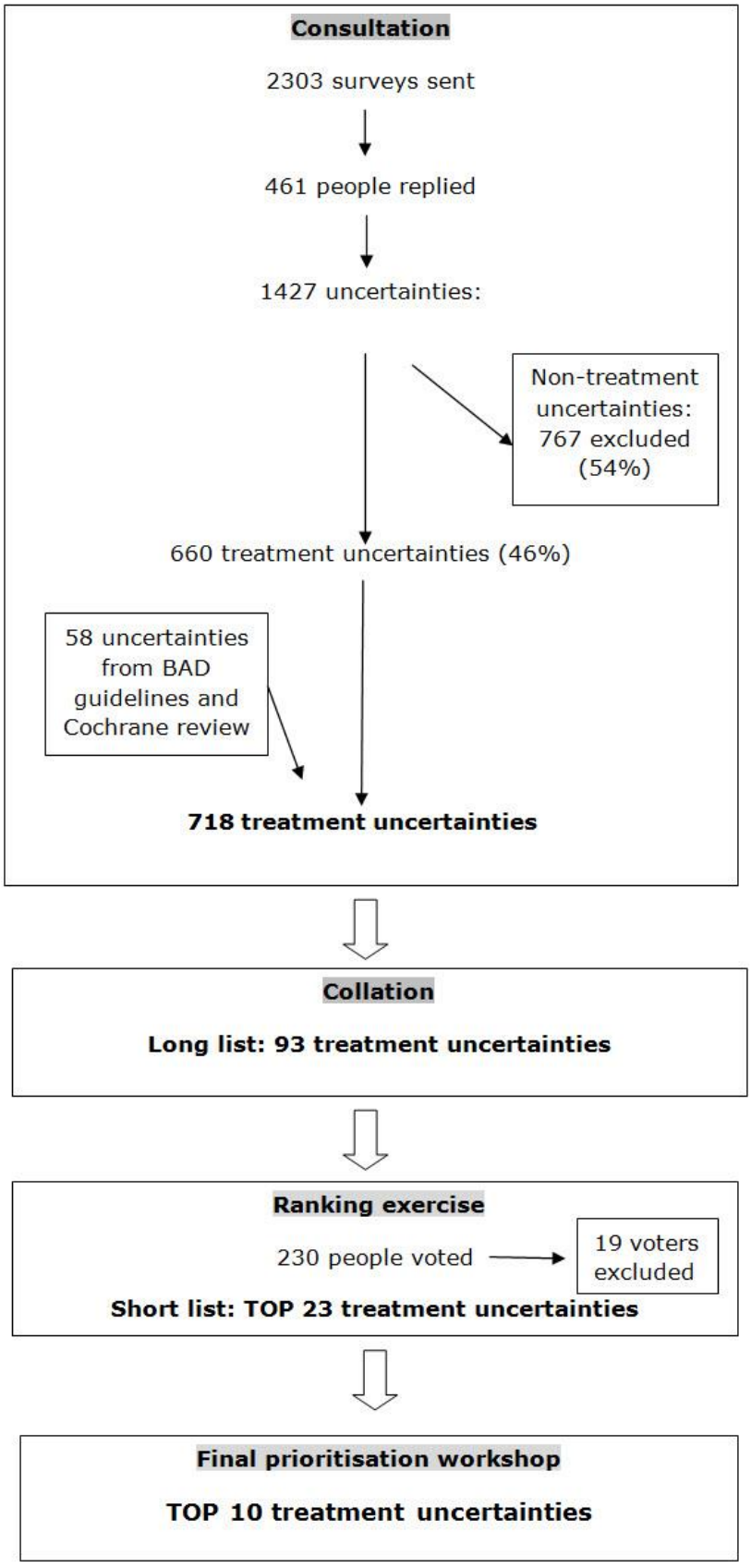
currently on-going (Table 2.5). A summary of the results of the vitiligo PSP is presented in Figure 2.2.

Table 2.5 The Top 10 and the two "to watch" treatment uncertainties (grey shading) and the raking order of all 23 treatment uncertainties (short list) for vitiligo, following the final prioritisation workshop

Rank	Indicative uncertainty
1	How effective are immunosuppressants in treating vitiligo?
2	How much do psychological interventions (such as counselling) help people with vitiligo?
3	Which treatment is more effective for vitiligo: light therapy or calcineurin inhibitors (e.g. tacrolimus, pimecrolimus)?
4	How effective is UVB light therapy when combined with creams or ointments (e.g. steroid creams) in treating vitiligo?
5	What role might gene therapy play in the treatment of vitiligo?
6	How effective are hormones or hormone related substances that stimulate pigment cells (MSH analogues, afamelanotide) in treating vitiligo?
7	Which treatment is more effective for vitiligo: calcineurin inhibitors (e.g. tacrolimus, pimecrolimus) or steroid creams/ointments?
8	Which treatment is more effective for vitiligo: steroid creams/ointments or light therapy?
9	How effective is the addition of psychological interventions to patients using cosmetic camouflage for improving their quality of life?
10	How effective is pseudocatalase cream (combined with brief exposure to UVB light) in treating vitiligo?
11	How effective is piperine (black pepper) cream in treating vitiligo? ONE TO WATCH

12	What role might stem cell therapy play in treating vitiligo? ONE TO WATCH
13	How effective is the transplant of pigment cells (autologous melanocyte transplantation) in treating vitiligo?
14	Which treatment is more effective for vitiligo: PUVA or UVB light therapy?
15	Which treatment is more effective for improving the quality of life of patients with vitiligo: cosmetic camouflage or a treatment to aid repigmentation?
16	What role do vitamins and supplements play in the management of vitiligo?
17	How much does depigmentation help patients with vitiligo?
18	What role does diet play in the management of vitiligo?
19	How effective is natural sunlight in achieving repigmentation of the skin in patients with vitiligo?
20	What role might lifestyle (e.g. stress, smoking) play in the management of vitiligo?
21	How effective are steroid injections into the skin in treating vitiligo?
22	How effective is VITIX in treating vitiligo?
23	How effective are homeopathic remedies in treating vitiligo?

Figure 2.2 Summary of the results of the vitiligo priority setting partnership



In addition, important recurring themes for researchers to consider when developing future trials on vitiligo emerged from non-specific submissions (see collation stage: step 6) and are summarised below (Table 2.6).

Table 2.6 General themes to be considered when designing future vitiligo trials.

	General themes
1.	Which treatments are effective and safe for children?
2.	Do treatment success rates differ according to the site(s) affected, or the gender/age/ethnicity/skin phototypes of patients?
3.	What are the long term outcomes of treatments for vitiligo (especially side-effects)?
4.	What is the optimal duration and optimal timing for treatments of vitiligo?
5.	What is the optimal maintenance regimen in order to prevent relapse?
6.	Interventions for segmental vitiligo

Finally, feedback following the final prioritisation workshop showed that attendees were either very satisfied (8/22) or satisfied (14/22) with the workshop outcome: "Excellent, well organised", "Format allowed for varied expertise and sharing of views and opinions", "Excellent exchange of views"," People were listened to", "A very successful day". The chair of the JLA, Mr Lester Firkin, commented on the above results: "*All of these are very good indeed - I would be thrilled if any PSP I ran came back at half*

this level." Vitiligo PSP was announced the most successful PSP so far by the JLA.

2.4 Discussion

Vitiligo has traditionally been given a relatively low priority in the dermatology research agenda, as shown by the number and quality of studies on vitiligo to date. At present, the only intervention licensed for use in vitiligo patients is camouflage, and there is an urgent need for randomised controlled trials of interventions for vitiligo (Gawkrodger et al., 2008). The updated systematic review (Whitton et al., 2010) is helpful in identifying many important research gaps for clinical trials, but these have largely come from the research community, and may not reflect the questions that patients and clinicians have.

2.4.1 Implications for research

The identified uncertainties provide a steer for future research activity by guiding researchers and funding bodies to questions of importance to patients and healthcare professionals. All of the uncertainties have been added to DUETs, and are freely available at www.duets.nhs.uk. At this point it is important to remember that the vitiligo Priority

Setting Partnership aims to identify "treatment uncertainties". These, are then used as reference to inform future "research questions" as developed by individual research teams. It is entirely possible that one treatment uncertainty will result in several related research questions.

Based on the identified most important treatment uncertainties for vitiligo, the following are recommended:

- More research on the effectiveness and safety of systemic immunosuppresants for the treatment of vitiligo such as methotrexate, cyclosporine. Research in this field would potentially contribute to our knowledge about the aetiology of the disease, which is believed to have a strong autoimmune component (Rezaei et al., 2007; Westerhof and d'Ischia 2007) (1st uncertainty).
- Evaluation of NB-UVB combination therapies with topical agents (which also reflects the current research trend). It was shown by the Cochrane systematic review that combination treatments seem to be more effective than monotherapies (Whitton et al., 2010) (4th uncertainty).
- Evaluation of the effectiveness and safety of NB-UVB. More detailed information is needed to answer questions such as "should the first line treatment for vitiligo be topical agents (topical steroids or calcineurin

inhibitors) or more aggressive intervention such as NB-UVB". A factorial trial design could evaluate all three treatment options in one trial (3rd and 8th uncertainties).

- Evaluation of currently available and widely used treatments such as topical corticosteroids and calcineurin inhibitors in a "head to head" randomised controlled trial (7th uncertainty).
- Evaluation of psychological interventions by conducting a systematic review of the current literature, and substantial pilot / and exploratory qualitative work prior to progressing to a full randomised controlled trial. Together with active treatments, psychological interventions are believed to be of great importance. More evidence is needed to establish the role of psychological support as monotherapy (2nd uncertainty), as well as in combination with other treatments for vitiligo (9th uncertainty).
- Evaluation of innovative treatments such as afamelanotide and pseudocatalase, which seem to be important and promising to both clinicians and patients (6th and 10th uncertainty). It is prudent to express some degree of scepticism regarding the effectiveness of pseudocatalase based on the up-to-date evidence. Only one pilot non-randomised controlled trial has been

published claiming the effectiveness of pseudocatalase for the treatment of vitiligo (Schallreuter et al., 2002). However, a subsequent randomised double-blind placebo-controlled trial failed to confirm previous success (Bakis-Petsoglou et al., 2009). In addition, results of a large randomised controlled trial, funded by the pharmaceutical "Stiefel", is yet to be published despite the fact that the trial was finished many years ago (personal communication with participants of the trial from the Vitiligo Society).

- More research to be done into the pathophysiology and the aetiology of the disease, based on the great interest expressed by clinicians and patients on exploration of potential effectiveness of gene therapy and stem cells (5th uncertainty and 12th "one to watch" uncertainty).

To conclude, I would like to note that by recommending the above, I am not commenting on the legitimacy of the interventions that have been prioritised, but simply reporting what clinicians and patients identified as important research topics in order to meet their needs.

2.4.2 Reflections on the process

One might argue that the response rate for the vitiligo PSP was rather low (consultation stage response rate=20%); however the number of the participants by far exceeded our expectations and approximately doubled the number of participants who took part in previous priority setting partnerships (Elwyn et al., 2009). This was mainly due to the strength of existing collaborations with the UK DCTN and the Vitiligo Society. I believe that the innovative and unusual nature of this project means that it is inappropriate to apply the same criteria for the response rate of this PSP as for other surveys.

In order to inform future Priority Setting Partnerships, it is helpful to outline the following key challenges and considerations that I faced during the management of this PSP:

- *Large number of participants*. Involving such a large number of participants in all stages of the process was extremely challenging. This was mainly due to various levels of expertise, background information, and experience of the vitiligo PSP participants. This was particularly relevant during the final prioritisation workshop, where participants were making decisions based on very different frames of reference. It is

prudent, therefore, to identify attendees of the final prioritisation workshop as soon as possible and keep them fully informed at every stage of the PSP. It would also be helpful to allow time at the start of the final PSP workshop to ensure that all participants are aware of the current evidence base for the treatment uncertainties being considered on the day.

- *Online ranking website.* Previously, the interim prioritisation stage of a PSP was done by using a paper copy of the "long list" of treatment uncertainties and asking participants to read through it and choose up to 3 uncertainties. In vitiligo PSP, with so many uncertainties involved and because I was concerned that members of the Priority Setting Partnership may not be sufficiently representative of the wider vitiligo community, I opted to develop an online ranking tool. This proved to be time-consuming and technically challenging; mainly because this hadn't been done before and it was difficult to estimate the amount of time and resources of IT personnel required to perform this task. Nevertheless, it held several methodological advantages, in that the website was open to anyone with an internet connection and an interest in vitiligo. The innovative voting system considerably reduced the number of uncertainties that

participants needed to review prior to submitting their votes, whilst still providing an overview of all the treatment modalities. Also, the website allowed us to provide far more information about the scope and aims of the project. By creating this online tool, less resources and time was required to print, pack and send paper questionnaires to the participants. Based on the voting results, roughly equal number of participants opted for paper and online ranking. However, 20% of paper votes were excluded as more than three options were submitted compared to none (0%) of online votes (as the tool did not allow submission of more than three uncertainties). Both paper and online, are suitable methods to use and both have their advantages and disadvantages. For future PSP exercises, the choice of method used will depend on the number of uncertainties created, and the availability of technical support.

- *Structure of indicative uncertainties.* Many of the originally submitted uncertainties (during consultation stage) were broad and non-specific, could imply various potential research questions, or did not specify the comparator, the duration of treatment or the population. On the other hand, some of the uncertainties derived from the systematic review, the BAD guidelines, and

individual responders, were very specific and focused. For that reason, it might be useful to keep the indicative uncertainties as broad as possible to allow flexibility but sufficiently narrow to ensure the question is meaningful. The following format for different types of questions submitted was proposed (Table 2.7).

2.4.3 Implementation of the results

The next step of my research was to conduct a pilot RCT on one of the top ten uncertainties and to work with the UK Dermatology Clinical Trials Network (UK DCTN) (www.ukdctn.org) to develop a protocol for a national multi-centre RCT.

Table 2.7 Structure used to refine the questions into indicative uncertainties.

Type of question	Format of question
Effectiveness of a single treatment	How effective is [treatment X] in treating vitiligo?
One treatment *compared to* another	Which treatment is more effective in treating vitiligo: [treatment X or treatment Y]?
One treatment *combined with* another	How effective is [treatment X] when combined with [treatment Y] in treating vitiligo?
Management of the disease, rather than "treatment" (e.g. camouflage or psychological interventions)	How much does [treatment X] help patients with vitiligo?
Speculative treatments not yet on the market (e.g. gene therapy, stem cell therapy)	What role might [treatment X] play in the treatment of vitiligo?

In March 2010, five research vignettes (Table 2.8) were submitted to the NIHR HTA prioritisation panel in order to try and influence their research agenda based on the identified topics. Following various stages of the process, two of the uncertainties (4th and 8th) were merged and the topic was advertised as an open call by the HTA, at the beginning of 2012 (see Chapter 5).

Table 2.8 Research activity and research suggestions following Vitiligo PSP (From 2007 until December 2012)

Treatment uncertainty on vitiligo	Research commissioned/notes
1. Does treatment with immunosuppressants help patients with vitiligo?	HTA suggest a case series first before trial feasibility (Oct 2010)
2. How much do psychological interventions (such as counselling) help people with vitiligo?	Submitted as an HTA vignette. Combined with 9th uncertainty: How effective is the addition of Cognitive Behavioural Therapy (CBT) to patients using cosmetic camouflage for improving their quality of life?
3. Which treatment is more effective for vitiligo: light therapy or calcineurin inhibitors (e.g. tacrolimus, pimecrolimus)?	Submitted as an HTA vignette: Is narrow band ultra-violet light therapy (NB-UVB) better than calcineurin inhibitors for the treatment of vitiligo?
4. How effective is UVB light therapy when combined with creams or ointments (e.g. steroid creams) in treating vitiligo?	Submitted as an HTA vignette. Feasibility trial on hand-held home phototherapy is now completed as part of SPRUSD Programme Grant (Chapter 4).
5. What role might gene therapy play in the treatment of vitiligo?	Too early for HTA Basic science research
6. How effective are hormones or hormone related substances that stimulate pigment cells (MSH analogues, afamelanotide) in treating vitiligo?	Clinuvel is running a small pilot multi-centre trial on afamelanotide for the treatment of vitiligo
7. Which treatment is more effective for vitiligo: calcineurin inhibitors	Submitted as an HTA vignette: Is combination of calcineurin inhibitors

(e.g. tacrolimus, pimecrolimus) or steroid creams/ointments?	with topical corticosteroids better than use of either treatment alone for the treatment of patients with vitiligo?
8. Which treatment is more effective for vitiligo: steroid creams/ointments or light therapy?	Submitted as an HTA vignette: Is narrow band ultra-violet light therapy (NB-UVB) better than calcineurin inhibitors for the treatment of vitiligo?
9. Does the addition of psychological interventions (e.g. counselling, support) to patients receiving cosmetic camouflage improve their quality of life?	See 2nd uncertainty
10. Is pseudocatalase cream combined with brief exposure to UVB light as recommended, effective in treating vitiligo?	Too early for HTA submission

A variety of research methodologies will now be required in order to start answering some of the questions that have been identified through this priority setting process.

For some areas, such as psychological interventions, work is needed to define the interventions themselves. In other areas, where the interventions are well defined and currently used in clinical practice, a large pragmatic, head-to-head trial of currently used treatments may be warranted.

Similarly, a factorial trial could answer two related questions by evaluating treatments both alone and in combination.

Dissemination of the results of the vitiligo PSP was an essential step towards bringing unity to the international efforts into the treatment of vitiligo. I presented the Top 10 treatment uncertainties at the 16th Meeting of the European Society of Pigment Cell research, Cambridge, UK (September 2010) and at the First Vitiligo World Congress, Milan, Italy (October 2010).

In addition, the vitiligo PSP was the first PSP with such a large number of originally submitted uncertainties; therefore, the methodology and taxonomy I developed, was adopted by the JLA in subsequent PSPs. I complemented the James Lind Alliance guidebook (http://www.jlaguidebook.org/) with a chapter on how to deal with originally submitted uncertainties in a systematic way. My methodologies as well as my recommendations, described in the "reflections on the process" section of this chapter, were implemented by the eczema PSP, the epidermolysis bullosa PSP, the cleft palate PSP and the sight loss and vision PSP.

I am hopeful that the Top 10 important treatment uncertainties have prompted other research groups and pharmaceutical companies to take a fresh look at vitiligo research and the needs of vitiligo patients.

Finally, I would recommend that researchers continue to work with patients and clinicians in meaningful partnerships in developing their future research activity, in line with current guidelines.

CHAPTER 3: WHICH OUTCOMES SHOULD BE MEASURED IN FUTURE VITILIGO TRIALS?

Abstract

Background

Relevant and reliable outcomes play a crucial role in the correct interpretation and comparison of the results of clinical trials. There is a lack of consensus around methods of assessment and outcome measures for vitiligo, which makes it difficult to compare results of randomised controlled trials and perform meta-analysis.

Objective

The objective of this study was to describe the heterogeneity in outcome measures used in published randomised controlled trials of vitiligo treatments, and to report the most desirable outcomes from patients' and clinicians' perspectives.

Methods

A systematic review of outcome measures used in randomised controlled trials (RCTs), as well as a survey of the most desirable outcomes identified by patients and clinicians was conducted, as part of a vitiligo Priority Setting Partnership.

Results

Outcomes from 54 eligible trials were analysed and compared to outcomes suggested by patients and clinicians.

In the systematic review, 25 different outcomes were reported. Only 22% of trials had clearly stated primary outcome measures. Repigmentation was the most frequently reported outcome in 96% of trials and was measured using 48 different scales. Only 9% of trials assessed quality of life. Thirteen per-cent measured cessation of spreading of the disease and 17% of studies reported patients' opinions and satisfaction with the treatment.

In contrast, out of 438 suggestions made by patients and clinicians, cosmetically acceptable repigmentation (rather than percentage of repigmentation) was the most desirable outcome (68%), followed by cessation of spread of vitiligo (15%), quality of life (6%) and maintenance of repigmentation (4%).

Conclusions

Future vitiligo trials should include the following outcomes: repigmentation, cosmetic acceptability of results, global assessment of the disease, quality of life, maintenance of repigmentation, stabilisation of vitiligo and side effects.

International consensus amongst clinicians, researchers and patients is needed to establish an agreed core outcome set for future vitiligo trials.

3.1 Introduction

Recently, it has been proposed that " core outcomes" should be agreed amongst researchers, to be measured and reported in all trials in order to allow the results of trials to be compared and combined in meta-analyses (COMET Initiative: Core Outcomes Measures Initiative www.comet-initiative.org). This does not imply that outcomes in a particular study should be restricted to the core outcomes only, but rather that the core outcomes should be collected and reported alongside others, that researchers feel are important.

There is currently a lack of consensus in the definition and methods of assessment of vitiligo (Whitton et al., 2010) which makes it difficult to perform meta-analyses or to compare the outcomes of different studies (Whitton et al., 2010; Gonzalez et al. 2011). Although a new international consensus definition and classification of vitiligo has been proposed, consensus for the measurement of disease response is still unclear (Gonzalez et al., 2011; Ezzedine et al., 2012). Over a period of 43 years, 82 different, single or combination interventions have been evaluated in 57 randomised controlled trials (RCTs) (Whitton et al., 2010). An updated Cochrane systematic review published in 2010 concluded that the majority of studies differ greatly in the

ways in which vitiligo is measured and in the myriad combinations of interventions assessed. The heterogeneity of studies in the review made it impossible to combine trial results in meta-analyses (Whitton et al., 2010).

In clinical trials the selection of appropriate outcomes, which are relevant to patients and those making decisions about healthcare (Tugwell et al., 2007), is crucial to the assessment of whether one intervention is better than another (Sinha et al., 2008). Vitiligo is a cosmetically and psychologically devastating disease causing great distress, embarrassment and difficulties in relationships (Lerner and Nordlund, 1978). Therefore, one would expect that subjective perception of the disease (i.e. patients' views on the effectiveness of a treatment) would be considered important. However, patient-centred outcomes have rarely been included in vitiligo trials, despite previous recommendations for inclusion in studies on vitiligo (Whitton et al., 2010) and other dermatological conditions (Townshend et al., 2008). Therefore, it is important to create consensus amongst researchers to ensure that the outcomes used in the trials for vitiligo treatment are reliable, clinically relevant and important to both clinicians and patients.

The main aim of this study was to extract and report all the outcomes reported in RCTs of vitiligo treatments and to

compare these to the outcomes that patients and clinicians considered to be important.

The secondary objectives were to establish:

I. What scales were used to measure these outcomes.

II. Methods of assessment of these outcomes.

III. Whether patients' views and their subjective perception of the treatment effectiveness were incorporated in the reported outcomes.

This is a first step towards developing recommendations for outcomes to be used in future trials of treatments for vitiligo.

3.2 Methods

3.2.1 Systematic review of outcome measures in randomised controlled trials of treatments for vitiligo

As mentioned in Chapter 1 (page 46), the updated Cochrane systematic review "Interventions for vitiligo" 2010, concluded that the majority of studies differ greatly in the ways in which vitiligo is measured. Despite the fact that the majority of the studies scored the percentage repigmentation, no two studies used exactly the same method of scoring; therefore the outcomes were pre-specified by the authors of

the Cochrane review. This meant that the authors of the Cochrane systematic review only retrieved the following outcomes from the included trials: quality of life measured by the Dermatology Life Quality Index (DLQI) or Skindex-29, percentage of repigmentation (more than 75%), cessation of spread of vitiligo, long term permanence of repigmentation and side effects (Whitton et al., 2010). The authors of the Cochrane review did not seek to report which outcomes were measured in randomised controlled trials for the treatment of vitiligo and what scales were used to measure these outcomes.

A review was conducted of the outcome measures used in RCTs published in English and included in the updated Cochrane systematic review "Interventions for vitiligo" published in 2010. The Cochrane review on the effectiveness of interventions for the treatment of vitiligo included 57 randomised controlled trials published up to November 2009. All the outcomes reported in the included RCTs were retrieved and the scales and measures used to monitor these were collated (see systematic review of outcome measures data extraction form in the appendix). Information on outcome assessors was also collected. Studies with no full English text available were excluded.

I extracted the data from each eligible study using a standardised proforma. A second data extraction was

performed by two other researchers. In the event of any discrepancies, a third researcher adjudicated.

3.2.2 Survey of the most desirable outcomes for vitiligo identified by patients and clinicians

A survey was conducted as part of the Vitiligo Priority Setting Partnership (Vitiligo PSP) (see chapter 2) (Eleftheriadou et al.2011). Patients and healthcare professionals were asked in an open-ended questionnaire to submit details of their uncertainties regarding vitiligo treatment, along with their views on what outcomes should be measured in future vitiligo trials. A question: "what should we measure in future vitiligo trials?" was asked.

3.2.3 Ethics

The survey was approved by the Medical School Research Ethics Committee, University of Nottingham, U.K, Ethics Reference No. G /2 /2009.

3.2.4 Statistical methods

Data was stored and analysed in MS Excel 2007 and processed by myself.

3.3 Results

3.3.1 Systematic review of outcome measures in randomised controlled trials of treatments for vitiligo

Fifty seven RCTs were evaluated. Fifty four trials were included and three were excluded as published English translations were not available. Only 22% (12/54) of trials had clearly stated the primary outcome measures in the abstract or the main text. The majority of these trials defined the primary outcome as repigmentation (10/12; 83%). Other primary outcomes included the size of target lesions (1/12; 8.3 %) and the number of new vitiliginous lesions (1/12; 8.3%).

In total, 25 different outcomes were reported in 54 RCTs on the treatment of vitiligo. The most frequently reported outcome was repigmentation (Table 3.1), which was measured in 96% (52/54) of trials, followed by side effects (46/54; 85%), number of treatment sessions or time (17/54; 31.5%) and cumulative dose (12/54; 22%) to reach repigmentation. Other outcomes, less frequently reported, included pattern of repigmentation (17%, 9/54), patient opinion on treatment efficacy and degree of satisfaction including cosmetic acceptability of the results (9/54; 17%), cessation of spread of vitiligo (7/54; 13%), quality of life (5/54; 9%), independent

assessment of colour matching of newly repigmented lesions compared with unaffected skin (3/54; 5.5%), clinical global assessment (3/54; 5.5%), stability of gained repigmentation (2/54; 4%), general health (1/54; 2%), body image (2/54; 2%), self-esteem (1/54; 2%), time to suction blister formation (1/54; 2%) and response to treatment in light vs. dark skin types (2/54; 2%).

Table 3.1 Outcomes assessed in 54 Randomised Controlled trials for the treatment of vitiligo from 1967 to 2009

	Outcome	Trials	References
1	Repigmentation	52 (96%)	(Anbar et al., 2008), (Arca et al., 2006), (Asawanonda et al., 2008), (Barman et al., 2004), (Bhatnagar et al., 2007), (Casacci et al., 2007), (Cestari et al., 2001), (Czajkowski 2004), (Dawid et al., 2006), (Dell'Anna et al., 2007a), (El-Mofty et al., 2006), (Ermis et al., 2001), (Esfandiarpour et al., 2009), (Farah et al., 1967), (Goldinger et al., 2007), (Hamzavi et al., 2004), (Hofer et al., 2005), (Kandil, 1974), (Kawalek et al., 2004), (Khalid et al., 1995), (Khandpur et al., 2005), (Kumaran et al., 2006), (Leone et al., 2006), (Lepe et al., 2003), (Lim-Ong et al., 2005), (Lu-yan et al., 2006), (Mehrabi and Pandya, 2006), (Middelkamp-Hup et al., 2007), (Navarro et al., 2002), (Ozdemir et al., 2002), (Parsad et al., 1998), (Parsad et al., 2003b), (Passeron et al., 2004), (Pathak et al., 1984), (Procaccini et al., 1995), (Radmanesh and Saedi, 2006), (Rath et al., 2008), (Reyes et al., 2006), (Rodriguez-Martin et al., 2009), (Rojas-Urdaneta et al., 2007), (Ruiz Mandonado and Tamayo, 1975), (Sanclemente et al., 2008), (Sassi et al., 2008), (Schallreuter et al., 2002), (Siddiqui et al., 1994), (Shi et al., 2008), (Tegta et al., 2006), (Tjioe et al., 2002), (Van Geel et al., 2004), (Vasistha and Singh, 1979), (Yones et al., 2007), (Westerhof et al., 1999)
2	Side effects and harms (including blood parameters for monitoring purposed only)	46 (85%)	(Anbar et al., 2008), (Asawanonda et al., 2008), (Barman et al., 2004), (Bhatnagar et al., 2007), (Casacci et al., 2007), (Cestari et al., 2001), (Czajkowski 2004), (Dawid et al., 2006), (Dell'Anna et al., 2007a), (Ermis et al., 2001), (Esfandiarpour et al., 2009), (Hamzavi et al., 2004), (Hofer et al., 2005), (Kandil, 1974), (Kawalek et al., 2004), (Khalid et al., 1995), (Khandpur et al., 2005), (Kumaran et al., 2006), (Leone et al., 2006), (Lepe et al., 2003), (Lim-Ong et al., 2005), (Lu-yan et al., 2006), (Mehrabi and Pandya, 2006), (Middelkamp-Hup et al., 2007), (Navarro et al., 2002), (Ozdemir et al., 2002), (Parsad et al., 1998), (Parsad et al., 2003b), (Passeron et al., 2004), (Pathak et al., 1984), (Radmanesh and Saedi, 2006), (Rath et al., 2008), (Reyes et al., 2006), (Rodriguez-Martin et al., 2009), (Rojas-Urdaneta et al., 2007), (Ruiz Maldonado and Tamayo, 1975), (Sanclemente et al., 2008), (Sassi et al., 2008), (Siddiqui et al., 1994), (Shi et al., 2008), (Tegta et al., 2006), (Tjioe et al., 2002), (Van Geel et al., 2004), (Vasistha and Singh, 1979), (Yones et al., 2007), (Westerhof et al., 1999)
3	Number of treatment sessions/time to reach repigmentation	17 (31%)	(Anbar et al., 2008), (Asawanonda et al., 2008), (Bhatnagar et al., 2007), (Casacci et al., 2007), (Czajkowski 2004), (Dell'Anna et al., 2007a), (Ermis et al., 2001), (Hamzavi et al., 2004), (Hofer et al., 2005), (Kawalek et al., 2004), (Kumaran et al., 2006),(Leone et al., 2006), (Lu-yan et al., 2006), (Radmanesh and Saedi, 2006), (Rodriguez-Martin et al., 2009), (Tegta et al., 2006), (Yones et al., 2007)

	Outcome	Trials	References
4	Cumulative dose	12 (22%)	(Asawanonda et al., 2008), (Casacci et al., 2007), (Cestari et al., 2001), (Ermis et al., 2001), (Goldinger et al., 2007), (Hofer et al., 2005), (Lim-Ong et al., 2005), (Lu-yan et al., 2006), (Middelkamp-Hup et al., 2007), (Passeron et al., 2004), (Procaccini et al., 1995), (Tjioe et al., 2002)
5	Pattern of repigmentation	9 (17%)	(Anbar et al., 2008), (Casacci et al., 2007), (Cestari et al., 2001), (Esfandiarpour et al., 2009), (Kumaran et al., 2006), (Radmanesh and Saedi, 2006), (Rodriguez-Martin et al., 2009), (Van Geel et al., 2004), (Yones et al., 2007)
6	Cessation of disease activity	7 (13%)	(Dawid et.al., 2006), (Dell'Anna et al., 2007a), (Lim-Ong et al., 2005), (Papadopoulos et al., 2004), (Parsad et al., 2003b), (Rath et al., 2008), (Siddiqui et al., 1994)
7	Quality of life	5 (9%)	(Agarwal et al., 2005), (Middelkamp-Hup et al., 2007), (Papadopoulos et al., 2004), (Sassi et al., 2008), (Yones et al., 2007)
8	Patient Global assessment	4 (7.5%)	(Hamzavi et al., 2004), (Middelkamp-Hup et al., 2007), (Rodriguez-Martin et al., 2009), (Yones et al., 2007)
9	Satisfaction with the treatment	4 (7.5%)	(Hofer et al., 2005), (Mehrabi and Pandya, 2006), (Passeron et al., 2004), (Westerhof et al., 1999)
10	Colour matching	3 (5.5%)	(Bhatnagar et al., 2007), (Tegta et al., 2006), (Yones et al., 2007)
11	Clinician global assessment	3 (5.5%)	(Hamzavi et al., 2004), (Middelkamp-Hup et al., 2007), (Sassi et al., 2008)
12	Histological samples	3 (5.5%)	(Rojas-Urdaneta JE, 2007), (Navarro et al., 2002), (Westerhof et al., 1999)
13	Cytokines, T-lymphocytes	3 (5.5%)	(Middelkamp-Hup et al., 2007), (Reyes et al., 2006), (Shi et al., 2008)
14	Stability of gained	2 (4%)	(Kumaran et al., 2006), (Lim-Ong et al., 2005)

	Outcome	Trials	References
	repigmentation		
15	Tolerability of treatment	1 (2%)	(Passeron et al., 2004)
16	Concentration of epidermal H_2O_2	1(2%)	(Schallreuter et al.,2002)
17	Change in colour	1(2%)	(Sanclemente et al.,2008)
18	Cosmetic acceptability	1(2%)	(Barman et al., 2004)
19	Stress	1(2%)	(Papadopoulos et al., 2004)
20	Body image	1(2%)	(Papadopoulos et al., 2004)
21	Self esteem	1(2%)	(Papadopoulos et al., 2004)
22	General health	1(2%)	(Papadopoulos et al., 2004)
23	Response to treatment (light vs. dark skin types)	1(2%)	(Middelkamp-Hup et al., 2007)
24	Catalase activity, ROS, saturation of lipids	1(2%)	(Dell'Anna et al., 2007a)
25	Time to suction blister formation & duration of cell cultures	1(2%)	(Czajkowski 2004)

3.3.1.1 Repigmentation

Although it was the most frequently reported outcome in the RCTs, repigmentation was measured using a great variety of scales (Table 3.1) including grades, scores (e.g. 0-4), categories (e.g. poor to excellent, partial to complete), quartiles and other quintiles (e.g. 0-24, 25-50, 51-74, 75-100), percentages (e.g. 0-40, 40-60, 60-100, 0-30, 31-50, 51-75, 75-100), mean difference in lesion size in mm. Five trials (9%) used more than one scale to measure repigmentation.

In total, repigmentation was measured using 48 different scales in 54 eligible trials. Although 30% of the trials used quartiles (16/54), 14 different scales were created including differences in the definition of quartiles and the names of the corresponding categories. For example, Kumaran et al (2006) and Bhatnagar et al. (2007) both used the "0-24%; 25-50%; 50-75%; 76-100%" quartiles, but one trial (Kumaran et al., 2006) reported moderate improvement as 25-50% repigmentation and the other (Bhatnagar et al., 2007) as 50-75% repigmentation of vitiliginous lesions. The definition of excellent repigmentation or success varied from trial to trial and included values from "any repigmentation" to 100% repigmentation of vitiliginous lesions.

Trials assessed repigmentation by combination of clinical assessment and other methods such as digital images, paper tracing, planimetry (29/54; 54%) or clinically only (17/54; 31.5%). Eleven percent of trials (6/54) used only objective methods in assessing repigmentation such as digital images, planimetry, and image analysis of reflected UV photographs. Only two trials (3.7%) incorporated patient assessed repigmentation.

3.3.1.2 Pattern of repigmentation and colour matching

Pattern of repigmentation was reported in 17% (9/54) of trials. This was usually briefly mentioned in the discussion section or the results section only. Perifollicular and peripheral/perifollicular patterns were mentioned in 4% (2/54) and 9% (5/54) of the trials respectively. Four percent of the trials reported all patterns (perifollicular, marginal and diffuse) of repigmentation (Table 3.2).

Change in colour (colorimetry) and colour matching of vitiliginous lesions was assessed in 5.5% (3/54) and 2% (1/54) trials respectively. These were assessed by either clinicians only (Bhatnagar et al., 2007; Tegta et al., 2006) or combination of clinical assessment and photographs (Yones et al., 2007) or by using digital images (Sanclemente et al., 2008). Patient assessment of colour matching was not

included in any of the trials (Table 3.3). Response to the treatment in light vs. dark skin types was reported in one trial (2%) and was measured clinically.

Table 3.2 Scales used to measure repigmentation in Randomised Controlled Trials for the treatment of vitiligo from 1967 to 2009

	Scale used to measure repigmentation	Details	Outcome assessor/Methods of assessment
Grades	Grades: 0-3	0=None; 1=Regular; 2=Good; 3-Excellent (Cestari et al., 2001)	Patient
		0=None; 1= up to 25%; 2= 25-50%; 3= 51-100% (Cestari et al., 2001)	Clinically
		0=none; 1+=minimal follicular; 2+=follicular; 3+=above 50% follicular/confluent repigmentation (Schallreuter et al., 2002)	Clinically, digital images
		0=none; 1= <50% (moderate); 2= 50-80%(good); 3= >80% (excellent) (Leone et al., 2006)	Clinically
	Grades: 0-4	0=No change; 1= 1-25%; 2= 26-50%; 3= 51-75%; 4= 76-100% (Asawanonda et al., 2008)	Digital images
		Presented in the article only: Initial=0-25%; complete=75-100% (Ermis et al., 2001)	Clinically

	Scale used to measure repigmentation	Details	Outcome assessor/Methods of assessment
		0=No change; 1 (poor)= 1-25%; 2 (moderate)= 26-50%; 3 (good)= 51-75%; 4 (excellent)= 76-100% (Casacci et al., 2007)	Clinically, photographs
		0=No response; 1 (minimal)= 1-24%; 2 (moderate)= 25-50%; 3 (marked)= 50-75%; 4 (complete)= 100% (Kawalek et al., 2004)	Clinically, photographs
	Grades: 0-5	0=0%, 1=1-5%, 2=6-25%. 3=26-50%, 4=51-75%, 5=76-100% (Hofer et al., 2005)	Clinically, digital images
	Points: 0-11	0=none; 1=up to 2mm; 3=2.1-4mm; 5=4.1-6mm; 7=6.1-8mm; 9=8.1-10mm; 11=above 10mm (Navarro et al., 2002)	Clinically
VASI	Vitiligo Area Scoring Index (VASI)	Quantitative parametric score (Hamzavi et al., 2004)	Clinically
Quartiles	Percentage quartiles	Minimal or no response: 0-24%; moderate or mild response: 25-50%; marked or moderate response: 50-75%; excellent, marked or complete response: 76-100% (Kumaran et al., 2006; Bhatnagar et al., 2007; Rath et al., 2008)	Clinically (Kumaran et al., 2006; Bhatnagar et al., 2007; Rath et al., 2008), paper tracing (Kumaran et al., 2006), digital images (Kumaran et al., 2006; Bhatnagar et al., 2007)
		Poor/minimal response:0-24%; moderate response:25-49%; good or marked response:50-74%; excellent/marked or complete response:76-100% (Rodriguez-Martin et al., 2009; Lu-yan et al.,	Clinically (Rodriguez-Martin et al., 2009; Lu-yan et al., 2006; Esfandiarpour et al., 2009; Passeron et al., 2004), digital images (Lu-yan

	Scale used to measure repigmentation	Details	Outcome assessor/Methods of assessment
		2006; Esfandiarpour et al., 2009; Passeron et al., 2004)	et al., 2006; Arca et al., 2006)
		L1=0-25%; L2=25-50%; L3=50-75%; L4=75-100% (Procaccini et al., 1995)	Clinically and photographs (Procaccini et al., 1995)
		Minimal (25%); Moderate (50%); Marked (75%) or complete (Parsad et al., 1998; Parsad et al., 2003b)	Clinically, photographs, paper tracing, written describing and measurement (Parsad et al., 1998; Parsad et al., 2003b)
		None: 0%; Poor or minimal response: 1-25%; moderate or mild response: 26-50%; good or moderate response: 51-75%; marked or excellent response: 76-100% (Lepe et al., 2003; Tegta et al., 2006), (Khalid et al., 1995; Yones et al., 2007)	Clinically (Tegta et al., 2006; Lepe et al., 2003; Khalid et al., 1995), digital images using morphometry (Lepe et al., 2003), photographs and planimetry (Yones et al., 2007)
Tertiles/ Quantiles	Percentages	Minimal response: 0-24%; mild or moderate response: 25-49 or 50%; moderate or marked or complete response: 50 or 51-100% (Arca et al., 2006; Reyes et al., 2006)	Clinically (Arca et al., 2006), (Reyes et al., 2006), digital images (Arca et al., 2006)
		Mild or minimal or poor response: 0-24 or 25%; moderate or good response: 25 or 26-75%; marked or excellent response: 76-100% (Anbar et al., 2008; Lim-Ong et al., 2005; Radmanesh and Saedi, 2006).	Clinically and planimetry (Anbar et al., 2008),(Radmanesh and Saedi, 2006), digital photographs and morphometry analysis (Lim-Ong et al., 2005)
		No response; beginning: 1-25%; good: 25-90%; complete cure:	Clinical assessment, photographs

	Scale used to measure repigmentation	Details	Outcome assessor/Methods of assessment
		90-100% (Kandil, 1974)	
		Absent: 0%; moderate: 1-49%; good: 50-75%; excellent: 76-100% (Dell'Anna et al., 2007a)	Clinically, photographs
		None: 0-50%; good: 51-100% (Farah et al., 1967)	Clinically, patient
		0%= none; 75%= significant and satisfying; 100%=complete (Westerhof et al., 1999)	Clinically
		Ineffective: worse or no difference; improved: <50%; marked: > 50%; cured:100% (Shi et al., 2008)	Clinically
		Deterioration; stable: no changes; partial: 25-40%; incomplete: 40-60%; good: >60% (Siddiqui et al., 1994)	Clinically, photographs
		Failure: 0%; poor: 0-40%; moderate: 40-60%; good/very good: >60% (El-Mofty et al., 2006)	
		Poor: <30%; fair: 31-50%; good: 51-75%; very good: 76-90%; excellent: 91-100% (Khandpur et al., 2005)	
mm/cm	Reduction of surface area	Pigment spread: millimetres(Barman et al., 2004)	

	Scale used to measure repigmentation	Details	Outcome assessor/Methods of assessment
	Mean size of lesions	Mean size of lesions in centimetres (Cestari et al., 2001)	
	Increase in pigmentation of surface area	0= absence of repigmentation; 1=3 mm; 3=3.1-5 mm; 5=5.1-7 mm; 7=7.1-9 mm; 9=9.1-11 mm; 11= >11mm (Rojas-Urdaneta, 2007)	Clinically and acetate sheets to mark the edges
Percentages	Mean percentage of surface repigmentation	Mean %: 0-100% (Goldinger et al., 2007; Sanclemente et al., 2008; Tjioe et al., 2002; Cestari et al., 2001; Lepe et al., 2003; Westerhof et al., 1999)	Clinically (Goldinger et al., 2007; Sanclemente et al., 2008; Tjioe et al., 2002),(Cestari et al., 2001; Lepe et al., 2003; Westerhof et al., 1999), digital images (Cestari et al., 2001; Goldinger et a; 2007; Lepe et al., 2003; Mehrabi and Pandya, 2006; Sanclemente et al., 2008; Tjioe et al., 2002; Middelkamp-Hup et al., 2007; Van Geel et al., 2004), digital morphometry (Sanclemente et al., 2008) and transparent sheets tracing (van Geel et al., 2004)
	Size of target lesions	0-100% (Dawid et al., 2006)	Planimetry
	Change of the % of the affected	0-100%	Clinically (Arca et al., 2006; Radmanesh and Saedi, 2006; Ruiz Maldonado and Tamayo,

	Scale used to measure repigmentation	Details	Outcome assessor/Methods of assessment
	skin		1975), photographs (Ruiz Maldonado and Tamayo, 1975) and tracing (Radmanesh and Saedi, 2006)
	Success	only 100% repigmentation (Czajkowski, 2004)	Clinically
Categories	Categories	No response; fair response: slight improvement; good response: increase in size of pigmented spots or decrease in size of lesions; excellent response: considerable increase in size of pigmented spots or decrease in size of lesions (Vasistha and Singh, 1979)	Clinically
	Clearance of lesions	Clear/not clear (Sassi et al., 2008)	Image analysis of reflected UV photographs
	Reduction of at least 75% of overall lesions	Reduction of at least 75%; no reduction of at least 75% (Sassi et al., 2008)	Image analysis of reflected UV photographs
	Number of new lesions	Number of new lesions (Agarwal et al., 2005)	Clinically

Table 3.3 Scales used to measure outcomes other than repigmentation in Randomised Controlled Trials for the treatment of vitiligo from 1967 to 2009

	Outcome	Details	Method of assessment	Trials
1	Depigmentation	-1= 1-25%; -2= 26-50%; -3= 51-75%; -4=76-100% (Asawanonda et al., 2008)	Digital images (Asawanonda et al., 2008)	1
2	Pattern of repigmentation	Follicular, peripheral, marginal, diffuse (Anbar et al., 2008; Casacci et al., 2007; Cestari et al., 2001; Esfandiarpour et al., 2009; Radmanesh and Saedi, 2006; Rodriguez-Martin et al., 2009; Yones et al., 2007; Kumaran et al., 2006)	Clinically (Kumaran et al., 2006; Anbar et al., 2008; Casacci et al., 2007; Cestari et al., 2001; Esfandiarpour et al., 2009; Radmanesh and Saedi, 2006; Rodriguez-Martin et al., 2009; Yones et al., 2007), planimetry (Anbar et al., 2008; Radmanesh and Saedi, 2006) and photographs (Casacci et al., 2007; Cestari et al., 2001; Esfandiarpour et al., 2009; Rodriguez-Martin et al., 2009; Van Geel et al., 2004)	9
3	Colour matching of newly repigmented lesion to the surrounding normal skin	Darker, same, lighter (Bhatnagar et al., 2007; Tegta et al., 2006)	Clinically (Bhatnagar et al., 2007; Tegta et al., 2006)	2
		Excellent, not excellent (not many details given) (Yones et al., 2007)	Clinically and photographs	1
4	Change in colour Colorimetry	Commission International de L'Eclairege L, a, b system (Sanclemente et al., 2008)	Digital images	1
5	Quality of life	DLQI (Yones et al., 2007; Agarwal et al., 2005;	Patients	3

		Papadopoulos et al., 2004)		
		Skindex 29 (Sassi et al., 2008; Middelkamp-Hup et al., 2007)		2
		WHOQOL-BREF questionnaire for quality of life (Agarwal et al., 2005)		1
6	General health	General health questionnaire (Papadopoulos et al., 2004)	Patients	1
7	Body image	Body image dysphoria-situational inventory of body image dysphoria, body image feelings-body image automatic thoughts questionnaire (Papadopoulos et al., 2004)	Patients	1
8	Self-esteem	Rosenberg self-esteem scale (Papadopoulos et al., 2004)	Patients	1
9	Stress	Perceived stress scale (Papadopoulos et al., 2004)	Patients	1
10	Cessation of spreading of vitiligo/Disease activity	Not clear (Parsad et al., 2003b)	Clinically, photographs, planimetry, written description and measurement	1
		Not clear (one sentence at the discussion section) (Rath et al., 2008)	Not clear (Rath et al., 2008)	1
		Vitiligo Index Disease Activity (VIDA) score (Dawid et al., 2006; Lim-Ong et al., 2005)	Patients	2
		No scale (Papadopoulos et al., 2004)	Photographs(Papadopoulos L, 2004)	1

		Positive, stable, deteriorating (Siddiqui et al., 1994)	Clinically and photographs	1
		Binary scale: stabilised/not stabilised (Dell'Anna et al., 2007a)	Clinically and photographs	1
11	Clinical Global assessment	Very severe; severe; more or less severe; not so severe (Middelkamp-Hup et al., 2007)	Clinically	1
		Complete improvement (100%); very much improved (76-99%); much improved (51-75%); improved 26-50%); minimal change(1-25%); no change (Hamzavi et al., 2004)		1
		Anchored Horizontal visual analogue scale (Sassi et al., 2008)		1
12	Patient global assessment	Visual analogue scale: -5 to +5 (Rodriguez-Martin et al., 2009)	Patients	1
		Visual analogue scale: 0 to 10 (Middelkamp-Hup et al., 2007; Yones et al., 2007)		2
		Complete improvement (100%); very much improved (76-99%); much improved 51-75%); improved 26-50%); minimal change(1-25%); no change (Hamzavi et al., 2004)		1
13	Satisfaction with the treatment	Visual analogue scale: 0 to 10 (Hofer et al., 2005)	Patients	1
		Questionnaire (no further details) (Mehrabi and		1

		Pandya, 2006)		
		Opinion on treatment and side effects questionnaire (no further details) (Westerhof et al., 1999)		1
		Opinion on treatment efficacy and degree of satisfaction questionnaire. Scale: poor; good; excellent (Passeron et al., 2004)		1
14	Cosmetic acceptability of the results	Satisfied/ unsatisfied (Barman et al., 2004)	Patients	1
15	Tolerability of the treatment	Visual analogue scale (Passeron et al., 2004)	Patients	1
16	Response to treatment in light vs. dark skin types	Descriptive (Middelkamp-Hup et al., 2007)	Clinically	1
17	Stability of gained regimentation and development of new lesions	Within 1 year after treatment; Scale: Not clear (Lim-Ong et al., 2005)	Not clear	1
		Within 20 weeks after treatment Categories: maintained repigmentation; continued to improve; pigmentation faded; development of new lesions (Kumaran et al., 2006)		1

3.3.1.3 Cessation of disease activity

Thirteen per-cent (7/54) of RCTs measured the cessation of spreading of vitiligo during treatment period; only 7% (4/54) stated the scale used.

3.3.1.4 Stability of gained repigmentation

Four per-cent of the trials (2/54) assessed stability of gained repigmentation and development of new lesions. The timescales of the assessment of this outcome were 1 year and 20 weeks after the completion of the treatment.

3.3.1.5 Patient's opinion on treatment efficacy

Only 17% (9/54) of studies reported patients' opinions regarding treatment efficacy and degree of satisfaction with the treatment including cosmetic acceptability of the results. In particular, 7.5% of trials (4/54) assessed patient satisfaction with the treatment by asking them directly using a questionnaire or a visual analogue scale. However details of which questions were asked were generally lacking. Cosmetic acceptability of the results and patient global assessment were monitored in 2% (1/54) and 7.5% (4/54) of trials respectively. The latter was measured in 3 different ways (Table 3.3). Tolerability of the treatment was briefly reported in one trial (2%).

3.3.1.6 Quality of life

Nine per-cent (5/54) of trials assessed quality of life of vitiligo patients. Different questionnaires were used: Dermatology Life Quality Index (DLQI) (3/54; 5.5%), Skindex-29 (2/54; 3.7%) and WHOQOL-BREF questionnaire for quality of life (1/54; 1.8%).

3.3.1.7 General health, stress, body image and clinician global assessment

One trial (Papadopoulos et al., 2004) reported several patient centred outcomes; stress, body image, self-esteem and general patient's health. Clinician global assessment was measured using 3 different scales in 3 trials (5.5%).

3.3.1.8 Side effects and harms

Various side effects and harms such as erythema, blistering, graft failure, Koebner phenomenon, hyperpigmentation around vitiliginous lesions, were reported in 46 trials out of 54 eligible trials (85%). Nine trials mentioned that various blood parameters such as full blood count, kidney and liver function tests were measured for the purpose of monitoring possible treatment side effects only and therefore were included in this category of outcomes. Side effects and harms were generally reported briefly in the results

or discussion section of the article with limited information on frequency or severity.

3.3.1.9 Specific blood, skin parameters and other outcomes

Histopathology of vitiliginous lesions (3/54; 5.5%), T-lymphocytes and cytokines (3/54; 5.5%); concentration of epidermal H_2O_2 (1/54; 2%), catalase activity and lipid saturation (1/54; 2%) were measured as an indicator of effectiveness of compared treatment.

Number of treatments to gain repigmentation, cumulative dose and time to suction blister formation were sometimes reported in trials where relevant to delivery of the intervention (Table 3.1).

3.3.2 Survey of the most desirable outcomes for vitiligo identified by patients and clinicians

Eighty seven percent (401/461) of vitiligo PSP participants suggested at least one outcome (response rate 87%).

In total, 438 suggestions were made and 23.5% (103/438) of these were excluded as non-relevant, such as questions on inheritance and trigger factors for vitiligo.

Of the remaining 335 suggestions, 68% of responses were from patients, 25% from clinicians and 7 % unknown. More women responded than men (53% women; 30% men and 17% did not specify), and most were aged 30-60 years old (8% ‹ 30 years , 50% 30-60 years, 25% › 60 years and 17% did not specify).

The most popular outcome amongst all responders was repigmentation of vitiliginous lesions (68%), followed by cessation of spreading of the disease (15%), quality of life of vitiligo patients (6%), maintenance of repigmentation (4%) and other outcomes such as camouflage effectiveness and depigmentation.

3.3.2.1 Repigmentation of vitiliginous lesions

Statements such as "cosmetically acceptable repigmentation rather than percentage", "normal looking skin", "90-100% repigmentation", and "quick and long lasting (at least 2 years) were made by survey responders. Repigmentation on visible areas such as face and hands was also considered important (Figures 3.1 and 3.2).

Figure 3.1 Desirable outcomes for patients

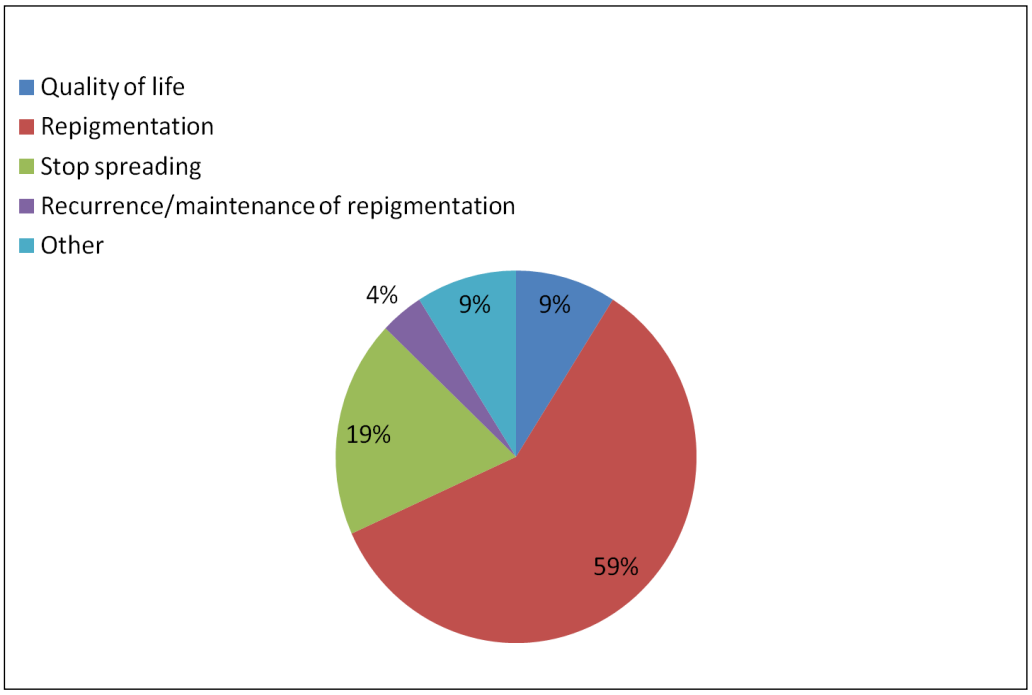
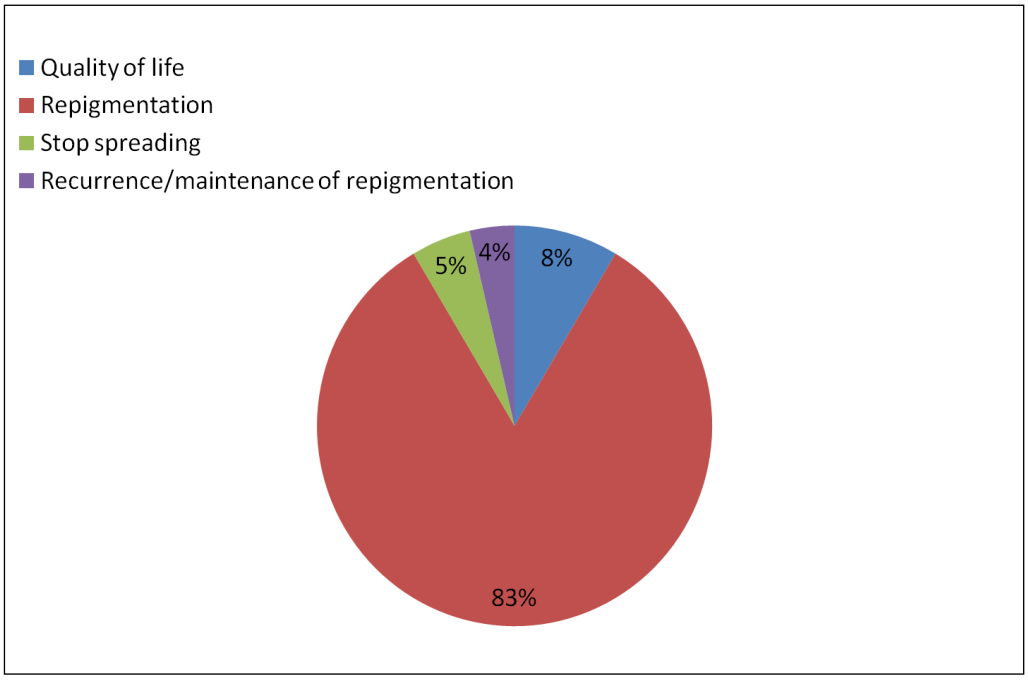


Figure 3.2 Desirable outcomes for clinicians



3.3.2.2 Cessation of spread of vitiligo

Nineteen percent of patients found cessation of the disease important compared to only 5% of clinicians (Figures 3.1 and 3.2).

3.3.2.3 Quality of life

Nearly equal percentages of patients (9%) and clinicians (8%) found the quality of life of vitiligo patients an important outcome. Statements such as: "to reduce the stress and embarrassment, psychological impact, support, coping strategies and self-confidence, psychological support for children with vitiligo" were reported (Figures 3.1 and 3.2).

Other submissions included depigmentation, camouflage improvement.

3.4 Discussion

Well-designed clinical trials are a fundamental aspect of evidence-based medicine. Relevant and reliable outcomes play a crucial role in the correct interpretation and comparison of the results of different treatment modalities (Charman et al., 2003). Lately, it has been increasingly recognised that outcome measures in trials should be relevant to patients and clinicians (COMET, 2010; Tugwell et al., 2007). However, no

attempts have been made, either by researchers or by pharmaceutical companies, to standardise outcome measures for the treatment of vitiligo.

Recently, it has been reported that 85% of research funding is wasted across all aspects of the research cycle (Chalmers and Glasziou, 2009). Three of the four sources of waste are closely related to the outcomes used in the trials: important outcomes are not assessed; published research fails to set the study in the context with all previous similar research and over 50% of planned study outcomes are not reported (Chalmers and Glasziou, 2009).

The majority of the trials in the systematic review reported repigmentation, but this was measured using 48 different scales. In total, 25 different outcomes were reported in 54 trials. Patients and clinicians put greatest emphasis on repigmentation, quality of life, cessation of spread of the disease and maintenance of gained repigmentation. However *cosmetically acceptable* repigmentation as assessed by patients, rather than percentage of repigmentation *per se,* should be measured where possible. Whilst it is encouraging that a clear candidate for a core outcome to be included in all clinical trials on vitiligo is repigmentation, with so many different ways of assessing treatment results, it will never be possible to perform a meaningful meta-analysis of vitiligo trials

until these issues have been resolved. Urgent action is required, if the field of vitiligo research is to move forward.

It is also disappointing that the definition of successful treatment or excellent repigmentation is unclear, and that patient involvement in assessing the success of treatments or quality of life is so limited.

To my knowledge, this study is the first to systematically summarise outcomes reported in RCTs of vitiligo treatments, and to compare these outcomes with the results of qualitative work amongst patients and clinicians to establish the outcomes of importance to them.

The survey responders included patients with vitiligo, their carers and parents, dermatologists and other healthcare professionals with an interest in vitiligo. Hence, the proposed outcomes reflect a broad spectrum of views.

A convenience sample of RCTs included in the updated Cochrane systematic review was chosen based on resources and time limitations. It is possible, that more recent trials have been more consistent in including patient-reported outcomes and quality of life scales in line with recent recommendations (Gonzalez et al., 2011).

Amongst the huge number of outcomes that have been reported in the RCTs to date, it is difficult to identify precisely which outcomes should be measured in vitiligo trials.

Initial attempts have been made to create a consensus in the way that vitiligo is assessed. An innovative scoring tool was proposed in 2007 by the Vitiligo European Task Force; however, this had not been used in the randomised controlled trials included in this review. This scoring system combines the three dimensions of the disease: extent, staging and spreading and takes into consideration the presence of white hair and the body sites of vitiliginous lesions (Taieb and Picardo, 2007).

Recent guidelines for designing and reporting clinical trials on vitiligo have suggested that patient-centred outcomes should be incorporated into the design of future trials of vitiligo treatment along with quality of life, percentage of repigmentation, permanence of gained repigmentation and the arrest of the progression of the disease (Gonzalez et al., 2011). To overcome the issue of different body sites responding differently to treatments, it has been suggested that studies perform stratified analyses based on body sites (Gonzalez et al., 2011) and that other important clinical parameters should

be collected such as resistance to previous treatment and presence of leukotrichia.

Although, quality of life has been reported in only 9% of trials, it is considered an important outcome from a patient's point of view (19%) and was also proposed as a primary outcome in the guidelines for designing and reporting clinical trials for vitiligo (Gonzalez et al., 2011).

Recently published revised international classification of vitiligo and definition of stabilisation of the disease recommends that disease stability is best assessed based on the stability of individual lesions rather than the overall stability of the disease, as the latter is difficult to define precisely and reliably (Ezzedine et al., 2012). Therefore the cessation of spreading of vitiligo is relevant to individual lesions as well as whole body or systematic treatments.

It has been reported that more research is needed into the establishment of the definition of successful repigmentation as well as methods of assessment of the proposed outcomes (Gonzalez et al., 2011).

I believe that the previously proposed outcomes, in combination with the findings of this review and survey are a good starting point for creating a consensus on a core outcome set for vitiligo trials. However, the questions of what

makes “cosmetically acceptable” repigmentation, “what scale to use” and “who should assess these outcomes” still remain unanswered and will require further research.

Meanwhile, the following outcomes should be clearly reported in all future trials for the treatment of vitiligo (Table 3.4).

Table 3.4 Proposed core outcomes for the trials on treatment of vitiligo

Proposed outcomes	Example of scale	Assessors/method of assessment	Comments
Repigmentation	% quartiles: 0-24%; 25-49%; 50-74%; 75-100%	Objective means such as planimetry, coloritmetry, digital photographs, UV photographs	The method of assessment will depend upon its availability and appropriate training of personnel.
Cosmetically acceptable repigmentation	Visual analogue scale (bad, fair, good, excellent)	Patient	This will take account of the colour match of the newly repigmented lesions to the surrounding normal skin including hyperpigmentation around the lesions if applicable
Global assessment	Visual analogue scale: Complete improvement; very much	Patient and clinician	A unified combined scale should be used by both patients and clinicians, which would be quick and easy to use in both

Proposed outcomes	Example of scale	Assessors/method of assessment	Comments
of the disease	improved; much improved; improved; minimal change; no change (Hamzavi et al., 2004))		clinical setting and research environment.
Quality of life	Skindex-29	Patient	Concerns have been recently reported regarding the use of DLQI in monitoring patients with mild to severe psoriasis and atopic dermatitis (Twiss et al., 2012; Fernandez-Penas et al., 2012).
Maintenance of gained repigmentation	2 years follow-up after completion of the treatment (Whitton et al., 2010)	Patient and clinician	It is well known that repigmentation of vitiliginous lesions can take months and that depigmentation can recur; therefore it is important to assess maintenance of gained repigmentation

Proposed outcomes	Example of scale	Assessors/method of assessment	Comments
			when weighting the treatment benefits against the harms.
Cessation of spread of the disease	Vitiligo Disease Activity (VIDA) score (Dawid et al., 2006; Bhor and Pande, 2006; Lim-Ong et al., 2005)	Patient and clinician	Cessation of spreading of the disease is an important outcome due to the unpredictable nature of vitiligo, which can be devastating and distressing for patients. Stabilisation of the disease until repigmentation occurs was reported as a realistic measure of outcome (Gonzalez et al., 2011).
Side effects and harms	Descriptive. Should also include convenience of the treatment from the patient's perspective	Patient and clinician	Side effects and harms of an intervention should be clearly reported in the results section with relevant frequencies.

Finally, following my presentation of the findings of the systematic review of outcome measures for vitiligo and a survey of most desirable outcomes amongst patients and clinicians at the International Pigment Cell Conference 2011, (IPCC 2011, France), I proposed the inclusion of establishment of a core outcomes set for vitiligo into the agenda of the International Federation of Pigment Cell Societies (IFPCS).

The next step was to undertake an international consensus amongst researchers, clinicians and patients on the core outcomes and unified scales to measure these.

The initiation meeting to establish core outcomes set for vitiligo was held during the 21st European Academy of Dermatology and Venereology Congress (EADV), in September 2012. I have been appointed as a leader of this international consensus and am in the process of initiation a three-round e-Delphi exercise to establish the core outcomes set.

CHAPTER 4: PILOT TRIAL OF HOME INTERVENTION OF LIGHT THERAPY FOR VITILIGO (HI-LIGHT TRIAL)

Abstract

Background

Hand-held NB-UVB units are portable and light weight devices. Currently in the UK, phototherapy is usually reserved for widespread vitiligo and requires frequent hospital visits. Some evidence exists that treating vitiligo early may enhance the chance of successful repigmentation. Early treatment of limited vitiligo may be a promising approach.

Methods

This pilot trial determined the feasibility of conducting a large multi-centre RCT involving hand-held, home phototherapy. The primary objective was to establish the proportion of eligible participants and their willingness to be randomised. Secondary objectives included preparing an educational package on how to use the intervention, to deal with possible side effects, establishing participants' adherence to the treatment and testing the primary outcomes for the main trial (repigmentation, quality of life, cessation of spread).

This was a three arm placebo-controlled, parallel trial. Two devices were tested: Group A-active Dermfix; Group B-active Waldmann; Group C-placebo Dermfix. Twenty nine participants were randomised and treated for four months with

NB-UVB at home. Patients received training on the baseline visit. Outcomes were assessed on baseline and after 16 weeks of treatment. Patients and investigators were blinded.

Results

Recruitment was completed in three instead of the anticipated six months. Response rate for primary care and secondary care were 40% and 79% respectively. We identified 54/97 (55.6%) eligible patients but were able to allocate only 29 due to limited resources available. Ninety per cent (25/29) of patients adhered to the treatment. Eleven out of seventeen patients (65%) in the active groups had some degree of repigmentation, especially on the face and neck. Both devices have similar characteristics including output pre and post-trial and acceptability to participants.

Conclusions

The pilot trial showed that vitiligo patients are keen in participating in trials of home light therapy. The educational package was comprehensive and suitable for implementation at home.

4.1 Introduction

In chapter 1 of this thesis, I have described the epidemiology, aetiology of vitiligo and the major impact on the quality of life that vitiligo has on its patients. Currently, there is lack of firm clinical recommendation for the treatment of vitiligo and a great need for a large well conducted trial on vitiligo treatments (Whitton et al., 2010).

In chapter 2, the vitiligo Priority Setting Partnership (PSP) identified the Top 10 treatment uncertainties, in order to steer the international research agenda on topics important to patients and clinicians. Four of these treatment uncertainties included phototherapy (Table 2.5).

In this chapter, I describe a pilot, double-blind, randomised, controlled, multi-centre trial of hand-held narrow band-ultra violet light B (NB-UVB) phototherapy for the treatment of focal or early vitiligo at home. This pilot trial was used to inform the design and conduct of a national, multi-centre randomised controlled trial (RCT) for the treatment of vitiligo.

4.1.1 Current clinical practice for the treatment of vitiligo in the UK

In the UK, vitiligo patients are treated in both primary and secondary care. This is a chronic condition that requires long-term treatment. Patients can experience periods of rapid spread, and periods when the vitiligo is relatively stable (Gawkrodger et al., 2008). In order to induce remission, treatment is often given over periods of several months. Current British Association of Dermatologists (BAD) clinical guidelines for the diagnosis and management of vitiligo, recommend NB-UVB, tacrolimus and topical steroids (Gawkrodger et al., 2008).

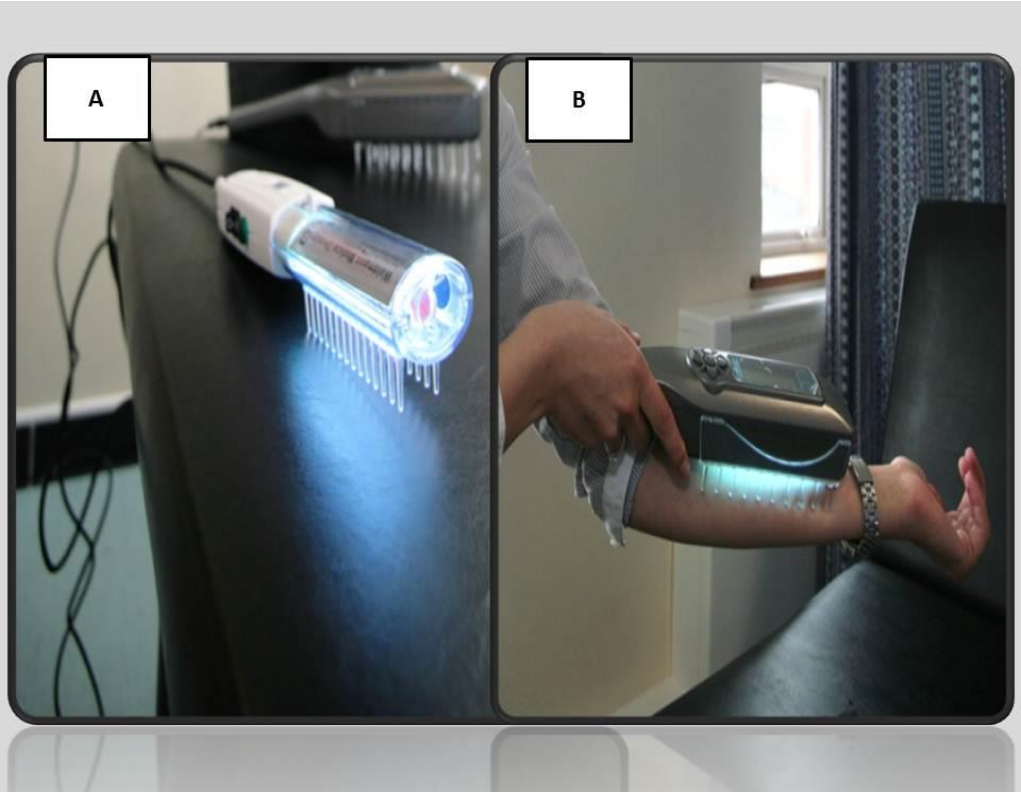
In the UK, NB-UVB is almost exclusively available in secondary care and most often used for **widespread vitiligo.** It requires regular visits to the hospital (usually three times per week for up to 12 months or 200 treatment sessions) (Gawkrodger et al., 2008).

Narrow-band refers to a specific wavelength of ultraviolet (UV) radiation, 311 to 312 nm. Currently, there are various devices available on the market for the delivery of NB-UVB: whole body units, hand and feet units and hand-held (targeted) units. The choice of the devices is usually based on

the size and location of the lesions and the percentage of the affected body surface (Ibbotson et al., 2004).

The lamps used in all units, including the hand-held devices, are TLO1 i.e. the same as hand/feet units and whole body units. Hospital NB-UVB usually involves whole body cabinets suitable for extensive, generalised vitiligo only i.e. large or multiple lesions. During the session, the participant goes into a specially designed cabinet containing fluorescent light tubes (whole body units). She/he stands in the centre of the cabinet, undressed except for underwear, and wears protective goggles. Usually the whole body is exposed to the UVB for a short time (seconds to minutes). NB-UVB is also used in the treatment of many other skin conditions including psoriasis and eczema.

The hand-held NB-UVB unit, is a portable and light weight NB-UVB device, which is slightly larger than a usual hairbrush (Picture 4.1).



Picture 4.1 Hand-held NB-UVB devices (A) Waldmann device and (B) Dermaray device

The hand-held device is held above any small area of the skin (10-12cm x 4-6.5 cm) and spacers are provided in order to standardise the distance from the skin. The lamp is held still, above the vitiliginous lesion. If the size of the lesion is bigger than mentioned above i.e. 10-12 cm X 4 cm, patients (or their parent or legal guardian) move the lamp slowly, above the vitiliginous area in circular movements. Hand-held NB-UVB units are suitable for small lesions, making phototherapy available for patients with limited disease.

Recently, a new European Guideline for vitiligo was introduced, suggesting early treatment of small lesions of recent onset and childhood vitiligo with combination of phototherapy and topical agents (Taieb et al., 2013); however suitable facilities and equipment are needed, if this new guideline is to be implemented in the UK.

Hand-held phototherapy units are currently used in Ninewells Hospital (Dundee, Scotland) for the treatment of psoriasis of the scalp mainly and in St. Woolos Hospital (Newport, Wales). Both hospitals have an international reputation for research into phototherapy and provide excellent phototherapy services. Hand-held phototherapy units have been trialled there as a way of meeting the needs of their patients due to the large geographical area covered.

Currently, there are several manufacturers of hand-held phototherapy units with the appropriate CE marking (IIb medical device) such as Waldmann and Androv. All have similar output as they use the same TLO1 bulb and are licensed to treat various skin conditions such as psoriasis of the scalp, vitiligo, and eczema. Hand-held phototherapy units are a new and potentially effective treatment for isolated areas of the body. Although no formal trials of the effectiveness of

this type of treatment have been conducted, participants have reported benefit (Yule, 2005).

4.1.2 Home phototherapy

Home phototherapy using whole body units is available for the treatment of other dermatological conditions such as psoriasis (Nolan et al., 2010). A recent, randomised, controlled trial comparing home (whole body units) versus hospital NB-UVB phototherapy for mild and severe psoriasis concluded that home phototherapy is equally effective and implies no additional safety hazards compared to hospital phototherapy. Most of the participants said they would prefer future phototherapy at home over hospital. Home phototherapy lowered the burden of the treatment and improved participants' quality of life (Koek et al., 2009).

Similarly, a small, retrospective questionnaire study for the treatment of non-segmental vitiligo showed participant-reported outcomes of home and outpatient NB-UVB therapy, as comparable, with similar repigmentation and occurrence of side-effects (Wind et al., 2010). In another questionnaire study that surveyed psoriasis, vitiligo, atopic dermatitis and mycosis fungoides, participants reported that all participants found home phototherapy to be effective, and agreed to continue, repeat and recommend it to others. The home

phototherapy units used in this study were hand/feet units and whole body units (Haykal and DesGroseilliers, 2006).

Although, there are currently no studies evaluating hand-held NB-UVB devices for vitiligo; trials on the effectiveness and safety of these devices on scalp psoriasis at home, showed that this treatment is effective, well tolerated, easy to use and safe for the treatment of psoriasis (Dotterud and Braun, 2000; Caccialanza et al., 1989).

4.1.3 NB-UVB phototherapy and carcinogenicity

The issue of how great is the risk of carcinogenicity of NB-UVB is still unclear as there is no good evidence to date. The information provided below, is a summary of existing evidence as well as recommendations of the British Association of Dermatologists (Gawkrodger et al., 2008) and the Photonet network (Managed Clinical Network (MCN) for Phototherapy) NHS Scotland.

Three studies, one with a very small number of participants (Weischer et al., 2004), and two others with limited follow-up (Man et al., 2005; Hearn et al., 2008) were unable to detect any definite increased risk of skin cancer following NB-UVB phototherapy. Few studies addressing the issue of possible carcinogenicity of broad-band UVB have been conducted but the overall impression has been that any

increased risk of skin cancer is low (Studniberg and Weller, 1993). A larger study on 1,380 participants, also showed that UVB remains a relatively low-risk treatment for psoriasis (Lim and Stern, 2005).

The adjusted (taking into account known risk factors, including PUVA exposure) incidence rate ratio for squamous cell carcinoma for >300 compared to <300 UVB treatments, was estimated at 1.37 (95% CI 1.03 to 1.83). Whether or not, the risk with narrow-band UVB is lower or higher than with broad-band UVB is not known (Photonet, 2010).

A recent study, performed on 1,514 participants with vitiligo and 2,813 participants with no vitiligo, showed that there is a mutually exclusive relationship between susceptibility to vitiligo and susceptibility to melanoma i.e. vitiligo patients may have protection against melanoma (Jin et al., 2010). However, there are no trials performed on the risk of carcinogenicity of NB-UVB phototherapy on vitiligo patients and the consensus is made mainly on data from psoriasis patients.

The BAD guidelines for diagnosis and management of vitiligo, advise that in view of the greater susceptibility of vitiliginous skin to sunburn and possible photo-damage (due to absence of melanin), it is advised that safety limits for NB-UVB

for the treatment of vitiligo are more stringent than those applied to psoriasis, with an arbitrary limit of 200 treatments for skin types I–III. This could be higher for skin types IV–VI at the discretion of the clinician and with the consent of the participant (Gawkrodger et al., 2008). However, this limit is based mainly on specialist consensus and more research is needed to establish the optimum number of treatment sessions as well as maintenance regimen for vitiligo.

4.1.4 Existing evidence behind phototherapy treatments for vitiligo

NB-UVB is considered to be more effective light therapy for the treatment of vitiligo compared to PUVA (Yones et al., 2007). Twelve trials compared NB-UVB as monotherapy to combination of NB-UVB with other agents (Whitton et al., 2010). The Cochrane systematic review concluded that the light combination interventions were superior to monotherapies. Some form of light therapy is probably needed in order to induce the development and proliferation of the pigment cells, hence repigment the skin. However, larger studies are needed in order to provide stronger evidence for the many combination interventions that have shown promise in treating vitiligo (Whitton et al., 2010).

Two studies have assessed the combination of ultraviolet light and topical corticosteroids (TCS) in treating vitiligo (Westerhof et al., 1999; Lim-Ong et al., 2005). Other studies have used a combination of these two treatments with other interventions (e.g. surgical treatments such as skin grafting) but the complexity of these multiple interventions make the findings less relevant. Many other studies have been published that assess combination treatments (including other light sources such as laser) with TCS, but again these combinations are sufficiently dissimilar to the proposed intervention in this pilot trial to limit their relevance. For example, the 308nm excimer light and excimer laser investigated in some of these studies has a similar wavelength to the NB-UVB, but the other properties of these light sources are very different from NB-UVB. A further update of the Cochrane review is currently underway, but this has not identified any other studies assessing the specific combination of UV light and TCS.

Previous studies, carried out to assess the effect of a combination of TCS and ultraviolet light, have considerable limitations. A trial conducted by Westerhof *et al (1999)* compared the combination of ultraviolet A light therapy and fluticasone propionate (a potent TCS) with mono-therapy, and showed evidence of improved pigmentation with combination

treatment. However, UVA is less widely used in recent years due to increased carcinogenicity compared to UVB.

Lim-Ong *et al* (2005) showed that a combination of clobetasol propionate (a superpotent TCS) and NB-UVB produced improved repigmentation relative to mono-therapy, but this trial recruited only 25 patients; five of whom did not complete the study. The dropout rate for this study was 20% (inconvenience of the hospital visits was cited as the main reason for this) (Lim-Ong et al., 2005).

Another study by Kroon et al in Amsterdam (trial registration: NCT01246921) assessing NB-UVB both alone and in combination with fluticasone propionate (a potent TCS) has recently been completed but final data are not yet available. This trial used full-body NB-UVB cabinets, as opposed to the hand-held devices to be used in this trial and aimed to recruit around 50 patients.

Recently, some evidence has emerged that, early treatment of generalised vitiligo may enhance the chance of successful repigmentation (Hallaji et al., 2012). An open, uncontrolled study on 63 patients, 26 patients with recent (up to 4 years duration) and 37 patients with long standing disease (greater than 4 years duration), found statistically significant difference in overall response between the two

groups. Good to excellent response (50-100% repigmentation) was noted in 61.5% of patients with recent vitiligo compared to 27% of patients in long standing vitiligo group (Hallaji et al., 2012). In addition, 2 case reports suggested that even acral vitiliginous areas, usually the most resistant body areas to any therapy, can be markedly improved by phototherapy if they have recent onset (up to three months duration) (Lee et al., 2010a). Finally, another 2 case reports, showed that recent (up to 5 weeks duration) vitiliginous lesions on the face were successfully treated with oral prednisolone and topical tacrolimus (Lee et al., 2010b).

In early stages of vitiligo (Chapter 1), some melanocytes are still present and functioning, providing a possible explanation for the results of the above described research. More studies are needed into the treatment of recent onset vitiliginous lesions (Lee et al., 2010a; Lee et al., 2010b).

4.1.5 The link between the Top 10 uncertainties and this pilot trial

The following four treatment uncertainties for vitiligo (out of the Top 10) refer to light therapy:

- Which treatment is more effective for vitiligo: calcineurin inhibitors or light therapy? (3rd uncertainty)

- How effective is UVB light therapy when combined with creams and ointments in treating vitiligo? (4th uncertainty)

- Which treatment is more effective for vitiligo: steroid creams or light therapy? (8th uncertainty)

- How effective is pseudocatalase cream (combined with brief exposure to UVB light) in treating vitiligo? (10th uncertainty)

Alongside the Top 10 treatment uncertainties, other important general themes to be considered when designing a trial for vitiligo are 1) the effectiveness and safety of vitiligo treatments for children and 2) the optimal timing to treat (early vs. late) vitiligo (Table 2.6) (Eleftheriadou et al., 2011). It is clear from the above that the evaluation of NB-UVB, for both children and adults is of great interest and importance amongst patients and clinicians.

Further evaluation of NB-UVB, both as combination therapy with topical agents as well as monotherapy, is needed. This would be feasible and more acceptable by using hand-held devices since topical treatments are already routinely used for focal disease, limited to a few small patches and/or early disease. Therefore, a pilot trial on home hand-held NB-UVB phototherapy would assist future research into the

treatment of vitiligo, based on the topics of importance for patients and clinicians (Eleftheriadou et al., 2011).

4.1.6 Significance of proposed pilot trial on home hand-held phototherapy for vitiligo

There are several benefits of using hand-held devices at home such as (Mysore, 2009):

- Reduction in attendance at hospital. Traditionally, patients receiving NB-UVB treatment would be required to attend hospital 2-3 times per week.
- Sparing of uninvolved skin as only vitiliginous skin is exposed to NB-UVB.
- Cheaper cost and less opportunity cost for patients such as travelling costs.
- Treatment can be provided at an early stage of their disease, when the intervention might be more effective. Whole body NB-UVB is normally limited to patients with extensive disease (Gawkrodger et al., 2008).

Should a hand-held device prove to be effective and safe for the treatment vitiligo at home, this could be an important addition to the treatment options available to participants with limited and/or early disease such as on the face, hands, ears,

lips, or early stages when only few patches are present. Also hand-held devices could be a suitable treatment option for patients wishing to treat visible areas of vitiliginous skin only such as face.

Feedback from patients (via the Vitiligo Society UK and the Vitiligo Support International) and healthcare professionals from the UK and other European countries also suggests that patients with vitiligo are currently buying these hand-held NB-UVB units for home use, and are using them in an unsupervised way. Questions such as how far away to hold the unit, how long to treat each area, whether the areas around the vitiligo should be covered/masked in some way, and how long before results are seen are persistently being asked (personal communication).

4.2 Objectives

The main aim of this pilot trial is to determine the feasibility of conducting a subsequent definitive randomised controlled trial (RCT) looking into the effectiveness and safety of home hand-held NB-UVB phototherapy units both compared to and in combination with a topical treatment for early or/and focal vitiligo.

The primary objective of this pilot trial is:

- To establish the proportion of eligible participants and their willingness to be randomised to home NB-UVB.

The secondary objectives are:

- To establish participants' adherence and satisfaction in using home phototherapy.
- To assess success of blinding of both participants and outcome assessors by using an identical placebo unit.
- To establish possible short term side effects i.e. if the device is suitable for home use with limited medical supervision.
- To manualise the treatment intervention (i.e. prepare a training package educating participants in how to use the intervention and how to deal with possible side effects).
- To define and test the primary and secondarily outcome measures and the methods of data collection for the main RCT.

This pilot trial did not aim to answer the question of whether the hand-held phototherapy devices are effective for

repigmentation and cessation of the spread of vitiligo or seek to change the CE authorisation for each device used.

4.2.1 Ethics approval

This trial was approved by the National Research Ethics Service (NRES) committee of East Midlands (REC reference: 11/EM/0031) and registered with the clinicaltrials.gov. The trial registration number is ISRCTN: NCT01478945. This trial was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the Department of Health Research Governance Framework for Health and Social care, 2005.

This study involved a CE-marked phototherapy unit that is being used within its normal licensing authorisation. As such, it did not require MHRA approval.

4.3 Methods

4.3.1 Trial configuration

This was a pilot, double blind, multi-centre, parallel group randomised controlled trial (RCT) of hand-held NB-UVB phototherapy for the treatment of focal or early vitiligo at

home. The trial was designed to establish the feasibility of conducting a large scale RCT. The acronym for this trial was *HI-Light trial* for vitiligo (**H**ome **I**ntervention of **Light** therapy **trial for vitiligo**).

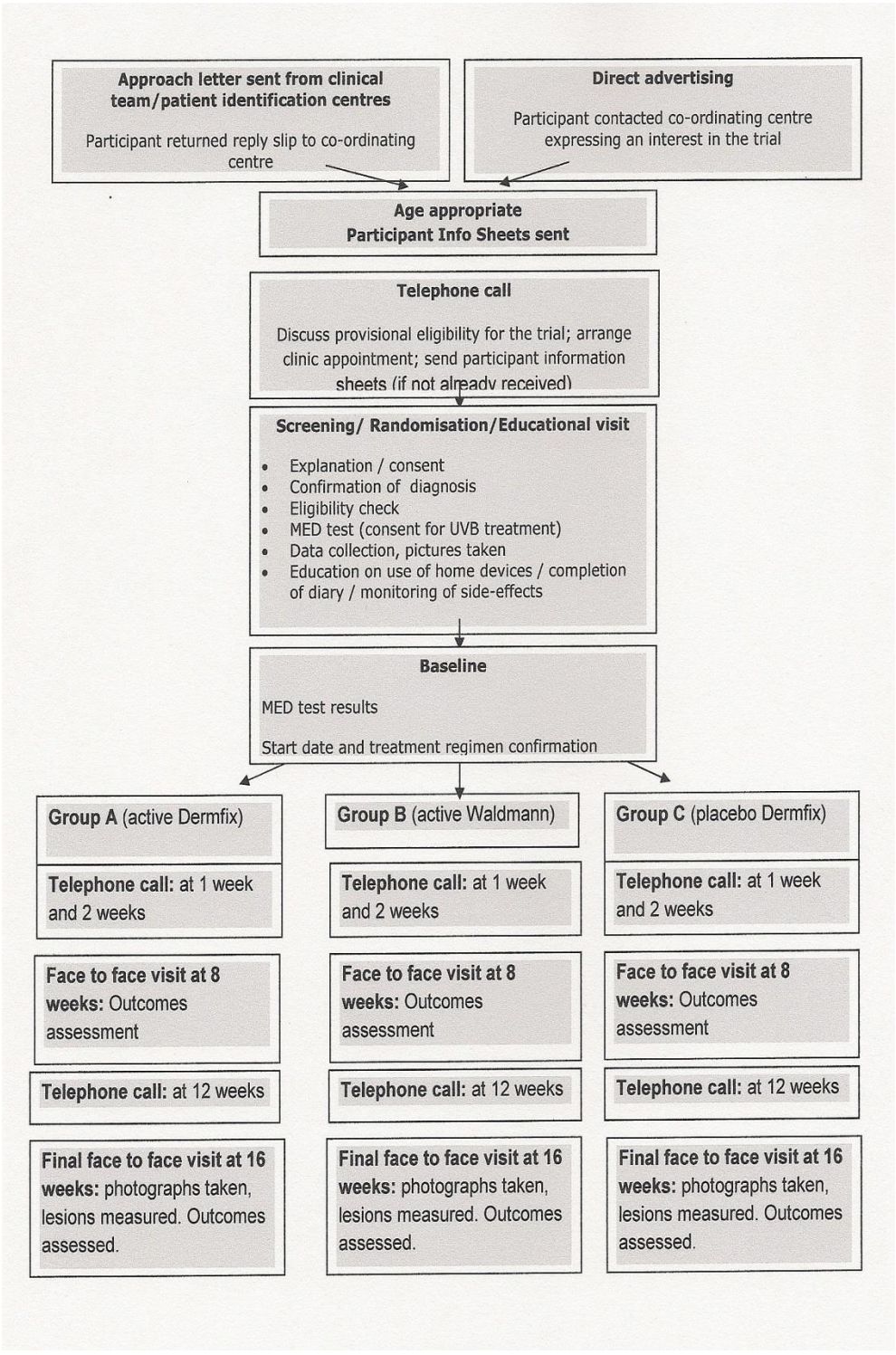
Overall duration of the trial was seven months: recruitment period lasted three months (1st of March to 31st of May) and treatment period lasted four months (until 31st of September). This treatment period was chosen due to time limitation for this pilot; therefore this is unlikely to be sufficient to achieve meaningful treatment response.

Participants were recruited from both primary and secondary care in Nottingham and Leicester. Mansfield community hospital and local GP practices (Nottingham and Leicester) were used as patient identification centres along with direct advertising to participants through the Vitiligo Society and the Centre of Evidence Based Dermatology (CEBD). Participants were randomly allocated to Group A (active Dermfix 1000), Group B (active Waldmann) and Group C (placebo Dermfix) in a 1:1:1 ratio. The allocation ratio to the active or placebo group was 2:1 (Figure 4.1).

This trial configuration was chosen as it reflected the participants' likely allocation to active and placebo groups in the main RCT, as the latter is most likely to be a three arm or

a factorial trial involving the use of NB-UVB in combination with topical treatment.

Figure 4.1 Flowchart of the pilot Hi-Light trial configuration



4.3.2 Participants, settings and outcomes

4.3.2.1 Recruitment and patient identification strategies

Recruitment into the trial took place in Nottingham, Queen's Medical Centre (QMC) and Treatment Centre (TC), and Leicester, Leicester Royal Infirmary (LRI). Mansfield community hospital and local GP practices (Nottingham and Leicester) were used as participant identification centres (PICs).

Patients' identification centres were asked to run search into their database and identify potential participants with diagnosis of vitiligo who were five years old or older i.e. to use only the above mentioned two criteria rather than all the inclusion/exclusion criteria of the trial. Primary Care Research Networks (PCRN) in both Leicester and Nottingham were involved. We focused on GP practices that were within 15 miles of the two recruitment centres (QMC and LRI). These included GP practices in Nottingham City, Nottingham county (southern part), Derby city, Derby county (southern part), Leicester city and Leicester/Rutland PCTs. Participants were only included in the trial if they were willing to travel to either Nottingham or Leicester-where the research teams were based.

The principal investigators of both recruiting centres (Dr Jane Ravenscroft and Dr Anton Alexandroff) were aware of this

pilot trial from the starting point of the development of the protocol (September 2011). Hence, they compiled a list of prospective vitiligo patients, who were willing to be informed about the trial.

The initial approach letter for potential participants identified in secondary and primary care was sent from their clinical care team in the first instance and included brief information about the trial and a reply slip (Figure 4.1). Adverts were placed on the website of the UK Dermatology Clinical Trials Network (UK DCTN), the Centre of Evidence Based Dermatology and patient support group, the Vitiligo Society UK. In the event of the number of participants identified by using the above means was not sufficient, our research team was prepared to also place adverts in local newspapers and radio, targeting black and ethnic minorities. Finally, posters were placed in the dermatology departments of recruitment sites. A dedicated website (www.vitiligostudy.org.uk) was available for the purpose of this trial.

The following criteria were used to identify suitable participants for this trial:

Inclusion criteria

1. Participants with a diagnosis of vitiligo confirmed by a dermatologist. Participants with focal disease, less than 25% of body surface area.

2. Age: children and adults (no upper age limit). Children aged ≥ 5 years of age were eligible as long as they were mature enough to understand that the eyes must be kept closed, and to remain still for the duration of treatment sessions.

3. No therapy for vitiligo in the previous two weeks and no other vitiligo treatment during the trial other than as per trial protocol.

4. Participants with both spreading and stable disease

5. Participants able to give informed consent (or their parents/legal guardians).

Participants were instructed to treat all their vitiliginous lesions; however for the purpose of the trial, up to three representative lesions were chosen by the research nurse and patient, preferably on three different anatomical areas e.g. face, hand, and leg, in order to assess treatment response and trial logistics at different body sites. Only representative lesions were included in the analysis. If there were any lesions that participants did not want to treat, such as on non-

exposed sites or areas difficult to reach, e.g. back, this was agreed with the research nurse at the beginning of the trial.

The body surface area was estimated and recorded using the rule of nine (Chapter 1, page 47, VEFT vitiligo scoring and evaluation form) by calculating the affected area as a percentage of the whole body i.e. face and neck, upper limbs as 9% of the whole body surface each, 18% for the lower limps and anterior trunk each and 1% each for genitals, each palm and the back of each hand.

Exclusion criteria

1. Segmental vitiligo
2. Universal vitiligo
3. Previous history of skin cancer
4. Recent or concurrent radiotherapy
5. Photosensitivity
6. Use of immunosuppressive or photosensitive drugs
7. Pregnant or lactating women
8. Any major medical co-morbidities
9. Patients with vitiligo limited to the genitalia only, as these areas would not be suitable for phototherapy.

4.3.2.2 Informed consent

All participants (or their parent/legal guardian if a participant was under the age of 16) provided written informed consent before they entered the trial. In addition to the main trial consent form, an additional consent form was signed on completion of the NB-UVB training session to confirm that the training took place and that participants (or their parents / legal guardians) understood how to use the devices during the trial. Once the consent forms were signed, a letter was sent to the participant's GP informing them about their recruitment in the trial.

4.3.2.3 Outcomes

The primary outcome measure of interest for this pilot trial was the proportion of eligible participants with vitiligo who were willing to be randomised. This is the most critical component of the success of any future trial examining the effectiveness of hand-held NB-UVB for the treatment of vitiligo.

The secondary outcomes were designed to further facilitate the design of a larger, controlled multi-centre trial:

- Number of participants accepting the initial invitation to participate

- Proportion of participants fulfilling trial eligibility criteria
- Proportion of participants adhering to the treatment protocol
- Proportion of participants who were satisfied with the treatment and the Dermfix units in groups A and C and the Waldmann units in group B.
- Proportion of participants for whom the blinding of the assessor was maintained
- Proportion of participants for whom the blinding of the allocated group (active or placebo) was maintained
- Percentage of missing data and withdrawal rates
- Incidence of NB-UVB short term adverse events
- Outcome measures for the main large trial were also tested:
    - Repigmentation rate of vitiliginous lesions presented in percentage of repigmentation quartiles: negative-0%, 1-24%, 25-49%, 50-74%, 75-100%. Size of each representative lesion was traced by using skin mapping technique at baseline and week 16 visits. ConvaTec transparencies were

used to trace the lesions. These were later transferred onto clear film sheets and scanned. Scanned lesions were measured by using a freely available software for analysis and measurements of digital images, the ImageJ 1.47d (Image processing and analysis in Java by the National Institute of Health, USA; http://imagej.nih.gov/ij)

- Cessation of spreading of vitiligo. Disease activity, both overall as well as for each representative lesion separately, was assessed on the baseline and the 16 week visits. In particular, patients were asked if they had noticed any new vitiligo lesions appearing or spreading of old ones during the past year. The same question was asked for each representative lesion i.e. whether the lesion in question was stable, spreading or spontaneously repigmenting during the last 12 months.

- Impact on the quality of life of participants. This was assessed using Dermatology Life Quality Index (DLQI) for adults (Finlay and Khan, 1994) and Children Dermatology Life Quality Index (CDLQI) (Lewis-Jones and Finlay, 1995) for

children on baseline and week 16 hospital visits. DLQI and CDLQI estimate the effect of a disease on patients quality of life i.e. the larger the score the bigger the effect is on patient's life (0-1 = no effect at all; 2-5 = small effect; 6-10 = moderate effect; 11-20 = very large effect; 21-30 = extremely large effect). Therefore, reduction in DLQI and CDLQI scores are interpreted as satisfaction with the treatment.

- Global improvement in disease assessed by participants and researchers. The patient, research nurse and the independent outcome assessor, were asked at week 16 hospital visit, to rate the overall changes in patient's vitiligo ("How would you rate the overall changes in patient's vitiligo?") using a 5 point Likert-scale (much worse; a bit worse; no change; a bit better and much better).

- Participant-defined outcome questionnaire for vitiligo, Patient's Benefit Index (PBI) (Augustin et al., 2008) (Chapter 1, page 52). PBI was calculated on the basis of the patient's defined need questionnaire completed at baseline and the patient's benefit questionnaire completed at week

16 visit. The needs prior to therapy and the benefits achieved by therapy were converted to a weighted index value, the PBI. Its values range from zero (no benefit) to four (maximum benefit) (Augustin et al., 2008).

- Satisfaction with response, including cosmetic acceptability of the results. Satisfaction with the treatment response was assessed by asking participants to rate how satisfied they were after the completion of the trial ("How satisfied are you with the treatment?"). In addition, patients and research nurses were asked to rate the colour match of each representative lesion as bad, good, fair or excellent ("Please rate the colour match of your or your patient's vitiligo patches following light treatment") at week 16 appointment.

4.3.3 Trial procedures

4.3.3.1 Pre-trial contact (telephone call/ email) (Figure 4.1; Table 4.1 and 4.2)

On receipt of a potential participant's contact details (either in response to approach letter, or through advertising),

an age-appropriate information sheet was sent and a member of the research team based at the co-ordinating centre, made contact, either by telephone or e-mail. An overview of the trial was given and provisional eligibility was established. If the participant was potentially eligible and willing to attend for a screening visit, an appointment with a research nurse and a dermatologist was made, at the closest participating hospital.

4.3.3.2 Screening / randomisation / educational visit

During this visit the participant (or their parent/legal guardian) was given the opportunity to discuss the trial further, with a member of the trial team and answer any questions they might have had.

The initial trial visit took approximately 1.5-2 hours and included the following activities:

- Informed consent.
- Confirmation of diagnosis and suitability for NB-UVB treatment by a dermatologist.
- Confirmation of other eligibility criteria.
- Confirmation of vitiliginous lesions to be treated and assessed.
- Collection of outcomes and baseline data.

- Conduction of Minimum Erythema Dose (MED) test in order to establish participant's treatment plan (page 209 for MED test methods).

- Training session on how to use the UVB devices, how to complete the treatment diary and what to do in case of side effects (page 216).

4.3.3.3 Baseline visit

Participants returned to the hospital the following day and their MED results were read. MED results were recorded in the participants' notes. If a participant failed to return after 24 hours for the results of the MED test, then the starting dose for their skin type, determined by a dermatologist was used.

The start date of the treatment was confirmed with the participants, by taking into consideration the two weeks washout period, in case the participant was on any treatment for vitiligo. Participants were given their home UVB device (boxed and sealed in order to protect blinding of the research nurse).

4.3.3.4 Scheduled Interim Follow-up visits and Telephone calls

Interim follow-up contact with the participant was scheduled as follows:

- 7 days (telephone call)

- Week 2 (telephone call)
- Week 8 (2 months) (face-to-face visit at clinic)
- Week 12 (3 months) (telephone call)
- Week 16 (4 months) (face-to-face visit at clinics)

These follow-up contacts enabled the trial team to answer any questions and to address any areas of concern the participants had and provided support and reassurance for the participants, if needed.

During the follow-up contacts (telephone calls and face-to-face visits), all the participants were asked about adherence to their treatment plan and reminded about the correct use of hand-held phototherapy.

4.3.3.5 Week 8 clinic visit

The 8 week face-to-face visit was conducted at the hospital and relevant outcomes were measured (Table 4.1).

4.3.3.6 Final Trial visit at 16 weeks

At this visit, the following trial procedures were carried out:

- Participants were clinically examined and outcomes recorded by both their usual research nurse and by an independent assessor. This was done

primarily in order to test the feasibility of the blinding of the outcome assessor for the main RCT.

- Assessment of success of blinding was achieved by asking the research nurse and participants to guess the group to which the latter had been allocated (active Group A and B or placebo group C).

- Assessment of the secondary outcomes, such as re-pigmentation rate of representative vitiligo lesions, cessation of spread of vitiligo, impact on the quality of life, global improvement and short term side effects of phototherapy. Participants were asked to score their satisfaction with the treatment and global improvement in their vitiliginous lesions based on digital images taken on the baseline hospital visit.

- Adherence to the phototherapy regimen was assessed through the participants' diaries.

- Participants were asked for their opinion on their participation in the trial. Issues that were addressed, included acceptability of the intervention, reasons for non-adherence and any suggestions of how the trial could be improved from a participant's perspective. All the participants were asked if they would like to join the

Centre of Evidence Based Dermatology mailing list in order to be contacted regarding future research.

Participants, who were in the placebo group, were offered the opportunity to use the active device at home for further four months if they wished.

Table 4.1 Summary of Hi-light trial schedule and procedures which took place during each visit

	Pre-trial contact	**Screening/ enrolment/ educational visit**	**Baseline visit**	**Follow-up telephone calls (Weeks 1, 2, 6 & 12)**	**Follow-up face-to-face visit (Week 8)**	**Final trial visit (Week 16)**
Discuss trial-pre-screening	√	√				
Obtain informed consent		√				
Check eligibility Including MED test Randomisation		√				
MED test results			√			
Outcomes assessment		√			√	√
Education on hand-held devices including how to deal with side effects, detailed treatment schedule		√	√			
Assessment of phototherapy short-term side effects				√		√
Discuss trial progress and any skin problems				√	√	√
Discuss adherence to the treatment regimen and satisfaction with the device				√	√	√

Table 4.2 Summary of Hi-Light trial schedule and duties of each member of research team

	Dermatologist	CLRN nurse/staff	Trial manager (Dr Viktoria Eleftheriadou)	Central CLRN Administrator
Pre trial		• Provide info about the trial by telephone/email	• Provide info about the trial by telephone/email • Pre-eligibility check over the phone	• Provide info about the trial • Pre-eligibility check over the phone • Advertising and publicity
Screening/ Randomisation/education visit	• Confirm diagnosis • Confirm participant's skin type • Issue prescription for phototherapy	• Provide info about the trial and obtain informed consent • Data collection • Educational session on how to use the devices • Perform MED test	• Provide info about the trial and obtain informed consent • Data collection • Educational session on how to use the devices • Perform MED test	• Randomisation • Package hand-held phototherapy units ready for distribution according to randomisation schedule
Baseline visit	• MED test results	• MED test results	• MED test results	
Follow-up telephone calls		• Conduct telephone follow-ups including book appointments	• Coordinate appointments and follow-up calls at all recruitment	• Conduct telephone follow-ups and coordinate appointments at

		as appropriate • Refer to dermatologist if necessary	sites • Refer to dermatologist if necessary	sites
8 weeks visit		• Take digital images of vitiliginous lesions • Conduct outcome assessment • Monitor adherence • Monitor side effects and refer to dermatologist if any concerns	• Take digital images of vitiliginous lesions • Conduct outcome assessment • Monitor adherence • Monitor side effects and refer to dermatologist if any concerns	
16 weeks visit	• Conduct blinded outcome assessment*	• Take digital images of vitiliginous lesions • Monitor adherence • Monitor side effects Conduct outcome assessment • Conduct blinded outcome assessment*	• Take digital images of vitiliginous lesions • Monitor adherence • Monitor side effects • Conduct outcome assessment • Conduct blinded outcome assessment*	

Overall care	• Provide medical cover for any adverse events that require medical attention • Be the first point of contact for serious adverse events for out of hours or weekends (on-call dermatology SpR)	• Provide medical cover if needed for any adverse events that require medical attention	• Trial manager duties i.e. be the first point of contact and coordinate all the recruitment sites, ensure the appointments are booked, the CRFs are up to date, photos are taken • Be the first point for contact for participants and investigators regarding the trial configuration and conduction • Provide medical cover if needed for any adverse events that require medical attention	• Be the first point of contact for side effects or advice on how to use the device or deal with side effects (from 9:00 to 17:00 Monday to Friday) • Refer to dermatologist or nurse if needed for review

*A dermatologist or a research nurse was able to act as an independent outcome assessor only for patients, he (she) did not assess at baseline, week 8 or any unscheduled telephone calls or visits. In other words, the independent assessor should have not had any previous contacts with the patient during the trial except baseline visit in order to remain blinded.

4.3.3.7 Unscheduled and emergency calls/visits

Participants were asked to record any side effects in their diaries and contact the co-ordination centre for advice if needed, at any point during the trial. If the participant developed any side effects such as redness, dry skin, burn, blister, cold sores etc., they were asked to call the central administrator first, who then arranged for them to see a dermatologist if needed.

Participants were also given the contact details of their local hospital, which they were instructed to contact if they needed advice out of hours or over the weekend, regarding side effects. The on-call dermatology SpR (who was briefed in advance about the study) provided advice over the telephone or asked the participant to attend the dermatology department if needed.

4.3.3.8 Withdrawal

If a participant wished to withdraw from the trial, they were asked to attend for a final trial (withdrawal) visit. At this visit, the same procedures as for the final trial visit at four months were carried out, if the participant was willing to attend. If the participant was not willing to attend, then as a minimum, the trial team attempted to establish the reason for withdrawal by a telephone interview. The device had to be

returned to their local hospital or, if this was not feasible, sent back by recorded delivery.

4.3.3.9 Criteria for terminating the trial

This was a pilot trial to explore the logistics of the definitive main RCT. It involved CE-marked phototherapy units that were being used within their normal licensing authorisation. As such, this trial had a very low risk. However, if severe adverse effects, associated with the unit, would have occurred frequently, the study would have been terminated.

4.3.4 Trial management

The trial was co-ordinated from the Centre of Evidence based Dermatology, by the Trial Manager (myself). A Trial Management Group (TMG), which included me, Professor Hywel Williams, Dr Kim Thomas, Dr Jane Ravenscroft, Dr Robert Dawe, Mrs Maxine Whitton and Dr Jonathan Batchelor, held two teleconferences, every three months depending on the requirements of the trial as it progressed. The trial was supported by two part-time CLRN nurses in Nottingham and one in Leicester.

This small pilot trial and so both the Data Monitoring Committee (DMC) and the Trial Steering Committee (TSC) was not deemed necessary.

The Chief Investigator had overall responsibility for the study and oversaw all study management with a trial manager (myself) responsible for the day to day running of the study.

4.3.5 Data collection

Each participant was assigned a trial identity code number, allocated at the pre-screening stage, for use on the case report forms (CRFs), other trial documents and the trial database. The database also used the initials of the participant and their date of birth. CRFs were treated as confidential documents and held securely in accordance with Data protection regulations. A separate confidential record was kept of the participant's name, date of birth, local hospital number or NHS number, and Participant Trial Number (the Participant Screening and Enrolment Log), to permit identification of all participants enrolled in the trial, in case additional follow-up was required. CRFs were restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Site Delegation Log.'

All trial staff and investigators endeavoured to protect the rights of the trial's participants to privacy and informed consent, and adhered to the Data Protection Act, 1998. The CRFs were held securely, in a locked room and locked cabinet both centrally, at the Centre of Evidence Based Dermatology (CEBD), and locally, at the relevant hospital. Access to the information was limited to the trial staff and investigators and relevant regulatory authorities if needed.

The database was designed specifically for this trial (IT expert-Graham Watson). Once the paper CRFs were completed by the research nurse, they were then faxed over to the CEBD and entered onto the database by the co-ordination centre administrator. A sample of CRFs (10%) was checked for verification of all entries made, by the trial manager (VE). All electronically held data, including the trial database were held securely and password protected. Electronic data was backed up every 24 hours to both local and remote media in encrypted format.

4.3.6 Intervention

4.3.6.1 Hand-held devices

In the introduction section of this chapter, I outlined the basic characteristics of hand-held devices. These units are CE-marked and are being used within their licensing agreement.

In this trial I explored two different hand-held NB-UVB devices, Dermfix 1000 NB-UVB and Waldmann NB-UVB 109, with the same output, but a few differences such as the size of treatment area, weight of the unit and cable length (Table 4.3). By doing this I was able to monitor and assess which of the two units was best tolerated in terms of participants' satisfaction and minimisation of side effects, if any. The information gathered assisted in the choice of device for the main RCT.

Finally, I have also identified another hand-held NB-UVB device with various automated features such as treatment regimen based on skin type, dose reduction in case of side effects and calculation of total treatment sessions and total exposure time. However, this device is not approved for use in Europe yet.

Group A participants were using Dermfix 1000 NB-UVB (device A), Group B participants were using Waldmann NB-

UVB 109 (device B) and Group C received a placebo Dermfix 1000 NB-UVB (device C).

Both devices (A and B) are phototherapy lamps with an on/off switch and an external digital timer. The user of each device had to follow the written treatment plan, set and re-set the timer each time manually and keep an accurate diary of exposure times and post treatment side effects.

Table 4.3 Characteristics of various hand-held NB-UVB (311 nm) devices freely available for sale on the internet

Features	**Dermfix 1000 NB-UVB by Androv**	**Waldmann NB-UVB 109**	**Dermaray UV 109**
			
Digital timer	External "kitchen timer" Needs manual resetting prior each treatment session	External "kitchen timer" Needs manual resetting prior each treatment session	Integrated automated timer Calculates automatically treatment time based on patient's skin type
Automatic treatment plan	No	No	Yes Automatically reduce dose in case of side effects o
Integrated diary	No Patients must keep diaries: lesion name,	No Patients must keep diaries: lesion name,	Yes Able to store up to 32 lesions for each patients, automatically calculate

	treatment time and side effects	treatment time and side effects	treatment time based on 1) treatment session and 2) side effects from previous treatment session
Safety features from overexposure	Spacer (plastic teeth)	Spacer (plastic teeth)	Spacer (plastic teeth) Automatically switch off after each treatment session. Other alerts (i.e. lamp not hold correctly or if used a next day rather than the day after next of the previous treatment)
Power supply	Has to be connected to the socket all the time	Has to be connected to the socket all the time	Rechargeable battery (or connected to the socket)
Compliance monitoring	n/a	n/a	Stores total treatment session number and total exposure time.
Weight	Light	More heavy compared to other two	Light
Treatment window shape and size	Oval 12 X 6.5 cm	Rectangular 10 X 4 cm	Rectangular 10 X 6 cm
Price	£165	£256	$ 695
CE marking	Class IIb medical device	Class IIb medical device	Class I TGA (Australia) and CE medical device i.e. not licenced for medical use in Europe yet

The placebo device used (C), was identical to the active device Dermfix 1000, with the only difference, being that a special plastic cover which blocked the emission of NB-UVB rays was used, instead of the standard cover used on the active devices. Both covers (on active and placebo units) were visually identical.

4.3.6.2 Treatment plan

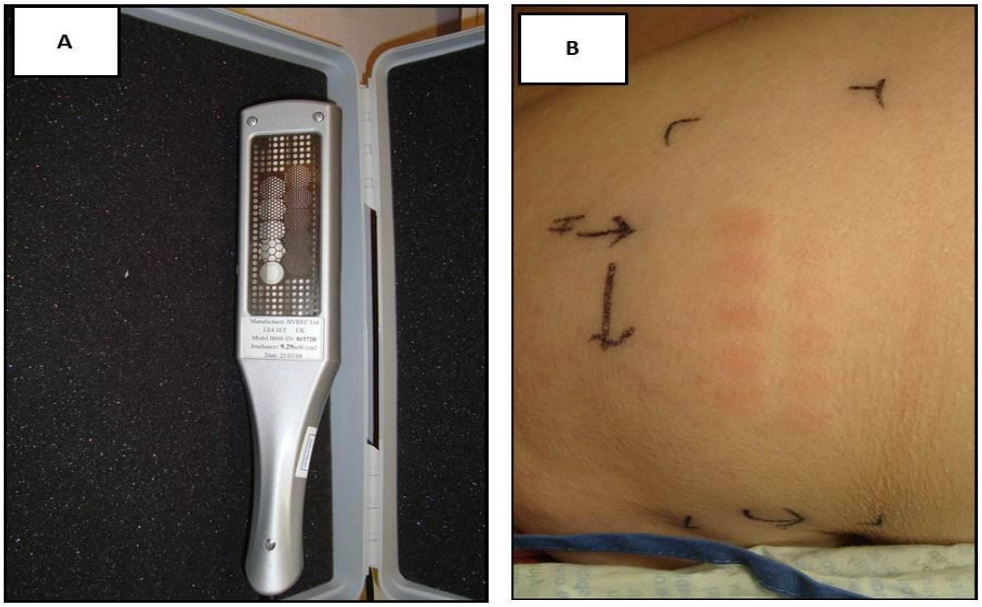
Each participant received a personalised treatment plan according to his/her Fitzpatrick skin type. There were four treatment plans available: skin type I, II, III and IV-VI (Table 4.4). Each plan included treatment times per session for the first 60 sessions i.e. until the maximum exposure time (MET) was reached (Table 4.4).

Table 4.4 Summary of treatment schedule according to the participants skin type

Skin Type	Starting time	Exposure time +20% of treatment 1	Exposure time -20% of treatment 1	Maximum exposure time (MET)	Total duration
I	15 sec	+3 seconds	-3 seconds	3 min	4 months
II	20 sec	+4 seconds	-4 seconds	4 min	4 months
III	25 sec	+5 seconds	-5 seconds	5 min	4 months
IV	30 sec	+6 seconds	-6 seconds	6 min	4 months
V	30 sec	+6 seconds	-6 seconds	6 min	4 months
VI	30 sec	+6 seconds	-6 seconds	6 min	4 months

At the screening/randomisation/educational visit, the skin type for each participant was established by 1) a dermatologist (criteria for Fitzpatrick skin type table 4.5) and 2) a Minimal

Erythema Dose (MED). During the MED test, the skin was exposed to 10 doses of NB-UVB. The test was performed by using Durham UVB erythema test device (Hybec MED tester), a portable device which is the same size as the hand-held NB-UVB lamps. The device has 10 apertures with different grid densities, which determined the dose of light emitted (Picture 4.2). The MED test was performed on inner surface of the participant's forearm. We aimed to perform the test on skin affected by vitiligo, however normal skin was used, if the above mentioned area was not affected by vitiligo or the patch was not big enough. Participants were required to return the following day for reading of the MED test result (Picture 4.2).



Picture 4.2 (A) Durham UVB erythema test device by Hybec (B) Picture showing skin after a Minimal Erythema Dose test

Manufacturers of the devices suggest a treatment plan according to the patient's skin type determined by standard criteria (Table 4.5) for Fitzpatrick skin type, rather than the results of the MED test. In order to test the suitability of the treatment plan provided by the manufacturers, I compared the results of the MED test determined skin type and the dermatologist recorded skin type. This was important in order to determine whether or not the MED test was necessary for the future RCT, or whether dose based on a dermatologist recorded skin type alone was safe and effective.

Table 4.5 Criteria for Fitzpatrick skin types

I	Always burns, never tans
II	Usually burns, tans less than average (with difficulty)
III	Sometimes mild burn, tans about average
IV	Minimally burns, tans more than average (with ease)
V	Rarely burns, tans profusely
VI	Never burns, tans profusely

Based on the average MED for various skin types (Palmer et al., 2006) (Figure 4.2), the initial dose (treatment session 1) was approximately ¼ of the dose causing erythema

for example, for skin type I, the median MED is 200 mJ/cm^2 and the dose that a participant with the same skin type received was 54 mJ/cm^2 (Table 4.5).

Figure 4.2 Median MED (in mJ/cm^2) for each Fitzpatrick skin type compared to initial treatment doses in this trial.

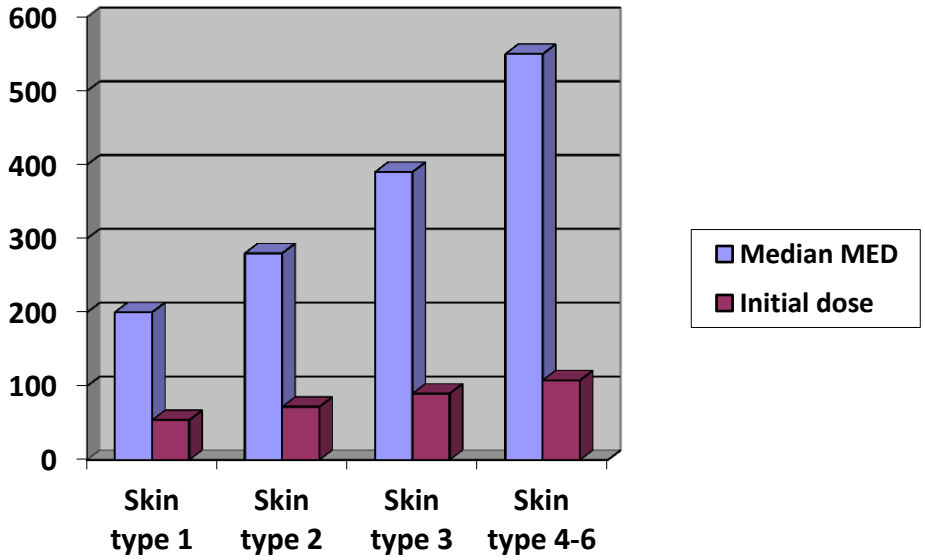


Table 4.6 Summary of the Minimal Erythema Dose (MED) test results (in J/cm^2) in correspondence to the phototherapy treatment plan prescribed.

Dosage in J/cm2				**0.50**	
MED tester aperture	**MED performed on normal skin (J/cm^2)**	Treatment regimen according to MED normal skin	MED tester Aperture	**MED performed on vitiligo skin(J/cm^2)**	Treatment regimen according to MED vitiligo skin
Open	0.5	**Fitzpatrick's skin type 4-6**	Open	0.5	**Fitzpatrick's skin type 4-6**
2	0.45	**Fitzpatrick's skin type 4-6**	2	0.45	**Fitzpatrick's skin type 4-6**
3	0.38	**Fitzpatrick's skin type 3**	3	0.38	**Fitzpatrick's skin type 4-6**
4	0.31	**Fitzpatrick's skin type 2**	4	0.31	**Fitzpatrick's skin type 4-6**
5	0.24	**Fitzpatrick's skin type 1**	5	0.24	**Fitzpatrick's skin type 4-6**
6	0.18	**Fitzpatrick's skin type 1**	6	0.18	**Fitzpatrick's skin type 3**
7	0.15	**Fitzpatrick's skin type 1**	7	0.15	**Fitzpatrick's skin type 2**
8	0.13	**Fitzpatrick's skin type 1**	8	0.13	**Fitzpatrick's skin type 1**
9	0.10	**Fitzpatrick's skin type 1**	9	0.10	**Fitzpatrick's skin type 1**
10	0.08	**Fitzpatrick's skin type 1**	10	0.08	**Fitzpatrick's skin type 1**

Skin type I	Treatment time
Treatment 1	15 sec
Treatment 2	18 sec
Treatment 3	21 sec
Treatment 4	24 sec
Treatment 5	27 sec

Table 4.7 Example of individualised treatment plan for skin type I for the first five sessions (see Appendix for treatment schedules for all skin types)

If the starting dose suggested in the table 4.6 was more than the MED for the individual participant, the protocol was adjusted i.e. the treatment plan prescribed was approximately 50% of the MED test results, performed on vitiliginous skin or approximately 25% of the MED test results performed on normal skin. In case the MED test results were unreadable, skin type recorded by the dermatologist was used as a guidance to determine participant's treatment plan.

By performing the MED tests and by using cautious treatment plan times, the safety of the trial participants was ensured (Palmer et al., 2006).

4.3.6.3 Treatment plan and erythema

The treatment was self-administered by the participants or their carers on alternate days i.e. participants were advised to undergo treatments at least three times a week and no

more than four times a week but never on consecutive days. The initial time of exposure on vitiliginous lesions corresponded to the starting time on the table 4.6 as above. For each treatment session, the exposure time was incremented by 20% of the treatment 1 time (Table 4.4 and 4.7). Participants continued to increase their exposure time if they did not have any erythema reactions, until the maximum exposure time (MET) (Table 4.4) was reached. Once the MET was reached, the exposure time of all consecutive treatment session remained the same i.e. equal to the MET.

In case of a Grade 1 erythema (settles within a day; NOT painful), participants were instructed to decrease the exposure time by 20% of treatment 1 time e.g. if the participant experienced grade 1 erythema after the 3rd treatment (21 seconds), she/he administered 18 seconds rather than 24 on the day of treatment four (Table 4.7).

In the case of a Grade 2 erythema (lasts for around two days. NOT painful), the participant missed a treatment day and was instructed to decrease the exposure time by 20% of the treatment 1 time e.g. if after treatment session three on Monday, the participant developed a Grade 2 erythema, he/she missed the next treatment day on Wednesday and

continued on Friday with decreased time exposure as per treatment two i.e. 18 sec.

In the case of a Grade 3/4 erythema (very red, like sunburn, lasts for two – three days, hot and painful, with possible blistering), the participant was instructed not to treat vitiliginous lesions and to seek medical advice from the research team. If this occurred, participants were instructed to stop treatment and to seek medical advice.

The following instructions relating to missed treatments that are NOT due to erythema reaction were given to the patients:

1) One or two missed treatments: administer exposure time decreased by 20% of treatment 1 time i.e. same as per erythema Grade 1.

2) Three treatments or more missed: contact the research team for advice.

4.3.7 Training sessions

4.3.7.1 Training sessions for research staff

Before the initiation of the trial the research nurses attended four training sessions on:

- How to deliver face-to-face training session to the participants of the trial. The session was delivered by both me and a phototherapy nurse from Dundee (Mrs Susan Yule). This session included a role play with a volunteer psoriasis patient, member of the Centre of Evidence Based Dermatology (CEBD) patient panel.

- How to measure outcomes, complete the appropriate CRFs and conduct the screening/randomisation/educational, baseline, week 8 and week 16 hospital visit training during the trial (three sessions). I organised and delivered these sessions. These sessions also included MED test training, reminder on what and how to advice the participants in case of side-effects during the trial and how to reduce the treatment times. A detailed guidance manual with all the above covered information was also given to the research nurses (see appendix).

Finally, the co-ordination centre administrator was also trained on how to provide information about the trial to the potential participants and pre-screen them over the telephone, how to complete the relevant follow-up calls CRFs and how to

provide guidance to the participants on possible side effects. The above training was performed by me.

4.3.7.2 Training session for participants

During the screening/randomisation/educational hospital visit, each participant received a one-to-one training session with a member of the research team (either by me or a research nurse) on how to self-administer phototherapy at home correctly. The training session lasted between 40 min and 1 hour.

The educational session included the following:

- Safe operation of the hand-held phototherapy device.
- Accurate recording of treatment i.e. how to fill in the treatment diary.
- Possible short term side-effects of the NB-UVB phototherapy and how to deal with them including the contact details of appropriate people to contact in case of emergency.
- Correct administration of treatment according to the treatment plan, which included adjustment of the treatment time according to the erythema response.

- A supervised treatment session.

If the participant was a child, the carer or parent was required to accompany him/her during the educational session in order to be taught how to administer the treatment at home. If the participant or their parent/carer did not demonstrate competence in administering treatment, then the training programme was extended.

On completion of the training session, each participant was supplied with a "participant pack", which included a training manual on how to deal with side-effects and adjust treatment times accordingly (see appendix), a treatment diary, UV protective goggles, a pair of cotton gloves to be worn during each treatment and protect hands from overexposure and a copy of consent forms (pre and post training session).

4.3.8 Adherence

Participants' adherence to the treatment was monitored by reviewing their treatment diaries. Participants or their parent/legal guardian (active and placebo) were asked to complete a treatment diary with details of the date of treatment, duration of treatment for each lesion and presence or absence of any side-effects from the previous treatment

session. Participants were instructed to complete their treatment diaries accurately and before each treatment session.

During the follow-up telephone calls and the week 8 hospital visit, participants were reminded to fill out their diaries in order to ensure their own safety.

Adherence was monitored using the following parameters:

- Number of treatment sessions per week i.e. three to four.
- At least one day should be left between consecutive treatment sessions.
- If a treatment session was missed due to side effects and the treatment plan was resumed correctly, participants were considered compliant with the treatment plan.
- In case of missed sessions due to side effects or any other reasons, the treatment time had to be reduced correctly, as per instructions given in the patient's manual and training session.

4.3.9 Output of the hand-held phototherapy units

During this trial, I collaborated with the Medical Physics and Clinical Engineering department of the Nottingham University Hospitals NHS Trust, Queens Medical Centre. This was necessary in order to 1) conduct the safety testing of the devices prior to the trial (as a standard procedure for all NHS trials involving devices) and 2) investigate the output of the two hand-held devices used in this trial in order to assist the decision on which one to use in the main trial.

For the characterisation of these devices, three main parameters were measured pre-trial and post-trial for each device: 1) device output (both irradiance and integrated dose), 2) output variation with respect to time and 3) tube spectral profile.

All the testing and measurements were performed and provided by Mr Richard Farley-clinical technologist (Radiation physicist) of the Medical Physics and Clinical Engineering.

4.3.9.1 Device output

In order to determine the variation of the irradiance output ($mWcm^{-2}$) across all the hand-held devices, the integrated dose ($mJcm^{-2}$) was recorded for each one. It was important that the setup was repeated the same for each device for both the pre and post-trial measurements. All the

irradiance and integrated dose measurements were recorded using an International Light Technologies ILT1700 radiometer with an International Light Technologies SED005 UVB detector.

The experimental setup involved using two retort stands with clamps to hold the hand-held device and UVB detector in a fixed position during the measurements. The centre of the UVB detector was positioned to a reference point for each of the hand-held devices. As both types of hand-held devices used comb attachments, the reference point for each device was centrally between the 7^{th} and 8^{th} tooth and at the tip of the comb attachment for the Waldmann units and centrally at the 7^{th} tooth and at the tip of the comb attachment for the Dermfix units.

Both the irradiance output and integrated dose measurements were achieved with the devices cold, i.e. they had been left to cool for at least 30 minutes before being used in order to ensure there was no effect of tube heating. Additionally, both the hand-held device and UVB detector were covered using a thick black shroud. This was to protect the operator from scattered UV radiation and to stop any external UV sources contributing to the measurement (i.e. the ceiling fluorescent lamps that have UVB mercury lines).

The irradiance measurements, involved recording the output at several different time points, with the timer started from the point of lamp ignition. The time points included measuring at two minutes which correlates with the local Quality Assurance (QA) routine testing protocol for TLO1 tubes. Additionally, the irradiance was measured at 20s, 50s and 85s which related to different treatment times based on the treatment plan; there was a further measurement at three minutes. The integration measurements were recorded in 15s increments (up to 210 s).

4.3.9.2 Output variation with time

Output variation with time measurements were performed in order to determine how the output varied during treatment and how uniform the output was over time. A Bentham double grating spectroradiometer with a Bentham D6 cosine response diffuser were used to perform the above measurements. The experimental setup was the same as the device output measurements, but instead the D6 diffuser was positioned in front of the UVB devices. The Bentham spectroradiometer was set to measure a stationary wavelength at 311nm rather than scanning across the UV range. The spectroradiometer system was initialised so that it continually

measured the irradiance at 311nm for 10 minutes after the UVB device lamp ignition, taking a reading every second.

4.3.9.3 Tube spectral profile

The final measurements involved recording the tube spectral profile of the hand-held devices across a selected range (specifically covering the UVB spectrum 280nm-315nm). This was performed in a same way as the output variation with time described above. The Bentham spectroradiometer was set to measure a pre-defined range of 250nm to 450nm, with a spectral resolution of 0.5nm.

The Minimal Erythema Dose (MED) testers used in the trial were also tested for output. Irradiance and integrated dose measurements were recorded using an International Light Technology ILT1700 radiometer with an International Light Technologies SED005 UVB detector.

Dosimetry for each of the hand-held active devices and of the MED testers were checked in the same way, so that we could be sure, within a reasonable margin of error (up to 20%) that 1 Jcm^{-2} delivered by the MED tester was the same as 1 Jcm^{-2} delivered by the hand-held active treatment unit.

4.3.10 Statistics and sample size

4.3.10.1 Statistical analysis

Demographic characteristics of the participants, measures of adherence to the treatment plan and all other outcomes data, including outcomes for the main RCT, were summarised by descriptive statistics (number[n], mean, standard deviation [SD], median, minimum and maximum) or frequency tables, stratified by active/placebo groups.

No formal testing or interim analyses was conducted since this was a pilot study to determine answers to questions for the definitive trial. No assessment of efficacy was performed. Only a few potential likely adverse events were envisaged for this pilot study and so all adverse events were tabulated by these adverse events categories. All randomised participants who participated in at least one treatment and for whom at least one post-baseline assessment of the primary endpoint was available, were analysed.

All analyses were performed using Stata SE 11 and MS Excel 2007.

The transparencies of vitiliginous lesions were used to assess area of involved skin at each representative lesion. Tracings were scanned and analysed using the ImageJ 1.47d

(Image processing and analysis in Java by the National Institute of Health, USA; http://imagej.nih.gov/ij).

4.3.10.2 Sample size and justification

This was a pilot study, with sample size being resource driven in terms of available participants in a reasonable time frame, for which no formal statistically based sample size estimate was applicable.

For this pilot study, 21 participants (seven participants in each group) from two recruitment sites allowed us to compare the devices and to measure recruitment rate for each site; it also gave a reasonable estimate of the acceptability and completeness of the outcome data.

4.3.11 Randomisation and blinding

4.3.11.1 Randomisation

The randomisation was based on a computer-generated pseudo-random code, using random permuted blocks of randomly varying size, created by the Nottingham Clinical Trials Unit (CTU) in accordance with their standard operating procedure (SOP) and held on a secure University of Nottingham server. The randomisation was stratified by the recruiting site (Nottingham and Leicester). Only the trial

administrator at the co-ordinating centre and the data manager at the Nottingham CTU were aware of the allocation to active or placebo group. The research nurse accessed the treatment allocation for each participant, by means of a remote, internet-based randomisation system developed and maintained by the Nottingham CTU. The sequence of treatment allocations was concealed until all interventions were assigned and recruitment, data collection, and all other trial-related assessments were complete. In other words, the research nurse randomised participants during the baseline visit, however the results of the randomisation were only visible to the co-ordination centre administrator, who subsequently packed all the devices identically.

4.3.11.2 Blinding

In order to assess the blinding for the main RCT, participants were given their home UVB device boxed and sealed in identical packages. At the end of the trial, each participant and research nurse, were asked to guess the participant's group allocation; active or placebo. To ensure that blinded outcomes assessment was performed at week 16 hospital visit, an independent research nurse or clinician assessed the representative lesions (Table 4.8).

4.3.12 Missing data

Every effort was made to reduce the proportion of missing data through trial quality assurance procedures and adherence to standard operating procedures, produced by the University of Nottingham.

Tabulation of missing data and looking for reasons for any missing data was performed for this study. This information was crucial to find out the main reasons for missing data (if any) and then amend the study procedures to minimise this loss, in the definitive trial.

Table 4.8 Summary of blinding status of participants and research team members and possible issues around their un-blinding

	Blinding status	Possible issues
Participants	Blinded	May be compromised if they experience side-effects (e.g. redness of the skin) or tanning.
Research nurses / trial manager (Dr V. Eleftheriadou)	Blinded	Potential to become unblinded if discussing side-effects with participants, and during clinic visits.
Outcome assessment (in clinic – clinician or independent research nurse)	Blinded	An independent research nurse / clinician assessed the vitiligo at week 16 in order to provide blinded outcome assessment. Blinding might have been compromised if the skin was tanned around the lesion.
Outcome assessment (digital image assessment by independent assessor)	Blinded	An independent assessor calculated the surface area of the vitiligo patches. Blinding may be compromised if the skin is tanned around the lesion.
Trial administrator at the co-ordination centre	Not blinded	Was the main point of contact for participants wishing to contact the research team, packaged and posted the devices to the participants according to the randomisation schedule, and provided general advice on how to deal with minor side-effects.
Statistician	Blinded	

4.3.13 Side effects

For this feasibility trial, only a limited number of known, common, short term adverse events that could possibly be related to the NB-UVB phototherapy were collected:

- Erythema
    - Grade 1 erythema (mild) –barely perceptible and resolves within 48 hours
    - Grade 2 erythema (moderate) - well defined erythema causing slight manageable discomfort.
    - Grade 3 erythema (severe) well defined symptomatic/ painful erythema.
    - Grade 4 (very severe) painful erythema, usually with bullae.
- Blistering
- Burns
- Pruritis
- Perilesional hyperpigmentation
- Hypersensitivity reactions
- Cold sores
- Dry skin

The above grading system for erythema is widely used in dermatology, however it was not validated.

The purpose of collecting these was to test the feasibility of recording and collecting this information for the main RCT.

In case of any serious adverse events (if any), these were reported to the REC and the Chief Investigator was responsible for this.

A Serious Adverse Event (SAE) was any adverse event occurring, that results in any of the following outcomes:

- Death
- Inpatient hospitalisation or prolongation of existing hospitalisation
- Persistent or significant disability / incapacity
- A congenital anomaly or birth defect in the offspring of a participant
- Other medical events may be considered to be a SAE if they require medical or surgical intervention to prevent one of the outcomes listed in this definition.

4.3.14 My personal contribution to this trial

I played a key role in all phases of this trial.

4.3.14.1 *Pre-trial*

I conceived the idea of conducting a trial on hand-held devices, did extensive research on what brands of devices are available in the UK, their prices and their licensing authorisation. After identifying two suitable "candidates", Androv and Waldmann, I established working relationship with the manufacturers, in order to secure an identically looking placebo unit for each device and subsequently choose which one was better for this pilot trial. I also negotiated with the manufacturers on the purchasing price of the devices, arranged their delivery and liaised with the medical physics department.

In addition, I visited the St. Woolos and Ninewells Hospitals' phototherapy departments. I collaborated with Dr Robert Dawe (co-investigator for Hi-Light pilot trial) and Ms Susan Yule (phototherapy nurse) during the conduction of this trial. In addition, I met Professor Alex Anstey, dermatologist and international expert in phototherapy, to share my ideas about this trial, gather information on how they perform output and calibration measurements and patients' education

on hand-held devices and what treatment plans they use in their clinical practice.

I wrote the trial protocol, the patient information leaflets and designed all the CRFs, patient's and researcher guidance manuals and all the rest of the necessary paperwork for this trial. Also, I applied for and was granted, all the necessary approvals for the trial including ethics, Comprehensive Local Research Network (CLRN) support and Primary Care Research Network (PCRN) support.

Finally, I delivered training sessions to the research nurses and trial administrators, as mentioned above.

4.3.14.2 During the trial

I was extensively involved in all stages of the trial (Table 4.2) as well as performed the duties of the trial manager. I recruited patients in both Nottingham and Leicester and supervised the research nurses when they were delivering training sessions to the patients. I also developed the idea of pre-screening potential participants over the phone, prior their attendance to the clinics. Finally, I performed all the final week 16 visits in Nottingham recruitment centre.

4.3.12.3 Post-trial

I analysed all the vitiliginous lesions transparencies (acetate sheets), including repigmentation measurements using the ImageJ 1.47d programme (http://imagej.nih.gov/ij) and MS office Excel 2010. For the statistical analysis of this trial, I performed the majority of the analysis and was also advised by a junior CTU statistician, who ran Stata code (Stata SE 10).

4.4 Results

4.4.1 Recruitment and eligibility

4.4.1.1 Proportion of participants accepting initial invitation to participate

The trial gained all the necessary approvals and started recruitment on the 1st of March 2012. Although this was four months later than originally anticipated, due to the overwhelming response, the trial closed for recruitment in only three months, on the 31st of May 2012 (instead of six months).

In total, 97 people approached us, expressed interest in this pilot trial and were subsequently pre-screened either completely or partially. People, who expressed interest in the

trial were identified through: primary care (28/97; 29%), secondary care (38/97; 39%), the Vitiligo Society UK (14/97; 14.5%), vitiligo newsletter (4/97; 4%), other sources such as Google search engine and personal contacts (13/97; 13.5%).

4.4.1.2 Secondary care

In total 48 invitation letters with reply slips were sent to vitiligo patients, who attended dermatology departments of the Queen's Medical Centre of the Nottingham University Hospitals (31 patients) and the Leicester Royal Infirmary(17 patients). We received 38 (response rate=79%) completed reply slips from patients, who were willing to be contacted and pre-screened by the research team (Nottingham response rate=93.5% (29/31), Leicester response rate=53% (9/17)).

4.4.1.3 Primary care

Two GP surgeries (one Leicester and one in Nottingham) sent 67 invitation letters (Leicester 35 letters and Nottingham 32 letters) and we received 28 completed reply slips (total response rate=40%). It was not possible to calculate the response rate per each surgery as the reply slips were not identifiable.

In addition, six more GP practices (three in Leicester and three in Nottingham) expressed interest in running the

searches and sending invitation letters and reply slips to vitiligo patients. However, due to the overwhelming response from the secondary care patients, these surgeries were asked not to send invitation letters.

Also, the Vitiligo Society UK sent 74 invitation letters to its members who live in Nottingham, Leicester and Birmingham. Fourteen patients were interested in the trial (response rate=19%).

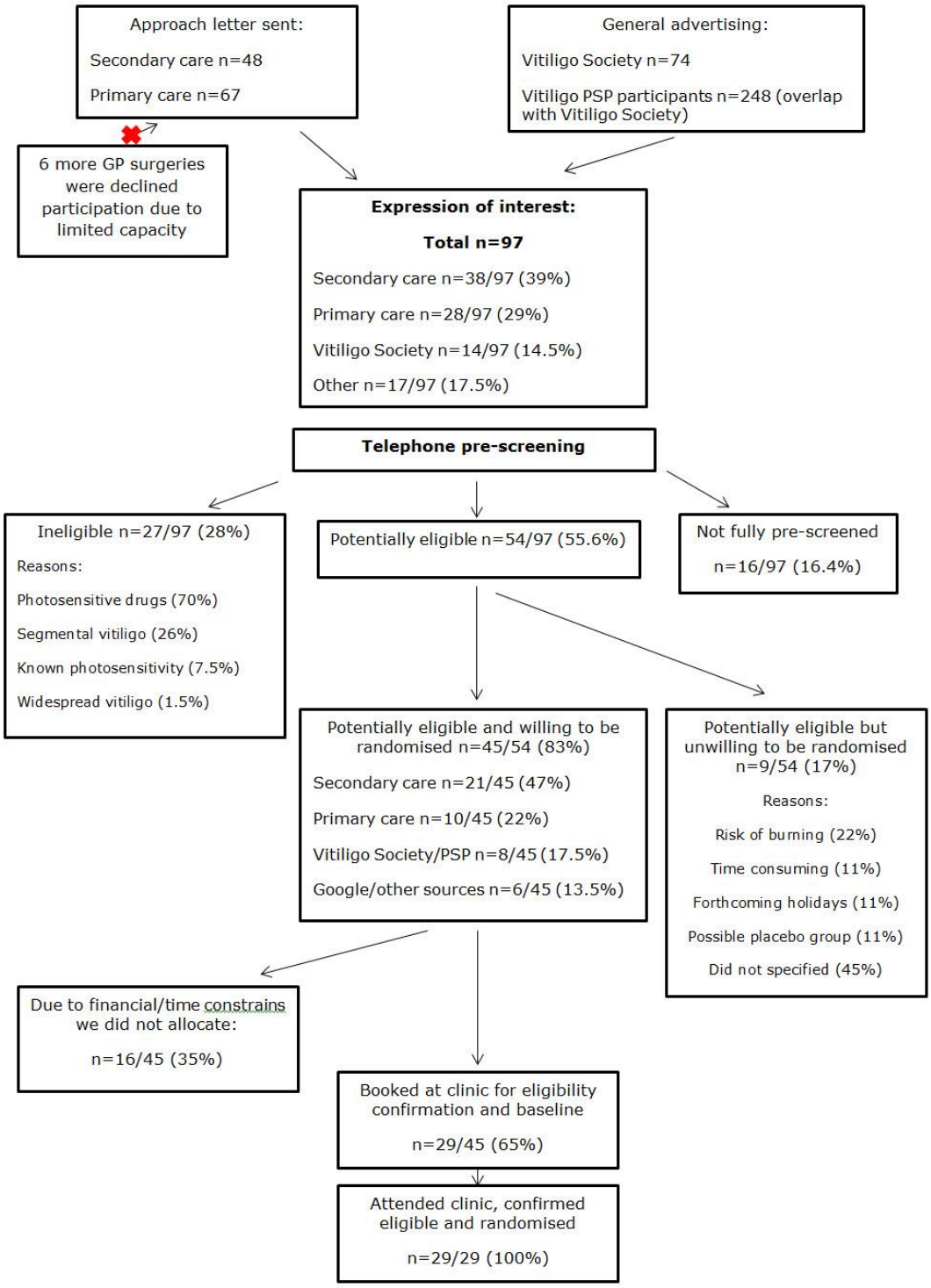
Finally, 284 vitiligo newsletters (via email) were sent to the participants of the vitiligo PSP informing them about the trial. There is a significant overlap between those and the Vitiligo Society UK members.

4.4.1.4 Pre-screening of participants prior baseline hospital visit

In total, 55.6% (54/97) of participants were successfully pre-screened and provisionally met the trial eligibility criteria. Twenty eight percept of participants were ineligible (27/97) and 16.4% (16/97) patients were not fully pre-screened (Figure 4.3). Due to the overwhelming response, we were forced to notify some of the people who sent us a reply slip that we had completed recruiting. Understandably, several people, although expressed interest in being informed about future trials, were not interested in answering all of the pre-

screening questions and therefore were only partially pre-screened.

Fig.4.3 Summary of recruitment sources into Hi-Light trial



Eighty three per cent of eligible participants (45/54) on the pre-screening phase were willing to attend the baseline visit and be randomised. These were identified through: 47% (21/45) secondary care, 22% (10/45) primary care, 13.5% (6/45) the Vitiligo Society UK, 4% (2/45) from vitiligo newsletter (i.e. participants of vitiligo PSP) and 13.5% (6/45) from other sources such as Google and personal contacts.

Provisionally eligible patients who were not willing to be randomised (9/54; 17%) gave the following reasons: concern about the risk of burning (2/9; 22%), treatment sounded too time consuming (1/9; 11%), inconvenient time period due to forthcoming holidays (1/9; 11%), possible allocation to placebo group (1/9; 11%). The rest did not specify any reasons (4/9; 45%).

Finally, reasons for exclusion from the trial were: regular photosensitive drugs (19/27; 70%), segmental vitiligo (7/27; 26%), widespread vitiligo (4/27; 1.5%) and known photosensitivity (2/27; 7.5%). There were patients with more than one exclusion criteria.

4.4.1.5 Proportion of participants fulfilling trial eligibility criteria at baseline hospital visit

We originally expected to recruit 21 participants into the trial. We identified 45, provisionally eligible and willing

participants by telephone pre-screening; however due to time and financial constrains we were not able to allocate them all into this trial.

Only twenty nine of the 45 potential participants were booked to attend for a baseline visit. Potential participants were booked into clinics on "first come-first served" basis: 17% (5/29) from primary care; 52% (15/29) from secondary care, 17% (5/29) from the Vitiligo Society, 7% (2/29) from vitiligo newsletter and 7% (2/29) from other sources such as Google).

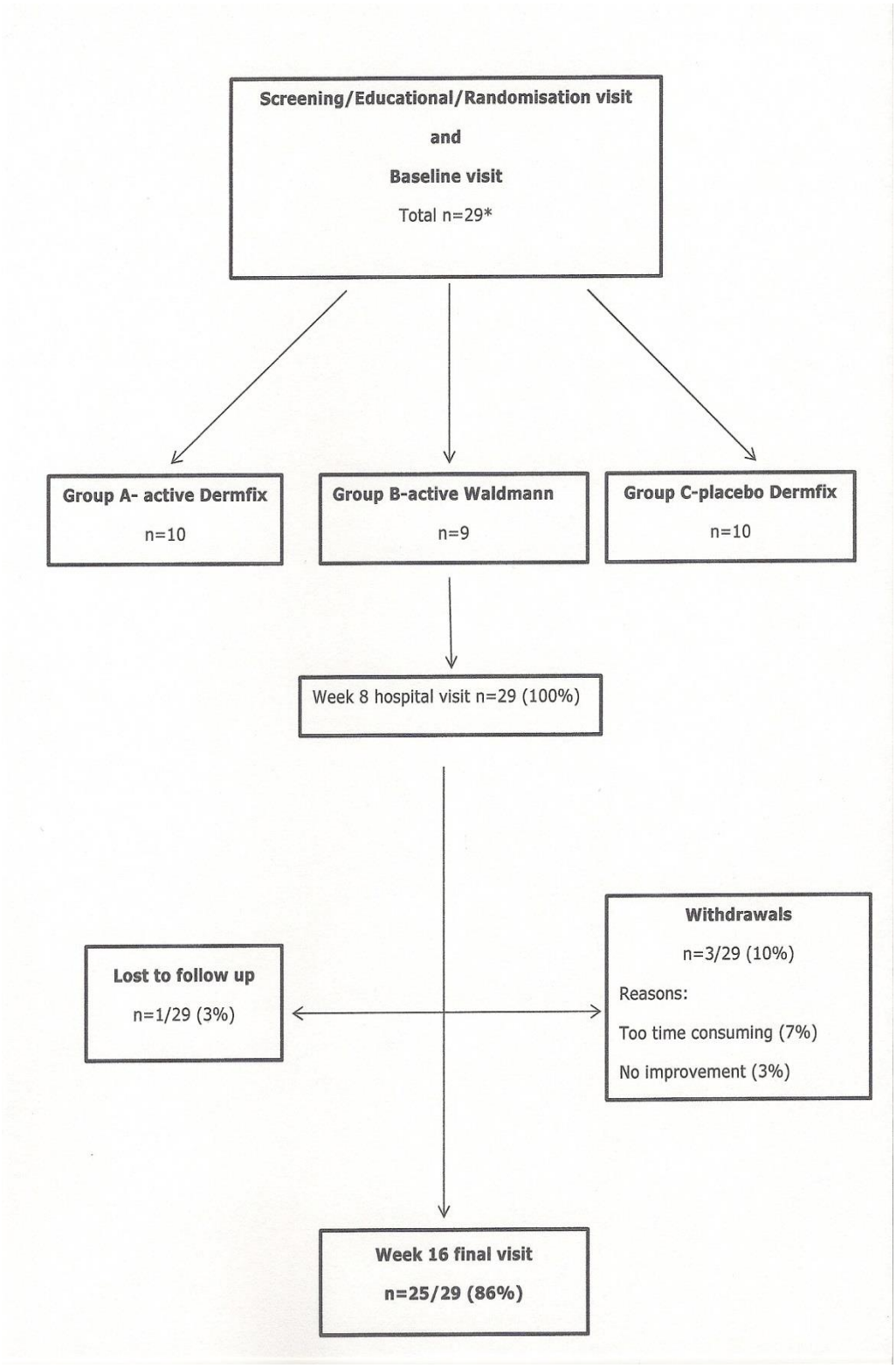
All participants who attended the baseline visit were confirmed eligible and were subsequently randomised into the trial (29/29; 100%) (Figure 4.4). In conclusion, 29 participants with 84 representative lesions were randomised into three intervention groups (Table 4.9).

Table 4.9 Baseline characteristics of participants

Baseline characteristics	All groups	Active intervention groups (A+B)	Placebo intervention group (C)
Number of participants	29	19	10
Age range (years)	5-71	5-71	13-51
Age mean (years); SD **Adults** **Children**	31.7+/-17.9 38.6+/-14.8 10.25+/-3.5	27.63+/-18.6 38+/-15.8 9.9+/-3.6	39.4+/-13.5 42.3+/-10.85 13+/-0
Sex	15/14	10/9	5/5

(Female/Male)			
Ethnicity:			
White British	20/29 (69%)	12/19 (64%)	8/10 (80%)
Mixed	1/29 (3.5%)	1/19 (5%)	None
Black/Black Caribbean	2/29 (7%)	2/19 (11%)	None
Indian	2/29 (7%)	1/19 (5%)	1/10 (10%)
Pakistani	1/29 (3.5%)	1/19 (5%)	None
Asian	2/29 (7%)	1/19 (5%)	1/10(10%)
Other ethnic group	1/29 (3.5%)	1/19 (5%)	None
Duration of vitiligo (years) Mean;+/-SD(min;max)	12.28+/-9.67 (min=2; max=33)	11.36+/-10.12 (min=2;max=33)	14.01+/-8.5 (min=5;max=28)
Vitiligo activity (Overall)			
Stable	6	3	3
Spreading	19	14	5
Repigmenting	4	2	2
BSA% covered by vitiligo Mean;+/-SD (min;max)	8.83+/-6.19 (min=2;max=25)	9.84+/-5.96 (min=3;max=25)	6.9+/-6.17 (min=2;max=21)
Number of lesions	84	56	28

Figure 4.4 Flow diagrams of randomised participants



4.4.2 Withdrawals, adherence and satisfaction with the treatment

4.4.2.1 Withdrawals

Three of 29 participants (10%) withdrew from treatment during the 4-month period (two patients (67%) from active groups and one patient (33%) from placebo group). Only one (3%) participant was lost to follow-up. The reasons for withdrawals were that the treatment was too time consuming (3%; 1/29) and the lack of improvement in vitiligo (7%; 2/29).

4.4.2.2 Adherence

Twenty eight of the 29 diaries (97%) were returned to the trial team and analysed. One diary was never returned to our research team as the patient was lost to follow-up during the trial. The diaries of the three participants who withdrew from treatment were also included in the analysis.

Twenty five of the 29 (90%) participants adhered to treatment i.e. performed treatment for four months.

Twenty one of the 28 (75%) participants administered phototherapy at home three to four times a week and left at least one day between consecutive treatment sessions. Six participants as instructed, omitted one session due to treatment side effects i.e. erythema grade 2, resumed their

treatment plan correctly and were deemed adherent to the treatment plan.

Seven participants (25%) did not follow the treatment plan as instructed. The following mistakes made were: 1) no treatment time reduction was made, following a missed treatment session and no reason for the missed session was noted (6/28; 21%) and 2) incorrect time reduction following one week missed sessions due to chickenpox (1/28; 4%).

When asked at the end of the trial, if the training received during the baseline visit was adequate and whether it was easy to decide on the grade of erythema, 100% (28/28) and 90% (25/28) replied positively respectively. The rest 10% (3/28) weren't sure if they could easily decide on the erythema grade.

4.4.2.3 Satisfaction with the treatment

Twenty eight participants replied to the question "How satisfied are you with the treatment?" by completing the end of study questionnaire (96.5%).Participants in the active groups were more likely to be satisfied with their treatment than participants allocated to placebo group (31.5% versus 20%) (Table 4.10).

Table 4.10 Proportion of participants satisfied with the treatment

Satisfaction with the treatment	Active groups (N=19)	Placebo group (N=10)	Total (N=29)
Very dissatisfied	5 (26%)	1 (10%)	6 (20.7%)
Somewhat dissatisfied	1(0.5%)	2 (20%)	3 (10.3%)
Neutral	6 (31.5%)	5 (50%)	11 (37.9%)
Somewhat satisfied	6(31.5%)	2 (20%)	8 (27.6%)
Very satisfied	0 (0%)	0 (0%)	0 (0%)
Missing	1 (0.5%)	0 (0%)	1 (3.4%)

When asked whether they would use the hand-held device again, 68% (19/28) of participants answered positively, 21% (6/28) weren't sure and 11% (3/28) said no.

When asked whether they would recommend the device to others, the results were similar to the previous question: 64% (18/28) said yes; 28% (8/28) said maybe and 8% (2/28) said no.

Both devices (Dermfix and Waldmann) received the following similar positive comments: easy to use, portable and compact, convenient to operate at home instead of coming to

the hospital. Additional positive comments on Dermfix devices were regarding their convenient size.

Negative comments about both devices were mainly about inconvenience of spacers (plastic teeth) and lack of treatment response.

4.4.3 Success of blinding

Overall, 30% (8/27) of participants and 40% (11/27) of research nurses did not guess the treatment allocation correctly when asked "Do you think you (your patient) have had an active or a dummy device?" (Tables 4.11 and 4.12). Three main reasons for unblinding of the research nurses were given. In the active treatment groups, erythema (3/10; 30%) and improvement in vitiligo (6/10, 60%) were cites as reasons for unblinding. In the placebo group, unblinding was driven by lack of treatment response (6/6; 100%).

Table 4.11 Proportion of participants for whom the blinding of the research nurse was maintained

"What device do you think the patient had?"	**Group allocation in the trial**		
	Placebo treatment (Group C; N=10)	Active treatment (Group A+B; N=19)	Total (N=29)
Active	4 (40%)	10 (52.6%)	14 (48.3%)
Placebo	6 (60%)	7 (36.8%)	13 (44.8%)
Missing data	0 (0%)	2 (10.5%)	2 (6.9%)

Table 4.12 Proportion of participants for whom the blinding was maintained

"What device do you think you had?"	**Group allocation in the trial**		
	Placebo treatment (Group C; N=10)	Active treatment (Group A+B; N=19)	Total (N=29)
Active	4 (40%)	13 (68.4%)	17 (58.6%)
Placebo	6 (60%)	4 (21.1%)	10 (34.5%)
Missing data	0 (0%)	2 (10.5%)	2 (6.9%)

4.4.4 Missing data

As described above, it was not always possible to fully pre-screen participants over the telephone (16/97; 16.4%).

All participants, except one who was lost to follow-up, completed the end of study questionnaire in full (28/29; 96.5%). The DLQI and PBI questionnaires at baseline and week 16 were completed by 96.5% (28/29) of participants also; at baseline one participant did not complete the questionnaires. One missing diary and week 16 questionnaire (3%; 1/29) belonged to the lost to follow-up patient. Our research team made every effort possible to contact and find the patient, including reaching out to his regular GP. Unfortunately neither the diary nor the device were recovered.

4.4.5 Side effects

Side effects such as erythema grades 1 and 2, pruritis, hyperpigmentation around the lesions and dry skin were self-reported by the participants in their diaries. In the case of erythema grades 3 and 4, hypersensitivity reaction and cold sores, participants were advised to call the research nurse or the co-ordination centre and an adverse event form was completed (Table 4.13).

Table 4.13 Side effects for active (A+B) groups and placebo (C) group per number of patients and incidents

Side effects	Active arms		Placebo arm		Total	
	Patients	Incidents	Patients	Incidents	Patients	Incidents
Erythema grade 1	6	18	2	14	8	32
Erythema grade 2	4	5	0	0	4	5
Erythema grade 3	1	1	0	0	1	1
Erythema grade 4	0	0	0	0	0	0
Sold sores	1	1	0	0	1	1
Dry skin	3	5	0	0	3	5
Hyperpigmentation	3	10	0	0	3	10
Pruritis	1	1	1	1	2	2

4.4.6 Repigmentation

Overall, mean size of all (84) representative lesions at baseline was 17.12 cm^2 (SD=+/- 20cm^2; min=0.35cm^2; max=107.5cm^2; median=90.6cm^2). After 16 weeks of treatment, only a slight decrease in mean lesions size was noticed; mean size of all representative lesions was 16.80 cm^2 (SD=+/- 19.37cm^2; min=0.05cm^2; max=83.9cm^2; median=10.95cm^2). In active groups (A+B), the mean size of all lesions was 15.42cm^2 at baseline (SD=+/- 20.2cm^2; min=0.35cm^2; max=107.5cm^2; median=67.7cm^2) and 14.43

cm^2 at week 16 visit (SD=+/- 18cm^2; min=0.05cm^2; max=83.87cm^2; median=67.1cm^2). For the placebo group, a slight deterioration in mean lesion size was seen, 20.54 cm^2 at baseline (SD=+/- 19.4cm^2; min=1.34cm^2; max=76.6cm^2; median=15cm^2) and 21cm^2 at week 16 visit (SD=+/- 20.85cm^2; min=1.5cm^2; max=76.9cm^2; median=15.4cm^2).

When analysing the overall treatment response per participant, mean percentage of repigmentation of all representative lesions for each participant was estimated. This was done by simply finding the total difference in size, of all lesions at baseline and week 16 in cm^2. The results were afterwards converted into percentages and allocated to one of the five groups (negative-0%, 1-24%, 25-49%, 50-74%, 75-100%). In active groups, 12% (2/17) of participants had high grade repigmentation (75-100%) compared to none in placebo group (Table 4.14).

Table 4.14 Mean percentage of repigmentation for all representative lesions per participant

Number of participants in	Mean % repigmentation after 16 weeks of treatment per participant					
	"-"-0	1-24	25-49	50-74	75-100	Total
Active groups (A+B)	6 (35%)	8 (47%)	1 (6%)	0	2(12%)	17
Placebo group (C)	4 (40%)	6 (60%)	0	0	0	10
Total	10 (37%)	14(52%)	1 (4%)	0	2 (7%)	27

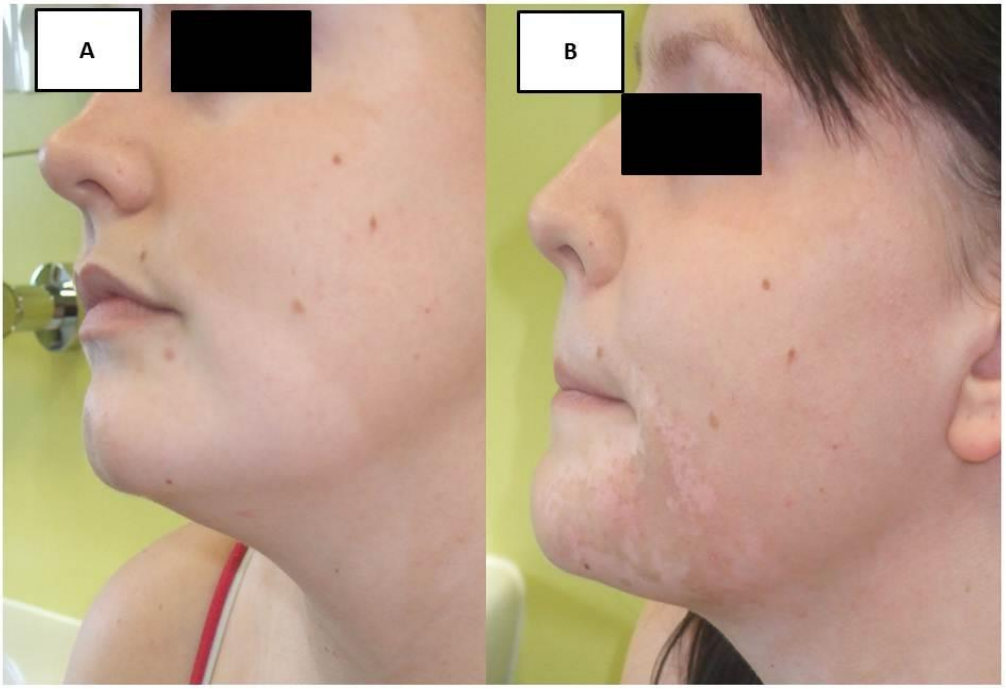
In the active groups, the anatomical sites which responded best to treatment were the face and neck. Thirty three percentage of lesions achieved repigmentation above 75% in these areas. In addition, 17% of lesions on the trunk and 8% of lesions on upper limbs (except hands) also showed very good treatment response i.e. repigmentation above 75% (Pictures 4.3 and 4.4). Overall, 75% (29/39) of all lesions in the active group showed some response to the treatment (Table 4.15).

On the other hand, in the placebo group, none of the anatomical areas achieved repigmentation above 40%. Thirty nine per cent of lesions showed some degree of repigmentation (9/23) (Table 4.16).

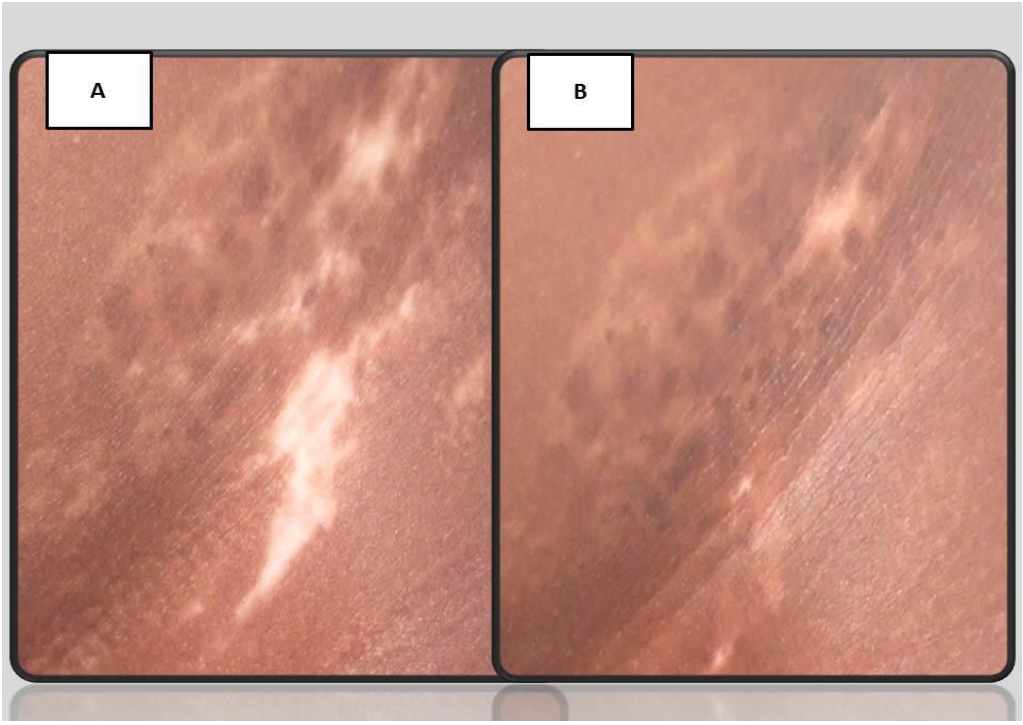
Table 4.15 Percentage of repigmentation (negative-0%, 1-24%, 25-49%, 50-74%, 75-100%) in active groups (A+B) for each anatomical site (face and neck, trunk, lower limbs except feet, upper limbs except hands, hands and feet)

	Anatomical site				
	Face/neck	Trunk	Upper limbs	Lower limbs	Hands/feet
Number of participants*	6	6	13	11	3
Repigmentation:					
Negative-0%	2 (33%)	3 (50%)	3 (22%)	2 (18%)	0
1-24%	1 (17%)	2 (33%)	8 (62%)	7 (64%)	2 (67%)
25-49%	1 (17%)	0	1 (8%)	2 (18%)	1 (33%)
50-74%	0	0	0	0	0
75-100%	2 (33%)	1(17%)	1 (8%)	0	0
Baseline: Mean lesion size (cm^2+/-SD)	75.4+/-7.4	13+/-15.9	11.2+/-10.9	21+/-29.1	18.9+/-25.7
16week: Mean lesion size (cm^2+/-SD)	47.4+/-4.4	13.7+/-17.4	10.3+/-9.6	20.6+/-25.8	22.6+/-26.6

* One lesion per anatomical site per participant was analysed. If two or more lesions were available on the same anatomical site, lesion on the right side was chosen. If no lesions were available on the right side, then the lesion, which repigmented the most, was included in the analysis.



Picture 4.3 Facial vitiliginous lesion (A) at baseline and (B) after 16 weeks of home NB-UVB phototherapy



Picture 4.4 Vitiliginous lesion on the trunk (A) at baseline and (B) after 16 week of treatment with home NB-UVB phototherapy

Table 4.16 Percentage of repigmentation (negative-0%, 1-24%, 25-49%, 50-74%, 75-100%) in placebo group (C) for each anatomical site (face and neck, trunk, lower limbs except feet, upper limbs except hands, hands and feet)

	Anatomical site				
	Face/neck	Trunk	Upper limbs	Lower limbs	Hands/feet
Number of participants*	5	1	8	5	4
Repigmentation:					
Negative-0%	3 (60%)	0	3 (37%)	5(100%)	2 (50%)
1-24%	1 (20%)	1(100%)	5 (63%)	0	2 (50%)
25-49%	1 (20%)	0	0	0	0
50-74%	0	0	0	0	0
75-100%	0	0	0	0	0
Baseline: Mean lesion size (cm^2+/-SD)	10.7+/-5.6	34.8	22.6+/-18.4	22.6+/-24	20.9+/-8.8
16week: Mean lesion size (cm^2+/-SD)	11.3+/-7	28.2	23.2+/-21.6	26.1+/-27.2	20.7+/-6.4

*One lesion per anatomical site per participant was analysed. If two or more lesions were available on the same anatomical site, lesion on the right side was chosen. If no lesions were available on the right side, then the lesion, which repigmented the most, was included in the analysis.

4.4.7 Cessation of spreading of vitiligo, global improvement and colour match

4.4.7.1 Cessation of spreading

Seventy eight representative lesions were assessed (93%; 78/84) at week 16 hospital visit due to withdrawal and loss in follow-up. In the active groups (A+B), 44% of lesions (22/50) remained stable throughout the trial. Twenty two per cent (11/50) of stable lesions started repigmenting. Fifty seven per cent (4/7) of actively spreading lesions stopped progressing (Table 4.17).

On the other hand, in the placebo group, eight lesions in the placebo group had also stopped spreading (28%; 8/28) during the trial (Table 4.18).

Table 4.17 Lesions stability in groups with active interventions (A+B)

Lesion stability at baseline visit	**Lesion stability at week 16 hospital visit**			
	Stable	Spreading	Repigmenting	Total
Stable	22 (44%)	7 (17.5%)	11 (27.5%)	40 (80%)
Spreading	4 (57%)	3 (43%)	0	7 (14%)
Repigmenting	0	0	3 (100%)	3 (6%)
Total	26 (52%)	10 (20%)	14 (28%)	50

Table 4.18 Lesions stability in group with placebo intervention (C)

Lesion stability at baseline visit	Lesion stability at week 16 hospital visit			
	Stable	Spreading	Repigmenting	Total
Stable	13 (72%)	1 (6%)	4 (22%)	18 (64%)
Spreading	8 (80%)	0	2 (20%)	10 (36%)
Repigmenting	0	0	0	0
Total	21 (75%)	1 (4%)	6 (21%)	28

4.4.7.2 Global improvement in vitiligo

When asked to rate the overall changes in vitiligo following treatment, around half of patients, research nurses and independent outcome assessors, rated changes in representative lesions as "a bit better" or "much better" (Table 4.19 and 4.20).

Table 4.19 Global improvement in vitiligo rated by patients, research nurses and independent outcomes assessors for active groups (A+B)

Global improvement in vitiligo	Patient	Research nurse	Independent outcome assessor
Much worse	1(5%)	0	0
A bit worse	0	3 (18%)	0
No change	7 (39%)	6 (35%)	5 (29.5%)
A bit better	7 (39%)	4 (23.5%)	8 (47%)
Much better	3 (17%)	4 (23.5%)	4 (23.5%)
Total number of assessments	18	17	17

Table 4.20 Global improvement in vitiligo rated by patients, research nurses and independent outcomes assessors for placebo group (C)

Global improvement in vitiligo	Patient	Research nurse	Independent outcome assessor
Much worse	0	0	0
A bit worse	0	1 (10%)	1 (10%)
No change	6 (60%)	5 (50%)	7 (70%)
A bit better	4 (40%)	4 (40%)	2 (20%)
Much better	0	0	0
Total number of assessments	10	10	10

4.4.7.3 Colour match of vitiliginous patches

In active groups, when asked to colour match the representative vitiliginous lesions, 30% of patients, 32% of research nurse and 24% of independent assessors, rated the colour on the newly repigmented lesions as good or excellent. On the other hand, no one rated the colour match of newly repigmented lesions as good or excellent in the placebo group (Table 4.21 and 4.22).

Table 4.21 Colour match in representative vitiliginous lesions as rated by patients, research nurses and independent outcomes assessors for active intervention groups (A+B)

Colour match at week 16 visit	**Patient**	**Research nurse**	**Independent outcome assessor**
Bad	27 (51%)	25 (50%)	23 (46%)
Fair	10 (19%)	9 (18%)	15 (30%)
Good	15 (28%)	14 (28%)	12 (24%)
Excellent	1 (2%)	2 (4%)	0
Total	53	50	50

Table 4.22 Colour match in representative vitiliginous lesions as rated by patients, research nurses and independent outcomes assessors for placebo intervention group (C)

Colour match at week 16 hospital visit	Patient	Research nurse	Independent outcome assessor
Bad	20 (71%)	21 (75%)	20 (71%)
Fair	8 (29%)	7 (25%)	8 (29%)
Good	0	0	0
Excellent	0	0	0
Total	28	28	28

4.4.8 Quality of life and benefit evaluation in vitiligo

4.4.8.1 Quality of life

Twenty eight participants (96.5%) completed either Dermatology Life Quality Index questionnaire (DLQI) or Children's Dermatology Life Quality Index (CDLQI). Overall, there was a little change in the DLQI scores from baseline to week 16, suggesting that the treatment had little impact on quality of life (Table 4.23).

Children's Dermatology Life Quality Index was not analysed due to insufficient numbers of children in the trial.

Table 4.23 Dermatology Life Quality Index at baseline and week 16 hospital visits

DLQI scores	Placebo group (C) (N=9)	Active groups (A+B) (N=12)	Total (N=21)
Baseline mean +/-SD	3.8+/-3.2	2.8+/-2.3	3.3+/-2.7
16 week mean +/-SD	3.7+/-3.8	3.2+/-2.3	3.4+/-3
Baseline min – max	0 - 10	0 - 6	0 - 10
16 week min – max	0 - 12	0 - 7	0 - 12
Baseline missing questionnaires	0	1 (8.3%)	1 (4.8%)
16 week missing questionnaires	0	1 (9%)	1(5%)

4.4.8.2 Benefit evaluation in vitiligo

Twenty seven participants (93%) completed both the patient's need questionnaire (PNQ) at the baseline visit and patient's benefit questionnaire (PBQ) at the week 16 hospital visit. The need prior to therapy (PNQ) and the benefits achieved by therapy (PBQ) were converted to a weighted index value, the patient benefit index (PBI). The values of PBI range from zero=no benefit to four=maximal benefit.

There was no difference between the active and placebo groups in the PBI index. The mean PBI for active groups (17 participants was 0.92 (SD+/- 1.16; min=0; max=3.68) and

mean PBI for placebo group (10 participants) was 0.91 (SD+/-0.99; min=0; max=3.26). Both groups reported a PBI of approximately 1, which equals to "slight benefit".

4.4.9 Other outcomes

4.4.9.1 Minimal Erythema Dose

It was important to detect any differences in the skin type determined by the MED test and by a dermatologist at baseline.

In only half of patients (16/29; 55%), was the same starting dose determined by both the MED test and a dermatologist. In 17% (6/29) of participants the MED test results showed that their skin was more sensitive to sunlight than determined by a dermatologist. In 24% (7/29) of participants the MED results were higher than the ones determined by dermatologists allowing them to be prescribed a higher dose of NB-UVB.

4.4.9.2 Future trials suggestions

When asked "what did you like about the trial" statements such as "treatment at home, easy to perform and flexible, comprehensive patient literature and forms to

complete, hope in vitiligo treatment, raising awareness" were made.

When asked if the future main trial should be on hand-held device compared to placebo or hand-held device compared to steroid or a trial on combination of light and steroid cream, the majority of participants said yes to all (Table 4.24).

Table 4.24 Participants opinion on future trials on vitiligo

Would you be willing to take part in future clinical trials on vitiligo comparing	**Yes**	**No**	**Unsure**	**Reasons for negative or unsure answers**
NB-UVB vs. placebo	23 (82%)	4 (14%)	1 (3.5%)	Previous use of steroids
NB-UVB vs. topical corticosteroids	21 (75%)	2 (7%)	5 (18%)	No treatment response in current trial
Combination of NB-UVB and topical corticosteroids	20 (71.5%)	5 (18%)	3 (11%)	Current trial was too time-consuming
Total number of participants	28	28	28	

4.4.10 Hand-held devices output

4.4.10.1 Device output

The mean post-trial outputs, both the Waldmann and Dermfix units, were less than the pre-trial values (Table 4.25)

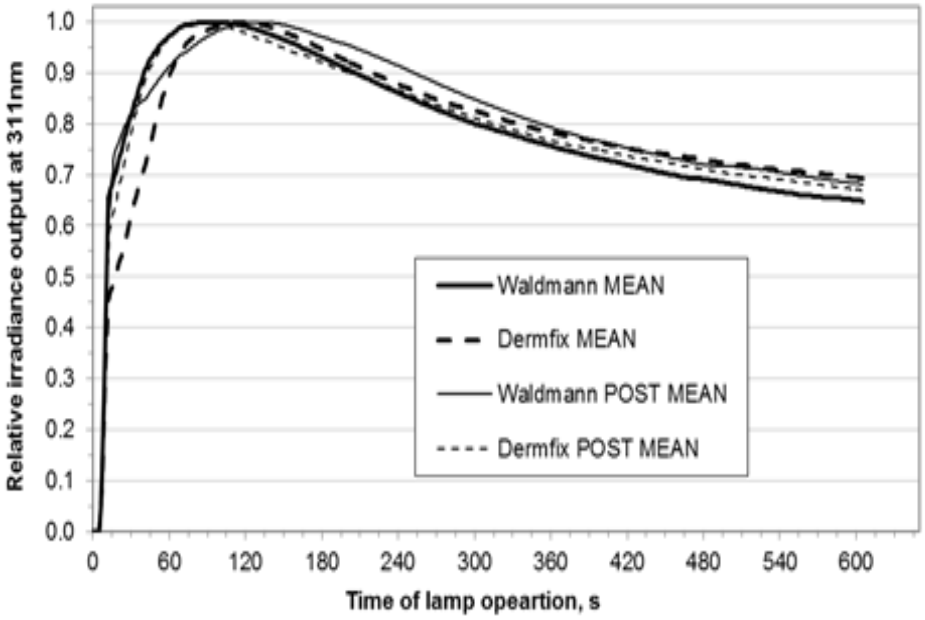
Table 4.25 Pre and post-trial output values for Waldmann and Dermfix hand-held devices

	Dermfix		**Waldmann**	
	Pre-trial	Post-trial	Pre-trial	Post-trial
Mean output mW/cm^2	3.81	3.24	4.5	3.92
SD mW/cm^2	0.37	0.42	0.2	0.67
Coefficient of variation	9.7%	12.9%	4.4%	17%
Mean difference	-14.5%		-13%	
Maximum difference pre and post-trial	-28.5%		-38.5%	
Minimum difference pre and post-trial	-7.4%		+10.5%	

Additionally, the mean Waldmann output values were slightly greater compared to Dermfix devices. Interestingly one of the Waldmann devices had a greater post-trial output

than pre-trial output. The Dermfix devices showed more consistent decrease in output pre and post-trial (Figure 4.5).

Figure 4.5 – Comparison of both manufacturers (Waldmann and Dermfix) mean pre and post-trial device output measurements to the device operation time



4.4.10.2 Output with respect to time

Both the Waldmann and Dermfix hand-held units follow a similar pattern, with a sharp increase in output from lamp ignition to the peak value and then a gradual decay in output over time (Figure 4.5). The pre-trial output values of

Waldmann devices were more closely matched than their post-trial measurements, while for the Dermfix devices the variation in output looks more consistent both pre and post-trial (Figure 4.6 and 4.7).

Figure 4.6 – Mean output (mJ/cm^2) of Waldmann hand-held devices pre and post-trial in correlation with time (seconds)

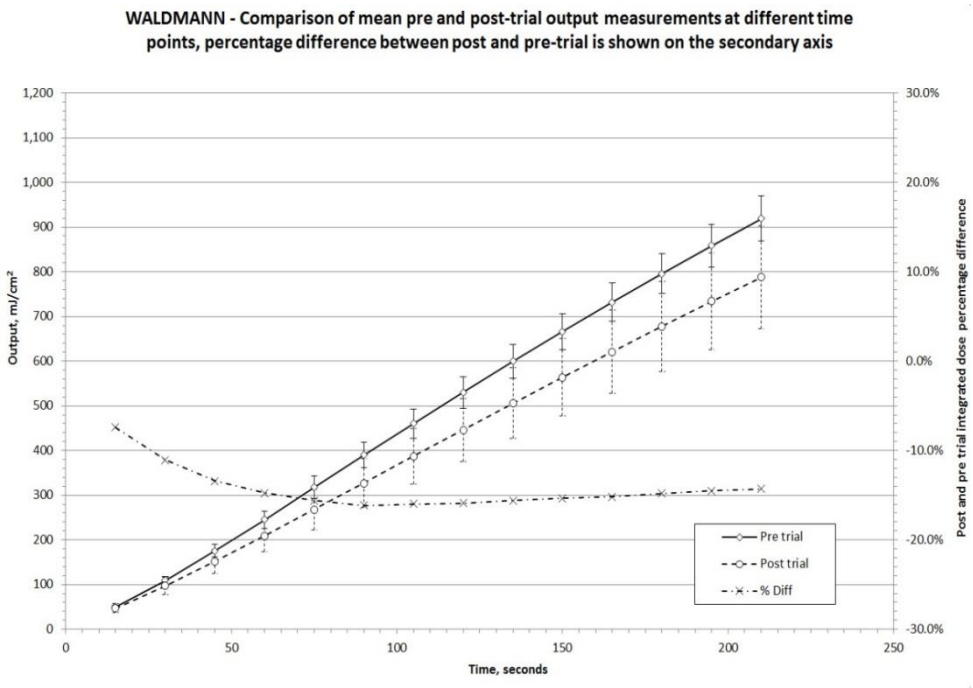
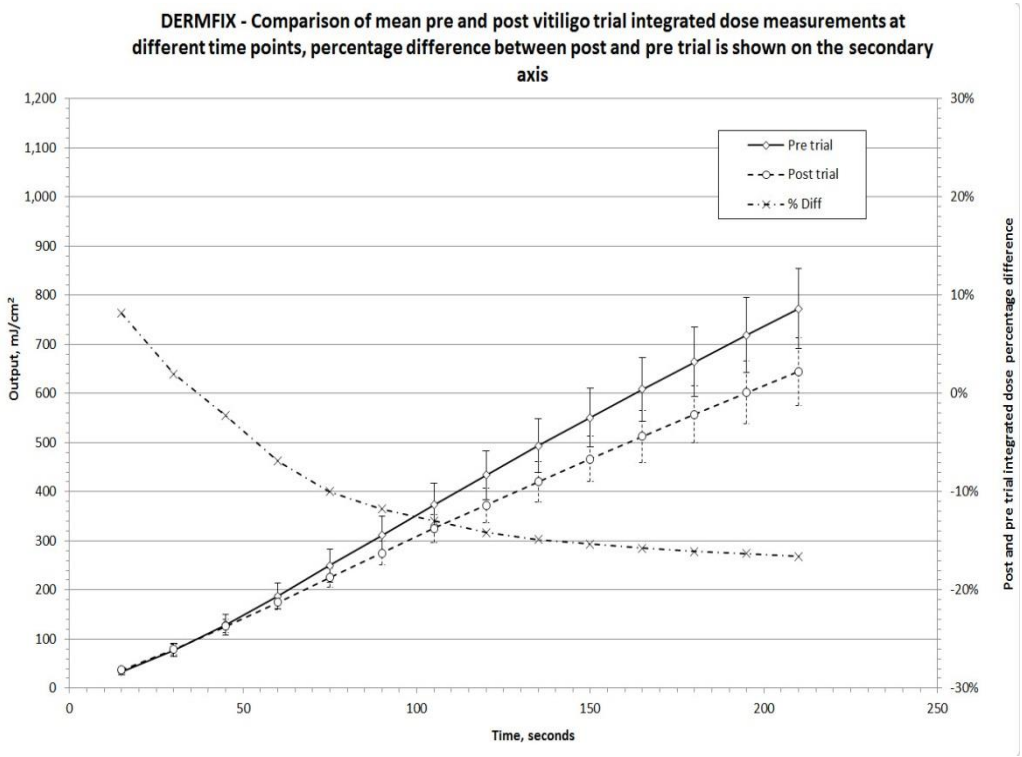


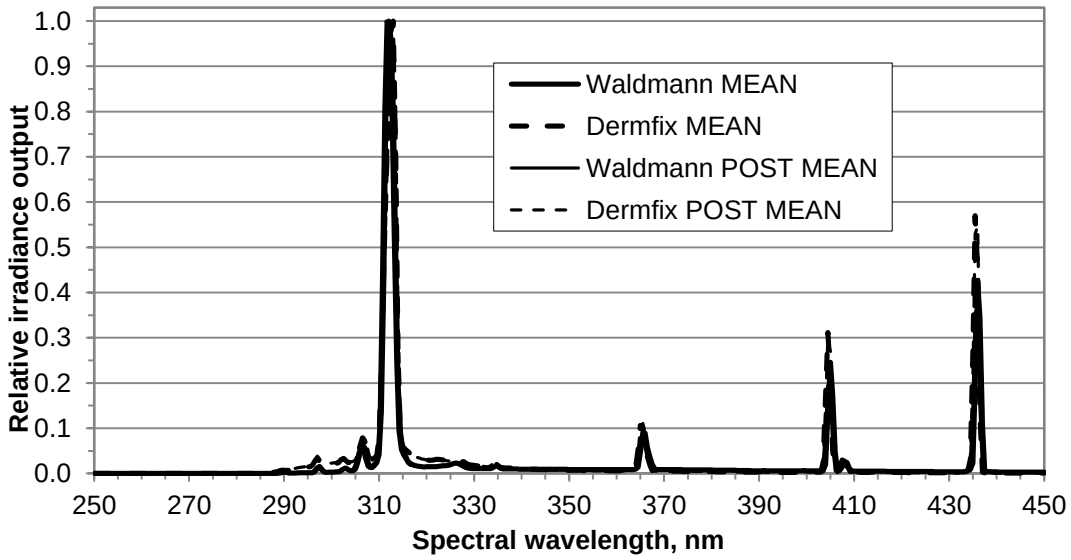
Figure 4.7 – Mean output (mJ/cm^2) of Dermfix hand-held devices pre and post-trial in correlation with time (seconds)



4.4.10.3 Spectral profile

All the devices showed that, pre and post-trial, the main UVB peak occurs in the range 310nm-315nm. The Dermfix devices spectral profiles, both pre and post-trial, showed that there was a greater relative UVB irradiance exposure (280nm to 315nm) and UVA irradiance exposure (315nm to 400nm) compared with the Waldmann device profiles (Figure 4.8).

Figure 4.8 Comparison of both manufacturers (Waldmann and Dermfix) mean pre and post-trial tube spectral profile output



4.5 Discussion

Although, vitiligo is the most common depigmentation disorder, it is greatly understudied. The majority of clinical treatment recommendations for vitiligo are based on small, inconclusive trials, specialist consensus and on data from other skin diseases (Whitton et al., 2010; Gawkrodger et al., 2008). Perhaps, unsurprisingly, patients often feel abandoned and believe that they do not receive adequate support from their doctors (Porter et al., 1987). Many patients obtain information about vitiligo from non-medical sources (Talsania et al., 2010).

For example, the Vitiligo Society UK and the Vitiligo Support International receive numerous enquiries about hand-held NB-UVB, which are freely available to buy form the internet (personal communication). Although, home phototherapy for psoriasis is widely available (whole body units), no randomised controlled trial to-date has evaluated the safety and effectiveness of hand-held home phototherapy for vitiligo.

The Hi-light pilot trial was the first trial evaluating the safety of using hand-held phototherapy at home and testing the feasibility of conducting the first national multi-centre randomised controlled trial (RCT) on home hand-held phototherapy for vitiligo. Although this was not an efficacy trial, this pilot trial was a crucial preliminary step to support a grant application for the main RCT and to develop a training package on home targeted phototherapy for vitiligo.

4.5.1 Summary and comments on the main findings

Recruitment into the trial went surprisingly well. The number of originally anticipated participants was exceeded and recruitment period lasted only three months instead of six. Secondary care recruitment (response rate=79%), especially in Nottingham (response rate=93.5%), was excellent. The higher response rate for Nottingham is probably explained by

the specialist interest of the principal investigator at this centre (JR), who mentioned the possibility of participation in the proposed trial during routine clinic visits (prior to sending out the invitation letters).

Recruitment in primary care was similarly successful, where we were forced to limit the number of surgeries conducting the mail-out.

Telephone pre-screening of potential participants prior to the hospital visit proved to be very successful. All potential participants, who attended clinic, were subsequently enrolled into the trial. Pre-screening participants over the phone, saved time and resources, considering that both a dermatologist and a research nurse had to be present during the initial hospital visit and a room had to be booked (2 hour slot) in a busy dermatology clinic for each potential participant. Thus, it was possible to arrange an appointment for a maximum of two to three patients per week in Nottingham and for only one patient in Leicester. Telephone pre-screening was one of the main reasons behind these excellent recruitment rates.

Only 10% of participants withdrew from the trial compared to the previously reported 20%, in a trial on hospital phototherapy (Lim-Ong et al., 2005). The findings of this trial, suggest that patients with vitiligo are very keen to

take part in trials on home light phototherapy using hand-held devices. Main reasons for the above were the fact that the treatment was self-administered at home, allowing flexibility around days and times for administration.

The training session and materials on how to self-administer home phototherapy and deal with short term side-effects were comprehensive, adequate and easy to follow, as evidenced by only one incident of erythema grade 3 and high level of adherence to the treatment plan (75%). Erythema grade 1 and 2 are generally considered adequate and sought after response to light therapy. Surprisingly, two patients in the placebo group also reported Erythema grade 1. The most likely explanation might be confusion of Erythema grade 1 with erythema which was caused by normal warming up of the device during treatment.

Two thirds of participants (68% in active groups and 60% in placebo group) and half of the research nurses (55%) guessed group allocation correctly due to the response to treatment and erythema; therefore it is likely that the blinding in the main trial will be compromised and should be carefully planned for.

Only one third of patients in the active groups (31.5%) were somewhat satisfied with the treatment and no-one was

very satisfied. Just under half of patients in active groups (47%) rated overall changes in their vitiligo as "a bit better" or much better". This comes to no surprise as the treatment period was clinically inadequate. Similarly, only four lesions (10%) in active groups showed high degree of repigmentation (75-100%). On the other hand, 75% of lesions in the active groups showed some degree of repigmentation. In clinical setting, this is usually an indication to continue phototherapy treatment (Gawkrodger et al., 2008).

Finally, active and placebo groups reported only "slight benefit" from the treatment (Patient Benefit Index) and, in general, did not show any changes in their quality of life. This comes as no surprise given the limited duration of treatment for this pilot trial; these outcomes were collected primarily to test their use in the clinical setting, rather than as an assessment of efficacy.

4.5.2 Limitations of this trial

The main limitation of this trial was the short treatment period and I would recommend a much longer treatment period for the main trial. Nevertheless, four months was adequate to capture initial treatment response, if any, and

therefore to provide an indication as to whether or not treatment should be continued.

Although the secondary care recruitment was excellent, this is likely to be lower in centres where there is no adequate CLRN support or an investigator with a specialist interest in vitiligo. Primary care seems likely to be a good source of treatment-naive potential participants.

The unsuitability of the ConvaTec transparencies for skin mapping of vitiliginous lesions was a potential source of measurement error in the repigmentation measurements. As this pilot trial did not seek to answer efficacy questions on home hand-held phototherapy, the above did not affect the validity of this trial. For the main trial, however, alternative methods will be used as outlined below.

4.5.3 Challenges and recommendations for future trials

In order to inform future trials on home hand-held phototherapy, it is helpful to present some of the key challenges that were faced and to provide recommendations on how to overcome these.

Challenge 1: Assessment of repigmentation rate and skin mapping technique. The main reasons behind this challenge were:

- The pattern of repigmentation, perifollicular or diffuse, and the colour match of newly repigmented lesions, which tends to be either darker or lighter, than the normal skin. Sometimes, it was difficult to clearly identify the edges of the vitiliginous area.

- The transparencies used in this trial (ConvaTec) were not designed with vitiligo lesions in mind. Although their texture and size were convenient, they were too shiny, which made skin mapping difficult and time consuming; especially in light-coloured individuals.

- Transfer of the transparencies into digital images was very time consuming.

Recommendation 1: The main advantage of using skin mapping techniques, seems to be the fact that it captures the three dimensional character of vitiliginous lesions around eyes, mouth, armpits and other physical cavities, and does not require standardisation, specific body positioning or expensive equipment, which are all needed with digital imaging. It is also easy to replicate and relatively cheap. Based on the above, a different

transparency, which could also be scanned into a digital image without manual transferring, would be preferable. Good lighting in the clinic room and contouring of the vitiliginous lesion edges with a surgical skin mapping pen are also recommended.

Challenge 2: Great variability in the output of hand-held devices. In particular, although Waldmann units had greater mean output both pre and post-trial, they were also more "sensitive" to usage as the percentage difference between their pre and post-trial output varied from 10.5% increment to 38.5% decline. Two possible reasons behind greater pre-trial output of Waldmann devices compared to Dermfix are 1) the fact that the comb attachment on Dermfix units completely covers the NB-UVB tube, while for Waldmann units, there was no cover in the central part of the tube and 2) the distance between the surface of the tube and the tip of the comb was different. On the other hand, Dermfix units had more consistent output variation pre and post-trial. Correspondence with the devices' manufacturers (Waldmann and Androv) confirmed that the output of the units tend to decrease after the first 100 hours of use. They also advised that output may decrease if the device is continuously switched on/off when treating multiple lesions.

Recommendation 2: Considering previously mentioned features of Dermfix such as lighter weight, longer cable, cheaper price, slightly larger treatment window and more convenient shape, in comparison to Waldmann (Table 4.3) and the above output characteristics, Dermfix hand-held units seems to be a better candidate for future trials on targeted phototherapy. All the devices should be screened before the trial and potential "outliers" with a lower pre-trial output than the rest of the devices should be replaced. Output should also be monitored at the end of the trial. Close collaboration with local Medical Physics department is, therefore essential.

Challenge 3: Requirement for the Minimal Erythema Dose (MED) test. Additional strain was added to the pilot trial configuration with the decision to perform an MED test at the baseline visit. Each participant had to come back to clinic the following day and therefore additional clinic space and research staff time was needed. The results of the pilot trial showed that 41% of participants required a different starting dose following their MED results compared to the staring dose suggested by a dermatologist; therefore a second visit was necessary and justifiable.

Recommendation 3: MED test is recommended for future trials on home hand-held phototherapy and is necessary to ensure patients' safety and appropriate NB-UVB dose administration.

4.5.4 Conclusions

Home hand-held phototherapy is of a great interest amongst patients and clinicians. It is potentially dangerous and worrying that these devices are currently bought by patients and used in an unsupervised way. In light of newly emerged preliminary evidence that treatment of early or spreading lesions with combination of phototherapy and topical corticosteroids seems to be effective, a trial utilising hand-held phototherapy seems like an appropriate way forward.

The Hi-light pilot trial showed that the training provided to patients on hand-held devices was comprehensive and well tolerated. Home hand-held phototherapy seems to be a safe intervention for both adults and children.

In conclusion, the results of this pilot trial strongly suggest that a national multi-centre double blind randomised controlled trial for vitiligo involving home hand-held

phototherapy is both feasible and acceptable to patients. It would address an important area of unmet need, and potentially provide a useful treatment strategy for patients with limited and early disease.

CHAPTER 5: Impact of my research

Abstract

In this final chapter, I outline the impact that my research has had in the field of vitiligo research, and outline what will that led on to next. Priorities identified by the vitiligo Priority Setting Partnership lead to a HTA commissioning call for a multi-centred RCT for the treatment of vitiligo. The results of the outcomes systematic review and the survey amongst patients and clinicians, renewed interest in patient-reported outcomes in vitiligo, and is being used to inform an international initiative to establish core outcome measures for use in future trials. The results of the pilot RCT (Hi-Light trial) informed the trial design of the grant submission for a full scale multi-centred RCT. Personally, I have also acquired numerous experiences and academic skills and competencies such as scientific papers writing, collaboration, peer-reviewing and networking and developed as a researcher, an academic, a clinician and a person.

5.1 Introduction

In previous chapters, I outlined some of the issues around research into vitiligo (Chapter 1) and what have I done to address these. In particular, I described the process of selection of interventions to be tested (Chapter 2), outcomes measures to be used in a trial on vitiligo treatment (Chapter 3) and also tested the feasibility of conducting a multi-centre randomised placebo-controlled trial. In this chapter, I reflect on the impact that each of my projects has had, what it will lead on to next, and the lessons I have learned during my PhD research.

5.2 Vitiligo Priority Setting Partnership

As mentioned previously (Chapter 2), five vignettes from the Top 10 treatment uncertainties were submitted to the National Institute for Health Research Health Technology Assessment (NIHR HTA) programme's prioritisation panel. The choice of uncertainties to be submitted as vignettes was based on currently available evidence for each intervention in question. In May 2012, the HTA published a commissioning call on vitiligo treatments that addressed two of the original treatment uncertainties ("How effective is UVB light when

combined with topical preparations" and "Which treatment is more effective: topical corticosteroid of light therapy?") (Table 5.1).

Table 5.1 Summary of the HTA commissioning call on vitiligo

What is the clinical and cost effectiveness of home-based narrow band ultra-violet light therapy (NB-UVB) using a hand-held device with or without topical steroid treatment?
1. Intervention: Home-based NB-UVB using a hand-held device.
2. Patient group: Patients with early and limited vitiligo who are suitable for NB-UVB therapy (could include adults and children).
3. Setting: Initiated in secondary care with ongoing treatment delivered at home and supported by primary care.
4. Control or comparator: Topical corticosteroid or placebo. Applicants to define and justify choice of topical corticosteroid.
5. Study design: RCT comparing topical steroids, home-based handheld NB-UVB or both interventions. Applicants to define and justify study design in order to answer the main questions which are (i) is one monotherapy better than the other; and (ii) is combination treatment better than monotherapy. Applicants may wish to consider including placebo treatments for both NB-UVB and steroids.
6. Important outcomes: Percentage of repigmentation of vitiliginous skin, quality of life (psychological impact, self-esteem), patient satisfaction. **Other outcomes:** Cessation of spread of vitiligo, relapse, adverse effects (e.g. skin cancer), cost effectiveness.
7. Minimum duration of follow-up: 1 year after treatment cessation (with duration of treatment being 3-4 months)
8. Has the device in question been granted a CE mark for the use proposed in this study? Yes

The above commissioning call meant that vitiligo had been identified as an important NHS health topic and that a funding opportunity for the first large, multi-centre, randomised controlled trial (RCT) on vitiligo was available. In June 2012, in collaboration with colleagues from the Centre of

Evidence Based Dermatology and the Nottingham Clinical Trials Unit, an outline research proposal was submitted. I was a co-applicant on this bid. In April 2013, our research team was informed that our bid was successful.

5.3 Systematic review and survey on outcome measures for vitiligo

In chapter 3, I stressed the importance of core outcome sets for vitiligo trials. In an understudied skin disease such as vitiligo, it is extremely important that the findings of small trials are combined using meta-analysis, in order to produce meaningful results and clinical recommendations. These are not possible until a core outcomes set has been defined.

Recently, the COMET (Core Outcome Measures in Effectiveness Trials) initiative was established (http://www.comet-initiative.org/) and it has been increasingly recognised that outcomes measures in trials should also be relevant to patients and clinicians(COMET, 2010)(Chapter 3). Following my presentation on the results of the outcomes systematic review and the survey of most desirable outcomes amongst patients and clinicians (International Pigment Cell Conference 2011, Bordeaux,

France), I proposed the inclusion of core outcomes set for vitiligo into the agenda of the International Federation of Pigment Cell Societies (IFPCS). My proposal was accepted and core outcomes set for vitiligo was the topic of the next Vitiligo Global Issues Consensus Conference. I was appointed as a leader of this international project and am in the process of initiating a three-round e-Delphi consensus exercise. The first round of this international consensus is now underway. I am currently preparing for the next Vitiligo Global Issues Consensus Conference (28th of February 2013) during the American Academy of Dermatology annual meeting (Miami, USA), where the results of the first round will be presented and next steps will be discussed.

Finally, the findings of the systematic review and the results of the survey of the most desirable outcomes amongst patients and clinicians were crucial in defining the primary outcome in our subsequent full research proposal for the development of a multi-centre randomised controlled trial on vitiligo (see below).

5.4 Pilot Hi-light trial

Following the HTA Commissioning Board meeting on 16th and 17th of October 2012, our outline proposal on hand-held

home NB-UVB phototherapy in combination with topical corticosteroids was shortlisted and we were invited to submit a full research proposal.

The pilot Hi-Light trial was completed in time for the submission of the full proposal and helped to inform the design and conduct of the full scale RCT (Table 5.2). The pilot trial successfully recruited 29 participants from two recruiting centres (Nottingham and Leicester) with the support of the Comprehensive Local Research Network (CLRN) nurses. The treatment period lasted four months and participants were assessed at two-monthly intervals, with additional telephone support as required.

The primary outcome of the pilot trial was the proportion of the screened patients who were eligible and willing to participate (Chapter 4).

Table 5.2 Lessons learned from the pilot Hi-Light trial and implications they had on the main RCT proposal

Aspect of the trial	Lessons from pilot trial	Implications for main RCT
Recruitment into the trial	• 29 participants were randomised in three months at two centres. Recruitment of 4-5 participants per centre each month is realistic.	• Recruitment of 40 - 50 participants per centre in 18 months seems appropriate (at a rate of 3-5 per month in 8-12 recruitment centres).
	• Identifying patients through primary care is likely to be important. Response from GP mail out was as follows: 67 letters were sent from two GP practices; these generated 28 expressions of interest (42% response rate).	• Recruitment through primary care is likely to be the main source of potential participants (especially for early and limited disease).
	• Exclusion based on concurrent medication with potential photosensitive drugs was high (accounting for 70% of all exclusions).	• Eligibility criteria amended to be clearer as to which photosensitive drugs warrant exclusion. (Many drugs may potentially cause photosensitization but for most of these, it is a rare side effect).
	• Main limitations were in clinic space and availability of Principle Investigators (PIs) for confirmation of diagnosis and issuing of prescription. • Telephone pre-screening of trial participants worked well. All potential participants (100%) who attended clinic were subsequently enrolled into the trial.	• Trial participants will be sent trial information and pre-screened prior to attending their clinic appointment in order to reduce the burden on clinic space and availability of PIs.

Participant characteristics	• 69% of participants were white British	• Given the higher impact of vitiligo in patients with darker skin, special efforts will be made to engage with Black and Ethnic minority patients.
Retention in the trial	• 3 / 29 (10%) of participants withdrew from treatment during the 4-month intervention period (2 active UVB; 1 dummy UVB). • Only one participant (3%) was lost to follow-up	• Participants who stop treatment early will be encouraged to continue in the trial in order to provide follow-up data. • To reduce missing data at 9 months, participants will be asked to return postal questionnaires if they are unable to attend this clinic visit.
Assessment of outcomes	• Mapping vitiligo patches (three patches per participant) using transparencies is possible, but can be difficult. Transferring the transparencies into digital imaging software can be time consuming. • Photographs taken by research nurses were of variable quality.	• Tracing of only one target lesion will be performed and adequate data management support will be ensured. • Medical photography facilities at recruiting centres will be used to standardise the images and ensure their high quality. • The number of digital images required will be reduced. These will be taken only on baseline visit and will be used as a reference standard for participants to judge treatment response at the end of the trial
Use of hand-held UVB devices	• Greater than anticipated variability in the output of individual units was noted. • Re-cycling devices for re-use by other participants is time consuming and requires additional resources for re-testing of output and	• One device per participant will be issued. • Dermfix will be used in the main trial. • All units prior to distribution will be tested to ensure a baseline quality standard in output of

	subsequent distribution back to participants • Devices that log treatment usage electronically as part of the unit are attractive for research purposes, but are more expensive and are not currently licensed for use in Europe. • Both devices used in the pilot had appropriate CE marking and a very similar output. Dermfix showed to have a more convenient treatment window shape and costs half price less than Waldmann.	the device. • Co-applicant added with experience in this area (Medical Physicist).
Training and MED testing	• Training in the use of the devices at home was difficult to standardise across sites, despite the use of a training manual. • Compared to the starting dose suggested by the clinicians on the basis of skin type, 41% of participants required a different starting dose following their Minimum Erythemal Dose (MED) test (doses were adjusted down in 6 / 29 (17%) of cases, and up in 7 / 29 (24%) of cases).	• Training DVD produced in order to standardise the intervention and ensure consistency in the training provided. • MED testing is good practice prior to use of NB-UVB treatment and is necessary to ensure the safety of the patient in the trial. A second visit the day after baseline in order to read the test results is justified and necessary.
Blinding	• 65% of participants guessed their allocation correctly at the end of the 4-month treatment period (68% active; 60% dummy) • 55% of research nurses guessed the allocation correctly (53% active; 60% dummy) • Main reasons given: response to treatment;	• Although it is possible to mask the treatment allocation, this is likely to be compromised and should therefore be planned for. • Inclusion of active treatments in all groups should help avoid unblinding resulting from differential treatment

	erythema	response.
Use of diaries to collect treatment adherence and adverse events.	• 28/29 (97%) of diaries were returned to the trial team. • 75% of people adhered fully to the treatment plan (with appropriate stepping up and down of exposure times).	• Patient diaries will continue to be used as aid memoires for the collection of side effects and treatment adherence.

In addition, the importance of acceptability of treatment response by patients has been stressed as one of the most important outcomes to collect in vitiligo trials (Whitton et al., 2010; Eleftheriadou et al., 2012 and Gonzalez et al., 2011). Currently there are very few data on validity of outcome measures used in vitiligo trials (Eleftheriadou et al., 2012).

Intuitively, recording treatment success or failure, based on changes in the amount of repigmentation observed, would seem to be the most appropriate outcome and a simple matter to measure. However, when repigmentation of vitiliginous patches does occur, this tends to be perifollicular. Hyperpigmentation often appears around the lesions also. These can reduce the cosmetic acceptability of the treatment response and means that a simple assessment of percentage of repigmentation, may fail to capture important information i.e. patient-reported acceptability of treatment response.

For this reason, as a primary outcome for the main RCT, measurement of acceptability of treatment response from the patients' perspective was proposed. This will be assessed using the following question: "How worthwhile is the level of treatment response to you?" Responses will be recorded using a 5-Likert scale ranging from "very worthwhile" though to "not at all worthwhile". Since percentage of repigmentation has been used in the majority of the RCTs to date (Eleftheriadou et al., 2012), we will also measure this as one of the secondary outcomes in the trial. This will allow meta-analysis of the trial results in combination with previous research.

To conclude, assessing treatment results by measuring the acceptability of treatment response from patients' perspective has not been done previously in vitiligo trials and we hope that the results of the main RCT will help to inform the definition of "cosmetically acceptable repigmentation", which is part of the proposed core outcomes set for future vitiligo trials.

Finally, should our application of the full scale RCT on home hand-held phototherapy in combination with topical corticosteroids for the treatment of vitiligo (Hi-Light trial) be successful, this would be an important addition to the treatment options available in the NHS to patients with

localised disease. It could also improve treatment adherence and the quality of life of vitiligo patients by offering them a treatment option that they can use at home.

This trial addresses some of the most basic questions around the long-term management of vitiligo. In the absence of new and emerging treatments, these results will be relevant and important in determining clinical practice for many years.

5.5 Wider application of hand-held NB-UVB devices

Phototherapy is currently used in the NHS for the treatment of many skin diseases, such as psoriasis, eczema, vitiligo cutaneous T-cell lymphoma and lichen planus. Home phototherapy using whole body units is increasingly being used for the treatment of psoriasis.

My pilot trial showed that the educational package on how to use hand-held phototherapy and how to deal with short-term side effects at home was comprehensive and easy to implement. Treatment with hand-held devices was well tolerated, easy to use and safe. In conclusion, the education DVD, produced to assist standardisation of the intervention and to ensure consistency during the main trial, could also be used by other researchers and the NHS in the treatment of

other limited skin conditions such as scalp psoriasis and hand eczema.

The training video will be freely available on the website of the Centre of Evidence Based Dermatology (www.nottingham.ac.uk/scs/divisions/evidencebaseddermatology/index.aspx)

5.6 Lessons I learned during PhD research

Throughout my research, I have acquired new skills, competencies and experiences, which allowed me to develop both as a research-clinician and an individual:

- *Writing medical papers:* I have published 7 papers during my studies. A further three articles are being prepared for submission to major medical journals. I have subsequently improved my writing skills, learned how to write clear abstracts and to follow standard formats such as IMRAD (introduction, methods, results and discussion), CONSORT statement (Consolidated Standards of Reporting Trials) and PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

- *Protocol, regulatory approvals and clinical file records:* I had the opportunity during my pilot trial to learn how to write a study protocol, prepare for ethics submission and obtain Primary Care Research Network (PCRN) and Comprehensive Local Research Network (CLRN) support. It was time consuming to develop the clinical records files and other necessary paperwork such as researcher's manual for the pilot trial. Also, I learned how to address peer-review comments and deal with unexpected obstacles when identifying which hand-held device to use in the trial.

- *Membership of the Vitiligo European Task Force:* since 2010, I have been an active member of the Vitiligo European Task Force. My research enabled me to complement the work of this international group of experts in vitiligo by providing a steer for future research activity towards questions important to patients and clinicians, and in leading an international consensus on core outcomes set for vitiligo. In addition, I was asked to join the team of expert authors of the latest European guidelines for the management of vitiligo (Taieb et al., 2013). My contribution to this major international publication was to review and update the references, check the document for consistency and

ensure that all the subchapters were up-to-date with the latest evidence based research.

- *Collaboration and networking:* in May 2011, I won the Building Experience and Skill Travel Scholarships (BESTS) from the University of Nottingham. BESTS gave me a chance to visit the San Gallicano Institute (Rome, Italy), a well-known dermatological research centre for diagnosis and treatment of skin diseases including vitiligo with numerous national and international collaborations. This fully funded two-week visit broadened my experience and understanding of vitiligo and its treatment options, helped me to establish a network of new contacts, strengthened my understanding of what being a researcher means and the skills and attitudes one needs to make a success of a career in clinical research.

- *The International School of vitiligo and pigmentary disorders:* Recently, the first International School of vitiligo and pigmentary disorders was launched in Barcelona, Spain by the Vitiligo Research (VR) Foundation (http://vrfoundation.org/); a philanthropic organisation committed to research into vitiligo. I attended this course, which targeted mainly young

professionals. The event gave the opportunity for learning, sharing ideas and networking. Following the event, the VR Foundation has funded an international study on Quality of Life in vitiligo patients. I assisted in the development of the study protocol for this important initiative. Finally, I was invited to join the Scientific Advisory Board of the Vitiligo Research Foundation (VR Foundation). Together with the Scientific Committee, the Scientific Advisory Board helps to develop the VR Foundation research agenda, identify established and emerging researchers and evaluate grants application.

- *Other academic skills:* throughout my research I have gained experience on how to peer-review for various dermatology journals such as the Journal of American Academy of Dermatology, the Re-invention-journal for undergraduate research, the Clinical and Experimental Dermatology. I also act as a regular reviewer for the "Hot Line" section of the Dermatologic Therapy Journal. This experience has helped me to understand what a reviewer is looking for and subsequently to improve my own writing skills. In addition, during my second year, I was invited by the University of Nottingham's, School of Clinical Sciences, to conduct a viva examination of a 3rd year medical

student who completed her BMedSCi project on varicose veins. This experience assisted me in my understanding and preparation of my own viva examination.

- *Vitiligo Newsletter:* I developed a network of participants who took part in my projects and wished to be informed about the results as well as future studies on vitiligo. To keep them up-to-date, I developed a quarterly newsletter, the Vitiligo Newsletter, and published lay summaries of my own research as well as other important findings in vitiligo worldwide. So far, my database contains around 450 people, patients with vitiligo (mainly) and clinicians with an interest in the disease. I strongly believe that communicating research back to the patients is one of the most important aspects of bringing research results back to the heart of clinical care.

5.7 My future plans

My career aim is to become a Professor and Consultant Dermatologist. I aim to continue being involved in research until I complete my Specialty Training and further develop my skills and expertise. I am involved in the following research projects:

- International consensus on core outcomes set for future vitiligo trials. As mentioned above, I am leading this international e-Delphi consensus exercise.

- Cochrane Systematic reviews 2012 "Interventions for vitiligo". I work on the latest update of the Cochrane systematic review as one of the co-authors. It is anticipated that the update will be completed by the end of 2013.

- Vitiligo European Task Force and Vitiligo Research (VR) Foundation. I plan to carry on my involvement as a member of VEFT and member of the VR Foundation Scientific Research Committee.

- If our detailed proposal for the mail RCT is successful, I will work on the trial as a member of the Trial Management Group.

In conclusion, alongside research skills on various methodologies from systematic reviews to randomised controlled trials, I have also developed other skills of major importance to every academic such as writing scientific papers, peer-reviewing, teaching and networking. I have come to realise how crucial it is to communicate your research to a community of users, and to keep them updated. Finally, the most important lesson I have learned is to be patient and stay

calm, no matter the obstacles and delays in research as it can only get better.

REFERENCES

(1993) Severity scoring of atopic dermatitis: the SCORAD index. Consensus Report of the European Task Force on Atopic Dermatitis. *Dermatology,* 186 (1), 23-31.

ACHAUER, B. M., Y. LE and V.M. VANDER KAM. Treatment of vitiligo with melanocytic grafting. *Annals of Plastic Surgery,* 1994, 33(6), 644-6.

AGARWAL, S.,M. RAMAM, V. K. SHARMA, S. KHANDPUR, H. PAL and R. M. PANDEY. A randomized placebo-controlled double-blind study of levamisole in the treatment of limited and slowly spreading vitiligo. *British Journal of Dermatology,* 2005, 153(1), 163-6.

AGRAWAL, K. and A. AGRAWAL (1995) repigmentation with dermabrasion and thin split-thickness skin graft. *Dermatologic Surgery,* 1995, 21(4), 711-5.

AKHYANI, M., Z. HALLAJI, AH. EHSANI, T. MOKARRAMI, F. GOROUHI. A comparison between systemic PUVA therapy alone and combined with topical calcipotriol in the treatment of generalized vitiligo. *Iranian Journal of Dermatology,* 2005, 31(8).

AL'ABADIE, M. S., H. J. SENIOR, S. S. BLEEHEN, and D. J. GAWKRODGER. Neuropeptide and neuronal marker studies in vitiligo. *British Journal of Dermatology,* 1994, 131(2), 160-5.

AL-REFU, K. Vitiligo in children: a clinical-epidemiologic study in Jordan. *Pediatric Dermatology,* 2012, 29(1), 114-5.

ALBERT, D. M., J. J. NORDLUND and A. B. LERNER. Ocular abnormalities occurring with vitiligo. *Ophthalmology,* 1979, 86(6), 1145-60.

ALBERT, D. M., M. D. WAGONER, R. C. PRUETT, J. J. NORDLUND and A. B. LERNER. (1983) Vitiligo and disorders of the retinal pigment epithelium. *British Journal of Ophthalmology,* 1983, 67(3), 153-6.

ALDRIDGE, A. L. (Ed.). *Surveying the social world: principles and practice in survey research*, Buckingham, Open University Press, 2001.

ALKHATEEB, A., P. R. FAIN, A. THODY, D. C. BENNETT and R. A. SPRITZ. Epidemiology of vitiligo and associated autoimmune diseases in Caucasian probands and their families. *Pigment Cell Research,* 2003, 16(3), 208-14.

ANBAR, T. S., W. WESTERHOF, A. T. ABDEL-RAHMAN, A. A. EWIS and M. A. EL-KHAYYAT. Effect of one session of ER:YAG laser ablation plus topical 5Fluorouracil on the outcome of short-term NB-UVB phototherapy in the treatment of non-segmental vitiligo: a left-right comparative study. *Photodermatology Photoimmunology Photomedicine,* 2008, 24(6), 322-9.

ARCA, E., H. B. TASTAN, A. H. ERBIL, E. SEZER, E. KOC, and Z. KURUMLU. Narrow-band ultraviolet B as monotherapy and in combination with topical calcipotriol in the treatment of vitiligo. *Journal of Dermatolody,* 2006, 33(5), 338-43.

ASAWANONDA, P., J. KIJLUAKIAT, W. KORKIJ, and W. SINDHUPAK. Targeted broadband ultraviolet b phototherapy produces similar responses to targeted narrowband ultraviolet B phototherapy for vitiligo: a randomized, double-blind study. *Acta Dermato-Venereologica,* 2008, 88(4), 376-81.

ATTILI, V. R. and S. K. ATTILI. Lichenoid inflammation in vitiligo:a clinical and histopathologic review of 210 cases. *International Journal of Dermatology,* 2008, 47(7), 663-9.

AUGUSTIN, M., A. I. GAJUR, C. REICH, S. J. RUSTENBACH and I. SCHAEFER. Benefit evaluation in vitiligo treatment: development and validation of a patient-defined outcome questionnaire. *Dermatology,* 2008, 217(2), 101-6.

AYOTUNDE, A. and G. OLAKUNLE. Ophthalmic assessment in black patients with vitiligo. *Journal of National Medical Association,* 2005, 97(2), 286-7.

BAKIS-PETSOGLOU, S., J. L. LE GUAY and R. A. WITTAL. Randomized, double-blinded, placebo-controlled trial of pseudocatalase cream and narrowband ultraviolet B in the treatment of vitiligo. *British Journal of Dermatology,* 2009, 161(4), 910-7.

BARMAN, K. D., B. K. KHAITAN and K. K.VERMA. A comparative study of punch grafting followed by topical corticosteroid versus punch grafting followed by PUVA therapy in stable vitiligo. *Dermatological Surgery,* 2004, 30(1), 49-53.

BEHL PN, B. R. 400 cases of vitiligo: A clinico-therapeutic analysis. *Indian Journal of Dermatology,* 1972, 17, 51-56.

BENZEKRI, L., Y. GAUTHIER, S. HAMADA and B.HASSAM. Clinical features and histological findings are potential indicators of activity in lesions of common vitiligo. *British Journal of Dermatology ,* 2012, doi: 10.1111/bjd.12034. [Epub ahead of print]

BHATNAGAR, A., A. J. KANWAR, D PARSAD and D. DE. Comparison of systemic PUVA and NB-UVB in the treatment of vitiligo: an open prospective study. *Journal of the European Academy of Dermatology and Venereology,* 2007, 21(5), 638-42.

BHOR, U. and S.PANDE. Scoring systems in dermatology. *Indian Journal of Dermatology Venereology and Leprology,* 2006, 72(4), 315-21.

BIRLEA, S. A., P. R. FAIN and R. A. SPRITZ. A Romanian population isolate with high frequency of vitiligo and associated autoimmune diseases. *Archves of Dermatology,* 2008, 144(3), 310-6.

BISWAS, G., J. N. BARBHUIYA, M. C. BISWAS, M. N. ISLAM and S. DUTTA. Clinical pattern of ocular manifestations in vitiligo. *Journal of the Indian Medical Association,* 2003, 101(8), 478-80.

BOISSEAU-GARSAUD, A. M., P. GARSAUD, D. CALES-QUIST, R. HELENON, C. QUENEHERVE and R. C. CLAIRE. Epidemiology of vitiligo in the French West Indies (Isle of Martinique). *International Journal of Dermatology,* 2000, 39(1), 18-20.

BOISSY, R. E. and P. MANGA. On the etiology of contact/occupational vitiligo. *Pigment Cell Research,* 2004, 17(3), 208-14.

BUCKLEY, B., A. M. GRANT, L. FIRKINS, A. C. GREENE and J. FRANKAU. Working together to identify research questions. *Continence UK,* 2007, 1(1), 76-81.

BUCKLEY, B. S., A. M. GRANT, D. G. TINCELLO, A. S. WAGG and L. FIRKINS. Prioritizing research: Patients, carers, and clinicians working together to identify and prioritize important clinical uncertainties in urinary incontinence. *Neurourology and Urodynamics*, 2010, 29(5), 708-14.

BULBUL BASKAN, E., M. BAYKARA, I. ERCAN, S. TUNALI and A. YUCEL. Vitiligo and ocular findings: a study on possible associations. *Journal of the European Academy of Dermatology and Venereology,* 2006, 20(7), 829-33.

CACCIALANZA, M., R. PICCINNO, F. CAPPIO, M. ROZZA and L. MAINARDI. [Phototherapy of psoriasis of the scalp. Results in 21 patients treated with a special portable ultraviolet rays lamp]. *Giornale italiano di dermatologia e venereologia,* 1989, 124(11-12), LXI-LXV.

CARIO-ANDRE, M., C. PAIN, , Y. GAUTHIER, V. CASOLI and A. TAIEB. In vivo and in vitro evidence of dermal fibroblasts influence on human epidermal pigmentation. *Pigment Cell Research,* 2006, 19(5), 434-42.

CASACCI, M., P. THOMAS, A. PACIFICO, A. BONNEVALLE, A. PARO VIDOLIN and G. LEONE. Comparison between 308-nm monochromatic excimer light and narrowband UVB phototherapy (311-313 nm) in the treatment of vitiligo--a multicentre controlled study. *Journal of the European Academy of Dermatology and Venereology,* 2007, 21(7), 956-63.

CESTARI TF, D. M., E.I. FERNANDES and R. ALBANEZE. Comparative study of two psoralens in topical phototherapy for vitiligo [Estudo comparativo entre psoralenos na fototerapia topica do vitiligo]. *Anais Brasileiros de Dermatologia,* 2001, 76(5), 683-92.

CHALMERS, I. Well informed uncertainties about the effects of treatments. *British Medical Journal,* 2004, 328(7438), 475-6.

CHALMERS, I. and P. GLASZIOU. Avoidable waste in the production and reporting of research evidence. *Lancet,* 2009, 374(9683), 86-9.

CHANCO-TURNER, M. L. and A. B. LERNER. Physiologic Changes in Vitiligo. *Archives of Dermatology,* 1965, 91(4), 390-6.

CHARMAN, C., C. CHAMBERS and H. WILLIAMS. Measuring atopic dermatitis severity in randomized controlled clinical trials: what exactly are we measuring? *Journal of Investigative Dermatology,* 2003, 120(6), 932-41.

CHEN, Y. F., P. Y. YANG, D. N. HU, F. S. KUO, C. S. HUNG and C. M. HUNG. Treatment of vitiligo by transplantation of cultured pure melanocyte suspension: analysis of 120 cases. *Journal of the Americal Academy of Dermatology,* 2004, 51(1), 68-74.

CHUN, W. H. and S. K. HANN. The progression of nonsegmental vitiligo: clinical analysis of 318 patients. *International Journal of Dermatology,* 1997, 36(12), 908-10.

COCHRANE COLLABORATION. Available from: http://www.cochrane.org/ (last accessed 25 January 2013).

COMET Initiative. Core Outcomes Measures in Effectiveness Trials, 2010. Available from: http://www.comet-initiative.org/ (last accessed 25 January 2013).

CUI, J., Y.ARITA and J. C. BYSTRYN. Characterization of vitiligo antigens. *Pigment Cell Research,* 1995, 8(1), 53-9.

CUI, J., R. HARNING, M. HENN and J. C.BYSTRYN. Identification of pigment cell antigens defined by vitiligo antibodies. *Journal of Investigative Dermatology,* 1992, 98(2), 162-5.

CZAJKOWSKI, R. Comparison of melanocytes transplantation methods for the treatment of vitiligo. *Dermatologic Surgery,* 2004, 30(11), 1400-5.

CZAJKOWSKI, R., W. PLACEK, T. DREWA, B. KOWALISZYN, J. SIR and W. WEISS. Autologous cultured melanocytes in vitiligo treatment. *Dermatologic Surgery,* 2007, 33(9), 1027-36.

DAS, S. K., P. P. MAJUMDER, R. CHAKRABORTY, T. K. MAJUMDAR and B. HALDAR. Studies on vitiligo. I. Epidemiological profile in Calcutta, India. *Genetic Epidemiology,* 1985, 2(1), 71-8.

DAVE, S., D. M. THAPPA and M. DSOUZA. Clinical predictors of outcome in vitiligo. *Indian Journal of Dermatology Venereology and Leprology,* 2002, 68(6), 323-5.

DAVID E. E., *Lever's Histopathology of the Skin (Hardcover)*, London: Lippincott Williams & Wilkins.

DAWID M, M. GRASSBERGER and K. WOLFF. Efficacy and safety of pimecrolimus cream 1% in adult patients with vitiligo: Results of a randomized, double-blind, vehicle-controlled study [Wirksamkeit und Sicherheit von Pimecrolimus-Creme 1% bei erwachsenen Patienten mit Vitiligo: Ergebnisse einer randomisierten, Vehikel-kontrollierten Doppelblind-Studie]. *Journal der Deutschen Dermatologischen Gesellschaft,* 2006, 4(11), 942-6.

DELL'ANNA, M. L., A. MASTROFRANCESCO, R. SALA, M. VENTURINI, M. OTTAVIANI, A. P. VIDOLIN, G. LEONE, P. G. CALZAVARA, W.WESTERHOF and M.PICARDO. Antioxidants and narrow band-UVB in the treatment of vitiligo: a double-blind placebo controlled trial. *Clinical and Experimental Dermatology,* 2007a, 32(6), 631-6.

DELL'ANNA, M. L., M. OTTAVIANI, V. ALBANESI, A. P. VIDOLIN, G. LEONE, C. FERRARO, A. COSSARIZZA, L. ROSSI and M. PICARDO. Membrane lipid alterations as a possible basis for melanocyte degeneration in vitiligo. *Journal of Investigative Dermatology,* (2007b), 127(5), 1226-33.

DELL'ANNA, M. L. and M. PICARDO. A review and a new hypothesis for non-immunological pathogenetic mechanisms in vitiligo. *Pigment Cell Research,* 2006, 19(5), 406-11.

DENMAN, C. J., J. MCCRACKEN, V. HARIHARAN, J. KLARQUIST, K. OYARBIDE-VALENCIA, J. A. GUEVARA-PATINO and I. C. LE POOLE. HSP70i accelerates depigmentation in a mouse model of autoimmune vitiligo. *Journal of Investigative Dermatology,* 2008; 128(8), 2041-8.

DEREYMAEKER, A. M., J. P. FRYNS, J. ARS, J. ANDRESESCU and H. VAN DEN BERGHE. Retinitis pigmentosa, hearing loss and vitiligo: report of two patients. *Clinical Genetics,* 1989, 35(5), 387-9.

DOGRA, S., D. PARSAD, S. HANDA and A. J. KANWAR. Late onset vitiligo: a study of 182 patients. *International Journal of Dermatology,* 2005, 44(3), 193-6.

DOTTERUD, L. K. and R. BRAUN. [UV-B comb versus betamethasone solution in scalp psoriasis]. *Tidsskrift for den Norske Laegeforening,* 2000, 120(16), 1858-9.

EL-MOFTY M., W. MOSTAFA, R. YOUSSEF, M. EL-FANGARY, AZ. ELRAMLY, D. MAHGOUB *et al.* Ultraviolet A in vitiligo. *Photodermatology Photoimmunology Photomedicine,* 2006, 22(4), 214-6.

ELEFTHERIADOU, V.and K. THOMAS. Have your say in research into vitiligo. *Dermatological Nursing,* 2009, 8, 56-57.

ELEFTHERIADOU, V., M. E. WHITTON, D. J. GAWKRODGER, J. BATCHELOR, J. CORNE, B. LAMB, S. ERSSER, J. RAVENSCROFT and K. S. THOMAS. Future research into the treatment of vitiligo: where should our priorities lie? Results of the vitiligo priority setting partnership. *British Journal of Dermatology,* 2011, 164(3), 530-536.

ELEFTHERIADOU, V., K. S. THOMAS, M. E. WHITTON, J. M. BATCHELOR and J. C. RAVENSCROFT. Which outcomes should we measure in vitiligo? Results of a systematic review and a survey amongst patients and clinicians on outcomes in vitiligo trials. *British Journal of Dermatology,*.2012, 167(4), 804-14.

ELGOWEINI, M. and N. NOUR EL DIN. Response of vitiligo to narrowband ultraviolet B and oral antioxidants. *Journal of Clinical Pharmacology,* 2009, 49(7), 852-5.

ELWYN, G., S. CROWE, M. FENTON, L. FIRKINS, J. VERSNEL, S, WALKER, I. COOK, S. HOLGATE, B. HIGGINS and C. GELDER. Identifying and prioritizing uncertainties: patient and clinician engagement in the identification of research questions. *Journal of Evaluation in Clinincal Practice,* 2010, 16(3), 627-31.

ERMIS, O., E. ALPSOY, L. CETIN and E. YILMAZ. Is the efficacy of psoralen plus ultraviolet A therapy for vitiligo enhanced by concurrent topical calcipotriol? A placebo-controlled double-blind study. *British Journal of Dermatology,* 2001, 145(3), 472-5.

ESFANDIARPOUR, I., A. EKHLASI, S. FARAJZADEH and S. SHAMSADINI. The efficacy of pimecrolimus 1% cream plus narrow-band ultraviolet B in the treatment of vitiligo: a double-blind, placebo-controlled clinical trial. *Journal of Dermatological Treatment,* 2009, 20(1), 14-8.

EYRE, R. W. and G. G. KRUEGER. Response to injury of skin involved and uninvolved with psoriasis, and its relation to disease activity: Koebner and 'reverse' Koebner reactions. *British Journal of Dermatology,* 1982, 106(2), 153-9.

EZZEDINE, K., H. W. LIM, T. SUZUKI, I. KATAYAMA, I. HAMZAVI, C. C. LAN *et al*. Revised classification/nomenclature of vitiligo and related issues: the Vitiligo Global Issues Consensus Conference. *Pigment Cell Melanoma Research,* 2012, 25(3), E1-13.

FAAS, L., R. VENKATASAMY, R. C. HIDER, A. R. YOUNG and A. SOUMYANATH. In vivo evaluation of piperine and synthetic analogues as potential treatments for vitiligo using a sparsely pigmented mouse model. *British Journal of Dermatology,* 2008; 158(5), 941-50.

FARAH, F. S., A. K. KURBAN and H. T. CHAGLASSIAN. The treatment of vitiligo with psoralens and triamcinolone by mouth. *British Journal of Dermatology,* 1967, 79(2), 89-91.

FARROKHI, S., M. HOJJAT-FARSANGI, M. K. NOOHPISHEH, R. TAHMASBI and N. REZAEI. Assessment of the immune system in 55 Iranian patients with vitiligo. *Journal of the Eurean Academy of Dermatology and Venereology,* 2005, 19(6), 706-11.

FERNANDEZ-PENAS, P., M. JONES-CABALLERO, O. ESPALLARDO and A. GARCIA-DIEZ. Comparison of Skindex-29, Dermatology Life Quality Index (DLQI), Psoriasis Disability Index (PDI) and Medical Outcome Study Short Form (SF-36) in patients with mild to severe psoriasis. *British Journal of Dermatology*, 2012, 166(4), 884-7

FINLAY, A. Y. and G. K. KHAN. Dermatology Life Quality Index (DLQI)-a simple practical measure for routine clinical use. *Clinical and Experimental Dermatology,* 1994, 19(3), 210-6.

FITZPATRICK, T. B. Hypomelanosis. *Southern Medical Journal,* 1964, 57, 995-1005.

FITZPATRICK, T. B. and A. S. BREATHNACH. [the Epidermal Melanin Unit System]. *Dermatolische Wochenschrift,* 1963, 147, 481-9.

GAUTHIER, Y., M. CARIO ANDRE and A. TAIEB. A critical appraisal of vitiligo etiologic theories. Is melanocyte loss a melanocytorrhagy? *Pigment Cell Research,* 2003; 16(4), 322-32.

GAUTHIER, Y. and J. E. SURLEVE-BAZEILLE. Autologous grafting with noncultured melanocytes: a simplified method for treatment of depigmented lesions. *Journal of the American Academy of Dermatology,* 1992, 26(2 Pt 1), 191-4.

GAUTHIER Y.and A. Taieb. Proposal for a new classification of segmental vitiligo of the face (abstract). *Pigment Cell Research,* 2006, 19, 515.

GAWKRODGER, D. J., A. D. ORMEROD, L. SHAW, I. MAURI-SOLE, M. E. WHITTON, M. J. WATTS, A. V. ANSTEY, J. INGHAM and K. YOUNG. Vitiligo: concise evidence based guidelines on diagnosis and management. *Postgraduate Medical Journal,* 2010, 86(1018), 466-71.

GAWKRODGER, D. J., A. D. ORMEROD, L. SHAW, I. MAURI-SOLE, M. E. WHITTON, M. J. WATTS, A. V. ANSTEY, J. INGHAM and K. YOUNG. Guideline for the diagnosis and management of vitiligo. *British Journal of Dermatology,* 2008, 159(5), 1051-76.

GOLDINGER, S. M., R. DUMMER, P. SCHMID, G. BURG, B. SEIFERT and S. LAUCHLI. Combination of 308-nm xenon chloride excimer laser and topical calcipotriol in vitiligo. *Journal of the European Academy of Dermatology and Venereology,* 2007, 21(4), 504-8.

GOLDMAN, L., R. S. MORAITES and W. KITZMILLER. White spots in biblical times. A background for the dermatologist for participation in discussions of current revisions of the bible. *Archives of Dermatology,* 1966, 93(6), 744-53.

GONZALEZ, U., M. WHITTON, V. ELEFTHERIADOU, M. PINART, J. BATCHELOR and J. LEONARDI-BEE. Guidelines for designing and reporting clinical trials in vitiligo. *Archives of Dermatology,* 2011, 147(12), 1428-36.

GONZALEZ, U. and H. WILLIAMS. Implications for Research: Getting the Most out of Cochrane Reviews. *Cochrane Database of Systematic Reviews,* 2011, 1, doi: 10.1002/14651858.ED000037.

GREY, D. (Ed.). *Doing research in the real world.* London, Sage Publications 2004

GUERRA, L., PRIMAVERA, G., RASKOVIC, D., PELLEGRINI, G., GOLISANO, O., BONDANZA, S., PATERNA, P., SONEGO, G., GOBELLO, T., ATZORI, F., PIAZZA, P., LUCI, A. & DE LUCA, M. (2003) Erbium:YAG laser and cultured epidermis in the surgical therapy of stable vitiligo. *Archives of Dermatology,* 139, 1303-10.

GUPTA, D. K. (Ed.). *Microskin Grafting for Vitiligo*, London. Springer, 2009.

HALDER, R. M., P. E. GRIMES, C. A. COWAN, J. A. ENTERLINE, S. G. CHAKRABARTI and J. A. KENNEY. Childhood vitiligo. *Journal of the Americal Academy of Dermatology,* 1987. 16(5 Pt 1), 948-54.

HALLAJI, Z., M. GHIASI, A. EISAZADEH and M. R. DAMAVANDI. Evaluation of the effect of disease duration in generalized vitiligo on its clinical response to narrowband ultraviolet B phototherapy. *Photodermatology Photoimmunology Photomedicine,* 2012, 28(3), 115-9.

HAMZAVI, I., H. JAIN, D. MCLEAN, J. SHAPIRO, H. ZENG and H. LUI. Parametric modeling of narrowband UV-B phototherapy for vitiligo using a novel quantitative tool: the Vitiligo Area Scoring Index. *Archives of Dermatology,* 2004, 140(6), 677-83.

HANN, S. K., W. H. CHUN and Y. K. PARK. Clinical characteristics of progressive vitiligo. *International Journal of Dermatology,* 1997a, 36(5), 353-5.

HANN, S. K., Y. S. KIM, J. H. YOO and Y. S. CHUN. Clinical and histopathologic characteristics of trichrome vitiligo. *Journal of the American Academy of Dermatology,* 2000, 42(4), 589-96.

HANN, S. K., S. W. KOO, J. B. KIM and Y. K. PARK. Detection of antibodies to human melanoma cells in vitiligo and alopecia areata by Western blot analysis. *Journal of Dermatology,* 1996, 23(2), 100-3.

HANN, S. K. and H. J. LEE. Segmental vitiligo: clinical findings in 208 patients. *Journal of the American Academy of Dermatology,* 1996, 35(5 Pt 1), 671-4.

HANN, S. K., Y. K. PARK and W. H. CHUN. Clinical features of vitiligo. *Clinics in Dermatology,* 1997b, 15, 891-7.

HARNING, R., CUI, J. & BYSTRYN, J. C. Relation between the incidence and level of pigment cell antibodies and disease activity in vitiligo. *Journal of Investigative Dermatology,* 1991, 97, 1078-80.

HASEGAWA, T., Y. SUGA, A. IKEJIMA, S. MURAMATSU, Y. MIZUNO, H. TSUCHIHASHI *et al.* Suction blister grafting with CO(2) laser resurfacing of the graft recipient site for vitiligo. *Journal of Dermatology,* 2007, 34(7), 490-2.

HATCHOME, N., T. KATO and H. TAGAMI. Therapeutic success of epidermal grafting in generalized vitiligo is limited by the Koebner phenomenon. *Journal of the Americam Academy of Dermatology,* 1990, 22(1), 87-91.

HAYKAL, K. A. and J. P. DESGROSEILLIERS. Are narrow-band ultraviolet B home units a viable option for continuous or maintenance therapy of photoresponsive diseases? *Journal of Cutaneous Medicine and Surgery,* 2006, 10(5), 234-40.

HEARN, R. M., A. C. KERR, K. F. RAHIM, J. FERGUSON and R. S. DAWE. Incidence of skin cancers in 3867 patients treated with narrow-band ultraviolet B phototherapy. *British Journal of Dermatology,* 2008, 159(4), 931-5.

HOFER, A., A. S. HASSAN, F. J. LEGAT, H. KERL and P. WOLF. Optimal weekly frequency of 308-nm excimer laser treatment in vitiligo patients. *British Journal of Dermatology,* 2005, 152(5), 981-5.

HOWITZ J. BH., H. BRODTHAGEN, M. SCHWARTZ and K. Thomsen. Prevalence of vitiligo. Epidemiological survey on the Isle of Bornholm, Denmark. *Archives of Dermatology,* 1977, 113(1), 47-52.

HU, Z., J. B. LIU, S. S. MA, S. YANG and X. J. ZHANG. Profile of childhood vitiligo in China: an analysis of 541 patients. *Pediatric Dermatology,* 2006; 23(2), 114-6.

IBBOTSON, S. H., D. BILSLAND, N. H. COX, R. S. DAWE, B. DIFFEY, C. EDWARDS *et al.* An update and guidance on narrowband ultraviolet B phototherapy: a British Photodermatology Group Workshop Report. *British Journal of Dermatology,* 2004, 151(2), 283-97.

INVOLVE NHS: National Institute for Health Research. Available from: http://www.invo.org.uk (last accessed 25 January 2013)

JAMES LIND ALLIANCE, The James Lind Alliance Guidebook. Oxford: James Lind Alliance 2010. Available from: http://www.jlaguidebook.org/ (last accessed 25 January 2013).

JIMBOW, K., H. CHEN, J. S. PARK and P. D. THOMAS. Increased sensitivity of melanocytes to oxidative stress and abnormal expression of tyrosinase-related protein in vitiligo. *British Journal of Dermatology,* 2001, 144(1), 55-65.

JIN, Y., S. A. BIRLEA, P. R. FAIN, K. GOWAN, S. L. RICCARDI, P. J. HOLLAND *et al.* Variant of TYR and autoimmunity susceptibility loci in generalized vitiligo. *New England Journal of Medicine,* 2010, 362(18), 1686-97.

JIN, Y., C. M. MAILLOUX, K. GOWAN, S. L. RICCARDI, G. LABERGE, D. C. BENNETT, P. R. FAIN and R. A. SPRITZ. NALP1 in vitiligo-associated multiple autoimmune disease. *New England Journal of Medicine,* 2007, 356(12), 1216-25.

JOHN C., MAIZE M.D. *et al. Cutaneous Pathology (Hardcover)*. London:Churchill Livingstone, 1998.

KAHN, A. M. and M. J. COHEN. Repigmentation in vitiligo patients. Melanocyte transfer via ultra-thin grafts. *Dermatologic Surgery,* 1998, 24(3), 365-7.

KANDIL, E..Treatment of vitiligo with 0-1 per cent betamethasone 17-valerate in isopropyl alcohol- a double-blind trial. *British Journal of Dermatolody,* 1974, 91(4), 457-60.

KAWALEK, A. Z., J. M. SPENCER and G. PHELPS.Combined excimer laser and topical tacrolimus for the treatment of vitiligo: a pilot study. *Dermatologic Surgery,* 2004, 30(2 Pt 1), 130-5.

KEMP, E. H., D. J. GAWKRODGER, P. F. WATSON and A. P. WEETMAN. Immunoprecipitation of melanogenic enzyme autoantigens with vitiligo sera: evidence for cross-reactive autoantibodies to tyrosinase and tyrosinase-related protein-2 (TRP-2). *Clinical and Experimental Immunology,* 1997, 109(3), 495-500.

KHALID, M., G. MUJTABA and T. S. HAROON. Comparison of 0.05% clobetasol propionate cream and topical Puvasol in childhood vitiligo. *International Journal of Dermatology,* 1995, 34(3), 203-5.

KHANDPUR, S., V. K. SHARMA and Y. MANCHANDA. Comparison of minipunch grafting versus split-skin grafting in chronic stable vitiligo. *Dermatologic Surgery,* 2005; 31(4), 436-41.

WOLFF K., S. KATZ *et al. Fitzpatrick's Dermatology in General Medicine*, 7th edition.New York: McGraw-Hill Professional, 2007.

KOEK, M. B., E. BUSKENS, H VAN WEELDEN, P. H. STEEGMANS, C. A. BRUIJNZEEL-KOOMEN and V. SIGURDSSON. Home versus outpatient ultraviolet B phototherapy for mild to severe psoriasis: pragmatic multicentre randomised controlled non-inferiority trial (PLUTO study). *British Medical Journal,* 2009, 338, b1542.

KOGA, M.Vitiligo: a new classification and therapy. *British Journal of Dermatology,* 1977, 97(3), 255-61.

KOGA, M. and T. TANGO. Clinical features and course of type A and type B vitiligo. *British Journal of Dermatolody,* 1988, 118(2), 223-8.

KROLL, T. M., H. BOMMIASAMY, R. E. BOISSY, C. HERNANDEZ, B. J. NICKOLOFF, R. MESTRIL and C. LE POOLE. 4-Tertiary butyl phenol exposure sensitizes human melanocytes to dendritic cell-mediated killing: relevance to vitiligo. *Journal of Investigative Dermatology,* 2005, 124(4), 798-806.

KUMARAN, M. S., I. KAUR and B. KUMAR. Effect of topical calcipotriol, betamethasone dipropionate and their combination in the treatment of localized vitiligo. *Journald of the European Academy of Dermatology and Venereology,* 2006, 20(3), 269-73.

LABERGE, G., C. M. MAILLOUX, K. GOWAN, P. HOLLAND, D. C. BENNETT, P. R. FAIN and R. A. SPRITZ. Early disease onset and increased risk of other autoimmune diseases in familial generalized vitiligo. *Pigment Cell Research,* 2005; 18(4), 300-5.

LABERGE, G. S., D. C. BENNETT, P. R. FAIN and R. A. SPRITZ. PTPN22 is genetically associated with risk of generalized vitiligo, but CTLA4 is not. *Journal of Investigative Dermatology,* 2008, 128(7), 1757-62.

LAHIRI, K., S. MALAKAR, N. SARMA and U. BANERJEE. Inducing repigmentation by regrafting and phototherapy (311 nm) in punch grafting failure cases of lip vitiligo: a pilot study. *Indian Journal of Dermatology Venereology Leprology,* 2004, 70(3), 156-8.

LAXMISHA, C., R. KUMARI and D. M. THAPPA. Surgical repigmentation of leukotrichia in localized vitiligo. *Dermatologic Surgery, 2*006, 32(7), 981-2.

LE POOLE, C., P. K. DAS, R. M. VAN DEN WIJNGAARD, J. D. BOS and W. WESTERHOF. Review of the etiopathomechanism of vitiligo: a convergence theory. *Experimental Dermatology,* 1993, 2(4), 145-53.

LE POOLE, C., R. SARANGARAJAN, Y. ZHAO, L. S. STENNETT, T. L. BROWN, P. SHETH, T. MIKI and R. E. BOISSY. 'VIT1', a novel gene associated with vitiligo. *Pigment Cell Research,* 2001, 14(6), 475-84.

LE POOLE, C., R. M. VAN DEN WIJNGAARD, W. WESTERHOF and P. K. DAS. Presence of T cells and macrophages in inflammatory vitiligo skin parallels melanocyte disappearance. *Americal Journal of Pathology,* 1996, 148(4), 1219-28.

LE POOLE, C., A. WANKOWICZ-KALINSKA, R. M. VAN DEN WIJNGAARD, B. J. NICKOLOFF and P. K. DAS. Autoimmune aspects of depigmentation in vitiligo. *Journal of Investigative Dermatology Symposium Proceedings,* 2004, 9(1), 68-72.

LEE, D. Y., C. R. KIM and J. H. LEE. Recent onset vitiligo on acral areas treated with phototherapy: need of early treatment. *Photodermatology Photoimmunology Photomedicine,* 2010, 26(2), 266-8.

LEE, D. Y., C. R. KIM, J. H. LEE and J. M. YANG. Recent onset vitiligo treated with systemic corticosteroid and topical tacrolimus: Need for early treatment in vitiligo. *Journal of Dermatology,* 2010, 37(12), 1057-9.

LEE, S. [Vitiligo in a historic portrait]. *Hautarzt,* 1982, 33(6), 335-6.

LEONE, G., A. PACIFICO, P. IACOVELLI, A. PARO VIDOLIN and M. PICARDO. Tacalcitol and narrow-band phototherapy in patients with vitiligo. *Clinical and Experimental Dermatology,* 2006, 31(2), 200-5.

LEPE, V., B. MONCADA, J. P. CASTANEDO-CAZARES, M. B. TORRES-ALVAREZ, C. A. ORTIZ and A. B. TORRES-RUBALCAVA. A double-blind randomized trial of 0.1% tacrolimus vs 0.05% clobetasol for the treatment of childhood vitiligo. *Archives of Dermatology,* 2003, 139(5), 581-5.

LERNER, A. B. and J. J. NORDLUND. Vitiligo. What is it? Is it important? *Journal of the American Medical Association,* 1978, 239(12), 1183-7.

LEVAI, M. The relationship of pruritus and local skin conditions to the development of vitiligo. *American Medical Association Archives of Dermatology,* 1958a, 78(3), 372-7.

LEVAI, M. A study of certain contributory factors in the development of vitiligo in South Indian patients. *American Medical Association Archives of Dermatology,* 1958b, 78(3), 364-71.

LEWIS-JONES, M. S. and A. Y. FINLAY. The Children's Dermatology Life Quality Index (CDLQI): initial validation and practical use. *British Journal of Dermatology,* 1995, 132(6), 942-9.

LIM-ONG, M, R.M. LEVERIZA, B.E. ONG, M.L. FREZ. Comparison between narrow-band UVB with topical corticosteroid and narrow-band UVB with placebo in the treatment of vitiligo: A randomized controlled trial. *Journal of the Phillipine Dermatological Society,* 2005, 14, 17-22.

LIM, J. L. and R. S. STERN. High levels of ultraviolet B exposure increase the risk of non-melanoma skin cancer in psoralen and ultraviolet A-treated patients. *Journal of Investigative Dermatology,* 2005, 124(3), 505-13.

LINTHORST HOMAN, M. W., J. DE KORTE, M. A. GROOTENHUIS, J. D. BOS, M. A. SPRANGERS and J. P. VAN DER VEEN. Impact of childhood vitiligo on adult life. *British Journal of Dermatology,* 2008, 159(4), 915-20.

LIU, J. B., M. LI, H. CHEN, S. Q. ZHONG, S. YANG, W. DU *et al*. Association of vitiligo with HLA-A2: a meta-analysis. *Journal of the European Academy of Dermatology and Venereology,* 2007, 21(2), 205-13.

LIU, J. B., M. LI, S. YANG, J. P. GUI, H. Y. WANG, W. H. DU *et al.* Clinical profiles of vitiligo in China: an analysis of 3742 patients. *Clinical and Experimental Dermatology,* 2005, 30(4), 327-31.

LLOYD, K., D. ROSE and M. FENTON. Identifying uncertainties about the effects of treatments for schizophrenia. *Journal of Mental Health,* 2006, 15(3), 263-268.

LU-YAN, T., F. WEN-WEN, X. LEI-HONG, J. YI and Z. ZHI-ZHONG. Topical tacalcitol and 308-nm monochromatic excimer light: a synergistic combination for the treatment of vitiligo. *Photodermatology Photoimmunology Photomedicine,* 2006, 22(6), 310-4.

MAJUMDER, P. P., S. K. DAS and C. C. LI. A genetical model for vitiligo. *American Journal of Human Genetics,* 1988, 43(2), 119-25.

MALAKAR, S. and S. DHAR. Repigmentation of vitiligo patches by transplantation of hair follicles. *International Journal of Dermatology,* 1999, 38(3), 237-8.

MAN, I., I. K. CROMBIE, R. S. DAWE, S. H. IBBOTSON and J. FERGUSON. The photocarcinogenic risk of narrowband UVB (TL-01) phototherapy: early follow-up data. *British Journal of Dermatology,* 2005, 152(4), 755-7.

MARESCA, V., M. ROCCELLA, F. ROCCELLA, E. CAMERA, G. DEL PORTO, S. PASSI, P. GRAMMATICO and M. PICARDO. Increased sensitivity to peroxidative agents as a possible pathogenic factor of melanocyte damage in vitiligo. *Journal of Investigative Dermatology,* 1997, 109(3), 310-3.

MCGOVERN, T. W., J. BOLOGNIA and D. J. LEFFELL. Flip-top pigment transplantation: a novel transplantation procedure for the treatment of depigmentation. *Archives of Dermatology,* 1999, 135(11), 1305-7.

MCGUIRE, J. Adrenergic control of melanocytes. *Archives of Dermatology,* 1970, 101(2), 173-80.

MEHRABI, D. and A. G. PANDYA. A randomized, placebo-controlled, double-blind trial comparing narrowband UV-B Plus 0.1% tacrolimus ointment with narrowband UV-B plus placebo in the treatment of generalized vitiligo. *Archives of Dermatology,* 2006, 142(7), 927-9.

MIDDELKAMP-HUP, M. A., J. D. BOS, F. RIUS-DIAZ, S. GONZALEZ and W. WESTERHOF. Treatment of vitiligo vulgaris with narrow-band UVB and oral Polypodium leucotomos extract: a randomized double-blind placebo-controlled study. *Journal of the European Academy of Dermatology Venereology,* 2007, 21(7), 942-50.

MOFTY, M. E., H. ZAHER, S. ESMAT, R. YOUSSEF, Z. SHAHIN, D. BASSIONI and G. E. ENANI. PUVA and PUVB in vitiligo-are they equally effective? *Photodermatology Photoimmunology Photomedicine,* 2001, 17(4), 159-63.

MULEKAR, S. V. Melanocyte-keratinocyte cell transplantation for stable vitiligo. *International Journal of Dermatology,* 2003, 42(2), 132-6.

MULEKAR, S. V., M. ASAAD, B. GHWISH, A. AL ISSA and A. AL EISA. Koebner phenomenon in vitiligo: not always an indication of surgical failure. *Archives of Dermatology,* 2007, 143(6), 801-2.

MYSORE, V. Targeted phototherapy. *Indian Journal of Dermatology Venereology Leprology,* 2009, 75(2), 119-25.

NA, G. Y., S. K. SEO and S. K. CHOI. Single hair grafting for the treatment of vitiligo. *Journal of the American Academy of Dermatology,* 1998, 38(4), 580-4.

NAIR, B. K. Vitiligo-a retrospect. *International Journal of Dermatology,* 1978, 17(9), 755-7.

NAUGHTON, G. K., M. EISINGER and J. C. BYSTRYN. Antibodies to normal human melanocytes in vitiligo. *Journal of Experimental Medicine,* 1983a, 158(1), 246-51.

NAUGHTON, G. K., M. EISINGER and J. C. BYSTRYN. Detection of antibodies to melanocytes in vitiligo by specific immunoprecipitation. *Journal of Investigative Dermatology,* 1983b, 81(6), 540-2.

NAVARRO JR, C. A., H. SALADO PONCE *et al.* Autologous skin minigraft and ingestion of 8-methoxypsoralen in patients with stable vitiligo vulgaris. *Dermatologia Revista Mexicana,* 2002, 42, 260-7.

NICOLAIDOU, E., C. ANTONIOU, A. MINIATI, E. LAGOGIANNI, , A. MATEKOVITS, A. STRATIGOS and A. KATSAMBAS. Childhood- and later-onset vitiligo have diverse epidemiologic and clinical characteristics. *Journal of the American Academy of Dermatology,* 2012, 66(6), 954-8.

NIKIFORIDIS, G. C., D. G. TSAMBAOS, D. S. KARAMITSOS, C. C. KOUTSOJANNIS and S. V. GEORGIOU. Abnormalities of the auditory brainstem response in vitiligo. *Scandinavian Audiology,* 1993, 22(2), 97-100.

NJOO, M. D., P. K. DAS, J. D. BOS and W. WESTERHOF, Association of the Kobner phenomenon with disease activity and therapeutic responsiveness in vitiligo vulgaris. *Archives of Dermatology,* 1999, 135(4), 407-13.

NJOO, M. D., W. WESTERHOF, J. D. BOS and P. M. BOSSUYT. A systematic review of autologous transplantation methods in vitiligo. *Archives of Dermatology,* 1998, 134(12), 1543-9.

NOGUEIRA, L. S., P. C. ZANCANARO and R. D. AZAMBUJA. [Vitiligo and emotions]. *Anais Brasileiros de Dermatologia,* 2009, 84(1), 41-5.

NOLAN, B. V., B. A. YENTZER and S. R. FELDMAN. A review of home phototherapy for psoriasis. *Dermatology Online Journal,* 2010, 16(2), 1.

NORRIS, A., C. TODD, A. GRAHAM, A. G. QUINN and A. J. THODY. The expression of the c-kit receptor by epidermal melanocytes may be reduced in vitiligo. *British Journal of Dermatology,* 1996, 134(2), 299-306.

OLSSON, M. J. and L. JUHLIN. Transplantation of melanocytes in vitiligo. *British Journal of Dermatology,* 1995, 132(4), 587-91.

OLSSON, M. J. and L. JUHLIN. Leucoderma treated by transplantation of a basal cell layer enriched suspension. *British Journal of Dermatology,* 1998, 138(4), 644-8.

OLSSON, M. J. and L. JUHLIN. Long-term follow-up of leucoderma patients treated with transplants of autologous cultured melanocytes, ultrathin epidermal sheets and basal cell layer suspension. *British Journal of Dermatology,* 2002, 147(5), 893-904.

OPPENHEIM, A. (Ed.). *Questionnaire design, interviewing and attitude measurement.* London: Continuum International Publishing Group, 2000.

ORECCHIA, G., M. A. MARELLI, D. FRESA, L. ROBIOLIO. Audiologic disturbances in vitiligo. *Journal of the American Academy of Dermatology,* 1989, 21(6), 1317-8.

OZDEMIR, M., O. CETINKALE, R. WOLF, A. KOTOGYAN, C. MAT, B. TUZUN and Y. TUZUN. Comparison of two surgical approaches for treating vitiligo: a preliminary study. *International Journal of Dermatology,* 2002, 41(3), 135-8.

PAI, G. S., V. VINOD and A. JOSHI. Efficacy of erbium YAG laser-assisted autologous epidermal grafting in vitiligo. *Journal of the European Academy of Dermatology Venereology,* 2002, 16(6), 604-6.

PALMER, R. A., S. AQUILINA, P. J. MILLIGAN, S. L. WALKER, J. L. HAWK and A. R.YOUNG. Photoadaptation during narrowband ultraviolet-B therapy is independent of skin type: a study of 352 patients. *Journal of Investigative Dermatology,* 2006, 126(6), 1256-63.

PANDA, A. K. The medico historical perspective of vitiligo (Switra). *Bulletin of the Indian Institute of History of Medicine Hyderabad,* 2005, 35(1), 41-6.

PAPADOPOULOS, L., R. BOR and C. LEGG. Coping with the disfiguring effects of vitiligo: a preliminary investigation into the effects of cognitive-behavioural therapy. *British Journal of Medical Psychology,* 1999, 72(Pt 3), 385-96.

PAPADOPOULOS L, W. C. and L. ANTHIS. Living with vitiligo: A controlled investigation into the effects of group cognitive-behavioural and humanistic therapies. *Dermatology and Psychosomatics,* 2004, 5(4), 172-4.

PARSAD, D., S. DOGRA and A. J. KANWAR. Quality of life in patients with vitiligo. *Health and Quality of Life Outcomes,* 2003a, 1, 58.

PARSAD, D. and S. GUPTA. Standard guidelines of care for vitiligo surgery. *Indian Journal of Dermatology Venereology Leprology,* 2008, 74 Suppl, S37-45.

PARSAD, D., R. PANDHI, S. DOGRA and B. KUMAR, Clinical study of repigmentation patterns with different treatment modalities and their correlation with speed and stability of repigmentation in 352 vitiliginous patches. *Journal of the American Academy of Dermatology,* 2004, 50(1), 63-7.

PARSAD, D., R. PANDHI and A. JUNEJA. Effectiveness of oral Ginkgo biloba in treating limited, slowly spreading vitiligo. *Clinical and Experimental Dermatology,* 2003b, 28(3), 285-7.

PARSAD, D., SAINI, R. & VERMA, N. (1998) Combination of PUVAsol and topical calcipotriol in vitiligo. *Dermatology,* 197(2), 167-70.

PASSERON, T., N. OSTOVARI, W. ZAKARIA, E. FONTAS, J. C. LARROUY, J. P. LACOUR and J. P.ORTONNE. Topical tacrolimus and the 308-nm excimer laser: a synergistic combination for the treatment of vitiligo. *Archives of Dermatology,* 2004, 140(9), 1065-9.

PATHAK, M. A., D. B. MOSHER and T. B. FITZPATRICK. Safety and therapeutic effectiveness of 8-methoxypsoralen, 4,5',8-trimethylpsoralen, and psoralen in vitiligo. *National Cancer Institute Monograph,* 1984, 66, 165-73.

PIANIGIANI, E., M. RISULO, A. ANDREASSI, P. TADDEUCCI, F. IERARDI and L. ANDREASSI. Autologous epidermal cultures and narrow-band ultraviolet B in the surgical treatment of vitiligo. *Dermatologic Surgery,* 2005, 31(2), 155-9.

PICARDO, M., and A. TAIEB (Eds) (2010) *Vitiligo*, Berlin: Springer, 2010.

PORTER, J., A. BEUF, J. J. NORDLUND and A. B. LERNER, Personal responses of patients to vitiligo: the importance of the patient-physician interaction. *Archives of Dermatology,* 1978, 114(9), 1384-5.

PORTER, J., A. H. BEUF, A. LERNER and J. NORDLUND. Response to cosmetic disfigurement: patients with vitiligo. *Cutis,* 1987, 39(6), 493-4.

PORTER, J., A. H. BEUF, J. J. NORDLUND and A. B.LERNER. Psychological reaction to chronic skin disorders: a study

of patients with vitiligo. *General Hospital Psychiatry,* 1979, 1(1), 73-7.

PROCACCINI, EM, G. RICCIO and G. MONFRECOLA. Ineffectiveness of topical khellin in photochemotherapy of vitiligo. *The Journal of Dermatological Treatment,* 1995, 6(2), 117-20.

PHOTONET Dosimetry Protocols for Phototherapy. National: Managed Clinical Network For Phototherapy 2010. Available from http://www.photonet.scot.nhs.uk/ (last accessed 25 January 2013).

RADAKOVIC-FIJAN, S., A. M. FURNSINN-FRIEDL, H. HONIGSMANN and A. TANEW. Oral dexamethasone pulse treatment for vitiligo. *Journal of the American Academy of Dermatology,* 2001, 44(5), 814-7.

RADMANESH, M. and K. SAEDI. The efficacy of combined PUVA and low-dose azathioprine for early and enhanced repigmentation in vitiligo patients. *Journal of Dermatological Treatment,* 2006, 17(3), 151-3.

RADTKE, M. A., I. SCHAFER, A. I. GAJUR & M. AUGUSTIN. Clinical features and treatment outcomes of vitiligo from the patients' perspective: results of a national survey in Germany. *Dermatology,* 2010, 220(3), 194-200.

RATH, N., H. K. KAR and S. SABHNANI. An open labeled, comparative clinical study on efficacy and tolerability of oral minipulse of steroid (OMP) alone, OMP with PUVA and broad / narrow band UVB phototherapy in progressive vitiligo. *Indian Joural of Dermatology Venereology Leprology,* 2008, 74(4), 357-60.

REYES, E., P. JAEN, E. DE LAS HERAS, F. CARRION, M. ALVAREZ-MON, E. DE EUSEBIO, M. ALVARE, J. CUEVAS *et al*. Systemic immunomodulatory effects of Polypodium leucotomos as an adjuvant to PUVA therapy in generalized vitiligo: A pilot study. *Journal of Dermatological Science,* 2006, 41(3), 213-6.

REZAEI, N., N. G. GAVALAS, A. P. WEETMAN and E. H. KEMP. Autoimmunity as an aetiological factor in vitiligo. *Journal of the European Academy of Dermatology Venereology,* 2007, 21(7), 865-76.

RODRIGUEZ-MARTIN, M., M. GARCIA BUSTINDUY, M. SAEZ RODRIGUEZ and A. NODA CABRERA. Randomized, double-blind clinical trial to evaluate the efficacy of topical tacalcitol and sunlight exposure in the treatment of adult nonsegmental vitiligo. *British Journal of Dermatology,* 2009, 160(2), 409-14.

ROJAS-URDANETA J. E. and A.G. POLEO-ROMERO. Evaluation of an antioxidant and mitochondrial stimulating cream formula in the skin of patients with stable vulgar vitiligo [Evaluacion de una formlacion antioxidante y estimuladora mitocondrial en piel de pacientes con vitiligo vulgar estable]. *Investigacion Clinica,* 2007, 48(1), 21-31.

ROSENBAUM, J., A. BUNKE, E. COOPERMAN and G. M. GOMBOS. Bilateral retinal pigment epithelium changes associated with periorbital vitiligo and seizure disorders. *Annals of Ophthalmology,* 1979, 11(8), 1191-3.

RUIZ MALDONADO, R. and L. TAMAYO SANCHEZ. [4-5-8 trimethylpsoralen in vitiligo. Controlled study of its therapeutic and toxic effect in children]. *Actas Dermosifiliograficas,* 1975, 66(9-10), 513-26.

SANCLEMENTE, G., J. J. GARCIA, J. J. ZULETA, C. DIEHL, C. CORREA and R. FALABELLA. A double-blind, randomized trial of 0.05% betamethasone vs. topical catalase/dismutase superoxide in vitiligo. *Journal of the European Academy of Dermatology Venereology,* 2008, 22(11), 1359-64.

SASSI, F., S. CAZZANIGA, G. TESSARI, L. CHATENOUD, A. RESEGHETTI, L. MARCHESI, G. GIROLOMONI and L. NALDI. Randomized controlled trial comparing the effectiveness of 308-nm excimer laser alone or in combination with topical hydrocortisone 17-butyrate

cream in the treatment of vitiligo of the face and neck. *British Journal of Dermatology,* 2008, 159(5), 1186-91.

SCHALLREUTER, K. U., P. BAHADORAN, M. PICARDO, A. SLOMINSKI, Y. E. ELASSIUTY, E. H. KEMP *et al.* Vitiligo pathogenesis: autoimmune disease, genetic defect, excessive reactive oxygen species, calcium imbalance, or what else? *Experimental Dermatology,* 2008, 17(2), 139-40.

SCHALLREUTER, K. U., R. LEMKE, O. BRANDT, R. SCHWARTZ, , M. WESTHOFEN, R. MONTZ and J. BERGER. Vitiligo and other diseases: coexistence or true association? Hamburg study on 321 patients. *Dermatology,* 1994, 188(4), 269-75.

SCHALLREUTER, K. U., J. MOORE, S. BEHRENS-WILLIAMS, A. PANSKE and M. HARARI. Rapid initiation of repigmentation in vitiligo with Dead Sea climatotherapy in combination with pseudocatalase (PC-KUS). *International Journal of Dermatology,* 2002, 41(8), 482-7.

SCHMID-OTT, G., H. W. KUNSEBECK, E. JECHT, R. SHIMSHONI, I. LAZAROFF *et al.* A. Stigmatization experience, coping and sense of coherence in vitiligo patients. *Journal of the European Academy of Dermatology Venereology,* 2007, 21(4), 456-61.

SEHGAL, V. N. and G. SRIVASTAVA. Vitiligo: compendium of clinico-epidemiological features. *Indian Journal of Dermatology Venereology Leprology,* 2007, 73(3), 149-56.

SHARQUIE KE, A. M. Treatment of vitiligo with topical 15% lactic acid solution in combination with ultra-violet-A. *Saudi Medical Journal,* 2005, 26(6), 1013-5.

SHI, N., Y. J. CHEN, J. WANG and H. NI. Clinical observation on the effect of Zengse Pill in treating patients with vitiligo of qi-stagnancy and blood-stasis syndrome type.

Chinese Journal of Integrative Medicine, 2008, 14(4), 303-6.

SIDDIQUI, A. H., L. M. STOLK, R. BHAGGOE, R. HU, R. B. SCHUTGENS and W. WESTERHOF. L-phenylalanine and UVA irradiation in the treatment of vitiligo. *Dermatology,* 1994, 188(3), 215-8.

SINGH, M., G. SINGH, A. J. KANWAR and M. S. BELHAJ. Clinical pattern of vitiligo in Libya. *International Journal of Dermatology,* 1985, 24(4), 233-5.

SINHA, I., L. JONES, R. L. SMYTH and P.R. WILLIAMSON. A Systematic Review of Studies That Aim to Determine Which Outcomes to Measure in Clinical Trials in Children. *PLoS Medicine,* 2008, 5(4): e96. doi:10.1371/journal.pmed.0050096

SONG, S. H., P.S. AHN *et al*. Clinical study of vitiligo: Comparative study of type A and type B vitiligo. *Annals of Dermatology (Seoul),* 1994, 6, 22-30.

SOUTO MG, M. A., C.H. MILHOMENS, I. SUCCI. Comparative study between melagenina and placebo in the treatment of vitiligo [Estudio comparativo entre melagenina e placebo no tratamento do vitiligo]. *Anais Brasileiros de Dermatologia,* 1997, 72, 237-9.

STUDNIBERG, H. and P. WELLER. PUVA, UVB, psoriasis, and nonmelanoma skin cancer. *Journal of the American Academy of Dermatology,* 1993, 29(6), 1013-22.

SUKAN, M. and F. MANER. The problems in sexual functions of vitiligo and chronic urticaria patients. *Journal of Sex Marital Therapy,* 2007, 33(1), 55-64.

SWEET, R. D. Vitiligo as a Kobner phenomenon. *British Journal of Dermatology,* 1978, 99(2), 223-4.

TAIEB, A. Intrinsic and extrinsic pathomechanisms in vitiligo. *Pigment Cell Research,* 2000, 13 Suppl 8, 41-7.

TAIEB, A., A. ALOMAR, M. BOHM, M. L. DELL'ANNA, A. DE PASE, V. ELEFTHERIADOU, K. EZZEDINE *et al.* Guidelines for the Management of Vitiligo: the EDF consensus By the writing group of the Vitiligo European Task Force (VETF) in cooperation with the European Academy of Dermatology and Venereology (EADV) and the Union Europeenne des Medecins Specialistes (UEMS). *British Journal of Dermatology,* 2013, 168(1), 5-19

TAIEB, A. and M. PICARDO. The definition and assessment of vitiligo: a consensus report of the Vitiligo European Task Force. *Pigment Cell Research,* 2007, 20(1), 27-35.

TAIEB, A. and M. PICARDO. Clinical practice. Vitiligo. *New English Journal of Medicine,* 2009, 360(2), 160-9.

TALSANIA, N., B. LAMB and A. BEWLEY. Vitiligo is more than skin deep: a survey of members of the Vitiligo Society. *Clinical and Experimental Dermatology,* 2010, 35(7), 736-9.

TEGTA, G. R., D. PARSAD, S. MAJUMDAR and B. KUMAR Efficacy of autologous transplantation of noncultured epidermal suspension in two different dilutions in the treatment of vitiligo. *International Journal of Dermatology,* 2006, 45(2), 106-10.

TJIOE, M., M. J. GERRITSEN, L. JUHLIN and P. C. VAN DE KERKHOF. Treatment of vitiligo vulgaris with narrow band UVB (311 nm) for one year and the effect of addition of folic acid and vitamin B12. *Acta Dermato-Venereologica,* 2002, 82(5), 369-72.

TORIYAMA, K., Y. KAMEI, T. KAZETO, T. YASUE, Y. SUGA, M. INOIE, Y. TOMITA and S. TORII. Combination of short-pulsed CO2 laser resurfacing and cultured epidermal sheet autografting in the treatment of vitiligo: a

preliminary report. *Annals of Plastic Surgery,* 2004, 53(2), 178-80.

TOSTI, A., F. BARDAZZI, G. TOSTI and L. MONTI. Audiologic abnormalities in cases of vitiligo. *Journal of American Academy of Dermatology,* 1987, 17(2 Pt 1), 230-3.

TOWNSHEND, A. P., C. M. CHEN and H. C.WILLIAMS. How prominent are patient-reported outcomes in clinical trials of dermatological treatments? *British Journal of Dermatology,* 2008, 159(5), 1152-9.

TUGWELL, P., M. BOERS, P. BROOKS, L. SIMON, V. STRAND and L. IDZERDA. OMERACT: an international initiative to improve outcome measurement in rheumatology. *Trials,* 2007, 26(8), 38.

TWISS, J., D. M. MEADS, E. P. PRESTON, S. R. CRAWFORD, & S. P. MCKENNA. Can we rely on the Dermatology Life Quality Index as a measure of the impact of psoriasis or atopic dermatitis? *Journal of Investigative Dermatology,* 2012, 132(1), 76-84.

UK DATABASE OF UNCERTAINTIES ABOUT THE EFFECTS OF TREATMENTS (DUETs), NHS Evidence. Available from: http://www.library.nhs.uk/duets/(last accessed 25 January 2013).

VALYI-NAGY, I. T., G. F. MURPHY, M. L. MANCIANTI, D. WHITAKER and M. HERLYN. Phenotypes and interactions of human melanocytes and keratinocytes in an epidermal reconstruction model. *Laboratory Investigation,* 1990, 62(3), 314-24.

VAN DEN WIJNGAARD, R., A. WANKOWICZ-KALINSKA, C. LE POOLE, B. TIGGES, W. WESTERHOF and P. DAS. Local immune response in skin of generalized vitiligo patients. Destruction of melanocytes is associated with the prominent presence of CLA+ T cells at the perilesional site. *Laboratory Investigation,* 2000, 80(8), 1299-309.

VAN GEEL, N., K. ONGENAE, M. DE MIL, Y. V. HAEGHEN, C. VERVAET and J. M. NAEYAERT. Double-blind placebo-controlled study of autologous transplanted epidermal cell suspensions for repigmenting vitiligo. *Archives of Dermatology,* 2004, 140(10), 1203-8.

VASISTHA, L. K. and G. SINGH. Vitiligo and intralesional steroids. *The Indian Journal of Medical Research,* 1979, 69, 308-11.

VITILIGO EUROPEAN TASK FORCE (VEFT). Available from: http://www.espcr.org/vetf/ (last accessed 25 January 2013).

VITILIGO RESEACH (VR) FOUNDATION, 2011 (last accessed 25 January 2013). Available from:http://vrfoundation.org/

WEISCHER, M., A. BLUM, F. EBERHARD, M. ROCKEN and M. BERNEBURG. No evidence for increased skin cancer risk in psoriasis patients treated with broadband or narrowband UVB phototherapy: a first retrospective study. *Acta Dermo-Venereologica,* 2004, 84(5), 370-4.

WESTERHOF, W. and M. D'ISCHIA. Vitiligo puzzle: the pieces fall in place. *Pigment Cell Research,* 2007, 20(5), 345-59.

WESTERHOF, W., L. NIEUWEBOER-KROBOTOVA, P. G. MULDER and E. J. GLAZENBURG. Left-right comparison study of the combination of fluticasone propionate and UV-A vs. either fluticasone propionate or UV-A alone for the long-term treatment of vitiligo. *Archives of Dermatology,* 1999, 135(9), 1061-6.

WHITTON, M. E., M. PINART, J. BATCHELOR, C. LUSHEY, J. LEONARDI-BEE and U. GONZALEZ. Interventions for vitiligo. *Cochrane Database of Systematic Reviews*, 2010, 1, CD003263.

WIND, B. S., M. W. KROON, J. F. BEEK, J. P. VAN DER VEEN, L. NIEUWEBOER-KROBOTOVA, A. A. MEESTERS, J. D. BOS and A. WOLKERSTORFER. Home vs. outpatient narrowband ultraviolet B therapy for the treatment of nonsegmental vitiligo: a retrospective questionnaire study. *British Journal of Dermatology,* 2010, 162(5), 1142-4.

WU, C. S., S. C. HU, C. C. LAN, G. S. CHEN, W. H. CHUO and H. S. YU. Low-energy helium-neon laser therapy induces repigmentation and improves the abnormalities of cutaneous microcirculation in segmental-type vitiligo lesions. *The Kaohsiung Journal of Medical Sciences,* 2008, 24(4), 180-9.

YONES, S. S., R. A. PALMER, T. M. GARIBALDINOS and J. L. HAWK. Randomized double-blind trial of treatment of vitiligo: efficacy of psoralen-UV-A therapy vs Narrowband-UV-B therapy. *Archives of Dermatolology,* 2007, 143(5), 578-84.

YULE, S. Narrow-band UVB (TL-01) phototherapy comb (Psoracomb) for scalp psoriasis treatment. *Dermatological Nursing,* 2005, 4, 23-25.

APPENDICES

APPENDIX 1

VITILIGO SURVEY for the vitiligo Priority Setting Partnership

We think it is vital that **more research** is done into treatments for vitiligo, and this research focuses on the questions that are important to people who have vitiligo, parents of children with vitiligo and the health professionals (doctors and nurses) that treat vitiligo. We are therefore **collecting questions** that all these groups of people have about **treatments** for vitiligo. We will use these to identify where there is true uncertainty, that is to say where there is no existing research that already provides a reliable answer, so that future research can focus on the most important questions.

If you have vitiligo; are the parent of a child with vitiligo; or a health professional with an interest in the condition, you can **help us by completing this survey** and telling us what questions you have.

The sorts of things we would like to know about are any **questions you have about treatments for vitiligo**, for example: **prescribed medicines** (e.g. tablets or creams), **light therapy** (e.g. UVA), **surgical procedures** (e.g. skin grafting), **psychological therapy** (e.g. coping methods) or **cosmetic applications** (e.g. camouflage).

To help you, here are some **examples** of research questions for other health conditions:

- *Are breathing exercises helpful in controlling asthma?*
- *What is the evidence for gargling aspirin to relieve a sore throat?*
- *Are topical steroids for atopic eczema safe in the long-term?*

Q1 What questions about the treatments for vitiligo would you like to see answered by research?

1. ……
2. ……
   ……
3. ……
   ……
4. ……
   ……

Please feel free to continue on the back if you have more than 4 questions.

Q2 What desirable effects do you hope the treatments would produce?

……

……

……

More information about you

It would be really helpful for our research to know a little more about you, so we would be grateful if you could answer the questions in this box. However, if you would prefer not to, then just leave this section blank.

1. Which of these best describes you (please tick all that apply):

   ☐ Health professional (e.g. doctor, nurse)

   ☐ Person with vitiligo

   ☐ The parent of a child with vitiligo

   ☐ Other (please specify)…….....…….

2. What is your (or your child's) age (please tick)?

   0 – 5 ☐ 6-10 ☐ 11-17 ☐ 18 – 29 ☐ 30-60 ☐ over 60 ☐

3. What is your (or your child's) gender (please tick)?

   ☐ Male

   ☐ Female

Would you like more information about the next stage of this research study where we decide which research question is the most important and should be developed into a clinical trial proposal (please tick)?

☐ **Yes**

☐ **No**

Would you like to be informed of the results of this study (please tick)?

☐ **Yes**

☐ **No**

If you have answered **yes** to either of the above questions please provide your contact details:

Name:

……

Email/address:

……

Postal/address:

……

What is your preferred method of contact (please tick)? ☐ **email**

☐ **post**

Thank you for completing this survey

Please return this survey to: Vitiligo Study, Centre of Evidence Based Dermatology, University of Nottingham, King's Meadow Campus, Lenton Lane, Nottingham, NG7 2NR.

APPENDIX 2

Data extraction form
for the Systematic review of outcome measures for the treatment of vitiligo

First Author	
Year	
Country	
Intervention A	
Intervention B	
Intervention C	
Duration of treatment	
Duration of follow up	
Target lesions analysed or all lesions	
Primary outcome(s) specified?	Y/N
What was it (put as outcome A)	
Number of participants randomised	
Number of participants analysed	
Outcome A/ name of scale or categories if exists	
Scales or categories used for outcome A	
Outcome assessed by patient clinical assessment or digital image?	
Comments on outcome A	
Outcome A measured during treatment or follow up period	
Outcome A assessed on (indicate on what week(s) the outcome was assessed (e.g. on the 6^{th}, 9^{th} and 12^{th} weeks repigmentation was measured)	weeks
Outcome B/ name of scale	

or categories if exists	
Scales or categories used for outcome B	
Outcome assessed by patient clinical assessment or digital image?	
Comments on outcome B	
Outcome B measured during treatment or follow up period	
Outcome B assessed on (indicate on what week(s) the outcome was assessed (e.g. on the 6th, 9th and 12th weeks repigmentation was measured)	weeks
Outcome C/ name of scale or categories if exists	
Scales or categories used for outcome C	
Outcome assessed by patient clinical assessment or digital image?	
Comments on outcome C	
Outcome C measured during treatment or follow up period	
Outcome C assessed on (indicate on what week(s) the outcome was assessed (e.g. on the 6th, 9th and 12th weeks repigmentation was measured)	weeks
Outcome D/ name of scale or categories if exists	
Scales or categories used for outcome D	
Outcome assessed by patient clinical assessment or	

digital image?	
Comments on outcome D	
Outcome D measured during treatment or follow up period	
Outcome D assessed on (indicate on what week(s) the outcome was assessed (e.g. on the 6th, 9th and 12th weeks repigmentation was measured)	weeks
Outcome E/ name of scale or categories if exists	
Scales or categories used for outcome E	
Outcome assessed by patient clinical assessment or digital image?	
Comments on outcome E	
Outcome E measured during treatment or follow up period	
Outcome E assessed on (indicate on what week(s) the outcome was assessed (e.g. on the 6th, 9th and 12th weeks repigmentation was measured)	weeks

Instructions to the data extractors:

1. Please add the outcomes in the form in the order they appear in the text.

2. If outcome measured were the treatment's "harms", please do not specify which side effects were measured but put only "side effects" in the outcome box and continue to fill the rest of the questions as usual i.e. assessed by whom.

3. For "harms", please put N/A on the "assessed by" box

APPENDIX 3

GUIDANCE MANUAL FOR RESEARCHERS

The HI-Light Trial for vitiligo

Abbreviations

Co-I	Co-investigator
GCP	Good Clinical Practice
NIHR CRN	National Institute for Health Research – Clinical Research Network
PI	Principal Investigator
R&D	Research & Development Department
REC	Research Ethics Committee
RCT	Randomized Controlled Trial
TMG	Trial Management Group

Section 1: Overview

This study is a small pilot randomised controlled trial (RCT) comparing hand-held NB-UVB light devices with placebo devices. These devices will be used by the participants to treat their vitiligo at home for a period of four months. The main purpose of the trial is to provide feasibility data that can be used to inform the design of a future multi-centre RCT of these devices. Two similar types of hand-held UVB device are being tested during this pilot study. This trial will help us to establish which device is likely to be best for the main trial.

Participants will be approached in a variety of ways (through secondary care, primary care and through direct advertising). Potential participants who contact the co-ordinating centre expressing an interest in the trial will be given more information about the trial, checked for preliminary eligibility, and sent an appointment for a screening visit at the closest recruiting hospital (Nottingham or Leicester).

This screening visit will be conducted by a research nurse, but a dermatologist will also be present in order to confirm the diagnosis of vitiligo and to confirm the participant's suitability for UVB treatment at home. If eligible and willing to take part in the trial, participants will provide written informed consent and baseline data will be collected. In order to define the starting dose to be used when treating the vitiligo, a minimum erythema dose (MED) test will be conducted.

An educational session will be provided by the research nurse outlining how to use the devices, how to assess side-effects of the treatment and how to complete the treatment diary. Participants and nurses will sign an additional consent form on completion of the educational session to confirm that the session has taken place and that both nurse and participant understand how to use the devices appropriately.

It is anticipated that the screening visit and educational session will take place on the same day and may take up to 1.5 hours.

On the following day, a brief visit to the hospital will be required in order to examine the skin and read the MED results (if more convenient, the educational session may be delivered at this time). Once this has been done, participants will be given the devices to use at home – treatment is applied 3 times per week on alternate days. They will be followed up by telephone at week 1, week 2 and

week 12 - in order to provide support and to monitor side-effects. Participants will be asked to keep a treatment diary that records when the treatment has been used and records side-effects experienced. Emergency contact details will be provided in case of urgent medical need.

Participants will continue with treatment at home for the 16-week trial period. Two further hospital visits will take place in order to record outcome data (week 8 and week 16).

Section 4: MED test and reading

Please refer to the booklet provided with your MED tester for more detailed information

Please remember:

1. Please mark carefully the patient before the procedure skin so you know where is the open aperture (the highest dose) and the aperture 10 (lowest dose) the next day of the reading.
2. Leave the tester on for 10 min before performing the MED test.
3. Switch the unit off after 10 min BUT do not allow it to cool down. Perform the test immediately.
4. Allow the device to cool down completely (minimum 30 min) before starting the procedure again.

Use the following table to perform the MED test and decide upon the treatment schedule:

Dosage in J/cm2			0.50		
Aperture	**MED normal skin***	Treatment regimen according to MED normal skin	Aperture	**MED vitiligo skin****	Treatment regimen according to MED vitiligo skin
Open	0.5	**Fitzpatrick's skin type 4-6**	Open	0.5	**Fitzpatrick's skin type 4-6**
2	0.45	**Fitzpatrick's skin type 4-6**	2	0.45	**Fitzpatrick's skin type 4-6**
3	0.38	**Fitzpatrick's skin type 3**	3	0.38	**Fitzpatrick's skin type 4-6**
4	0.31	**Fitzpatrick's skin type 2**	4	0.31	**Fitzpatrick's skin type 4-6**
5	0.24	**Fitzpatrick's skin type 1**	5	0.24	**Fitzpatrick's skin type 4-6**
6	0.18	**Fitzpatrick's skin type 1**	6	0.18	**Fitzpatrick's skin type 3**
7	0.15	**Fitzpatrick's skin type 1**	7	0.15	**Fitzpatrick's skin type 2**
8	0.13	**Fitzpatrick's skin type 1**	8	0.13	**Fitzpatrick's skin type 1**
9	0.10	**Fitzpatrick's skin type 1**	9	0.10	**Fitzpatrick's skin type 1**
10	0.08	**Fitzpatrick's skin type 1**	10	0.08	**Fitzpatrick's skin type 1**

MED normal skin*- please refer to the "Treatment regimen according to MED normal skin" column if you have performed the erythema testing a patch of normal (pigmented) skin of a vitiligo patient

MED vitiligo skin**-**please refer to the "Treatment regimen according to MED vitiliginous skin" column if you have performed the erythema testing a patch of vitiliginous (depigmented) skin of a vitiligo patient

Section 5: How to deal with side effects and what to advice to the patients?

Side effect	Co-originating centre	Advice/action of phototherapy nurse
Erythema grade 1 -skin is slightly pink / red in colour. It will develop on the day of treatment, and settle **within a day**. Erythema does not feel hot and is **NOT painful**.	**No action required** Reassure Advice to complete the diary accordingly Advice to apply moisturizer on treated patches after session it itchy or dry skin Continue treatment as normal	No action required Reassure Advice to complete the diary accordingly Advice to apply moisturizer on treated patches after session if itchy or dry skin Continue treatment as normal
Erythema grade 2 - skin is obviously red in colour. It will develop on the day of treatment and will still be there approximately two days after the treatment. Erythema does not feel hot, might feel slightly uncomfortable but **is NOT painful.**	**Reassure that this is normal skin reaction** and ensure that the correct diagnosis was made (i.e. erythema grade 2). Skip one session i.e. until the erythema has completely resolved and continue the next session with reduced time (restart as per session BEFORE the burn occurred) Advice to complete the diary accordingly Advice to apply moisturizer on treated patches after session it itchy or dry skin If not sure or patient is still anxious arrange for Research nurse call.	Reassure that this is normal skin reaction and ensure that the correct diagnosis was made (i.e. erythema grade 2). Skip one session i.e. until the erythema has completely resolved and continue the next session with reduced time (restart as per session BEFORE the burn occurred) Advice to complete the diary accordingly Advice to apply moisturizer on treated patches after session it itchy or dry skin If not sure or patient is still anxious arrange an unscheduled visit.
Erythema grade 3 - skin is **very red and feels like sunburn**. Erythema feels hot, uncomfortable and **PAINFUL.** This will last for two to	**Stop treatment immediately and seek medical advice** Speak to the research nurse or oncall dermatologist if no-one available or out of hours. The patient will have to at least speak to a research nurse or a	Ensure that the correct diagnosis was made (i.e. erythema grade 3). If not sure or patient is still anxious arrange an unscheduled visit when clinics reopens. If the patient is not coping with the pain, advise they attend for review asap when clinics reopens.

three days. The symptoms will reduce in severity as the days pass.	dermatologist asap. Advice to apply regular moisturizers on the red skin to relieve the symptoms in the meantime. Advice to complete the diary accordingly.	The frequent application of emollient is advised. Topical steroid may be prescribed if the use of emollient does not relieve the symptoms. It is a good idea to store steroid and moisturizer it in the fridge so it is cool when applied to the skin. The treatment will be stopped until erythema is resolved completely. Arrange a follow up telephone call or visit to the patient in 2 or 3 days to ensure the erythema has resolved prior restarting the treatment. Restart on reduced by 50% time of the last treatment administered. Always consult the individual treatment schedule to ensure that the restarting time follows the schedule. Advice to complete the diary accordingly.
Erythema grade 4 or blisters -skin is very red and hot and has **blisters**. This reaction is **VERY PAINFUL**. This burn can last for four to five days. The symptoms will reduce as the days pass.	**Stop treatment immediately and seek medical advice** Speak to the research nurse or oncall dermatologist if no-one available or out of hours. The patient will have to at least speak to a research nurse or a dermatologist asap. Advice to apply regular moisturizers on the red skin to relieve the symptoms in the meantime. Advice to complete the diary accordingly.	Ensure that the correct diagnosis was made (i.e. erythema grade 4). Arrange an unscheduled visit asap when clinics reopens A dermatologist review is advisable. The frequent application of emollient alongside topical steroids is advised. It is a good idea to store steroid and moisturizer it in the fridge so it is cool when applied to the skin. The treatment will be stopped until erythema is resolved completely. Arrange a follow up telephone call or visit to the patient in 3 or 4 days to ensure the erythema has resolved prior restarting the treatment. Arrange an unscheduled visit with a dermatologist prior restarting the treatment to ensure all the symptoms are gone and to decide upon the restarting dose (e.g. reduce dose by 50% or more or even switch the patient to a lower skin type schedule)
Itchy	**No action required** Reassure	Same as Co-ordinating centre

	Advice to complete the diary accordingly Advice to apply moisturizer on treated patches after session Continue treatment as normal	
Hyperpigmentation (brown) around the patch	**No action required** Reassure this is normal reaction Advice to complete the diary accordingly Continue treatment as normal	Same as Co-ordinating centre
Cold sores	**Reassure that this can happen** **Advice to stop the treatment of the affected area** (lips) **only** and continue to treat the rest of the patches as normal. Ask the research nurse to give a patient a call if not sure or patient is anxious. This is not an emergency and therefore no unscheduled visit or referral to a dermatologist required. Advice to complete the diary accordingly Advice to apply topical acyclovir on the cold sores.	Reassure Ensure the correct diagnosis has been made. Application of topical Acyclovir would be advised. Depending on the area, it might be worthwhile advising the patient to apply sun block to the affected site, e.g. the lips (to help prevent recurrence). Ask the patient to restart the treatment of the affected area once the cold sores are completely resolved. Restart on reduced by 50% time of the last treatment administered. Always consult the individual treatment schedule to ensure that the restarting time follows the schedule. Advice to complete the diary accordingly.
Rash	**Stop treatment** immediately and contact the research nurse or the on call dermatologist if no-one is available or out of hours. Arrange for an **unscheduled visit** with a research nurse or a dermatologist	Confirm the diagnosis of polymorphic light eruption and consult with a dermatologist. **The patient will have to be withdrawn from the trial**

Sections 6: What to advice to the patient about missing sessions for reasons other than side effects?

1 treatment - continue treatment as normal

2-3 treatments - administer the same dose as per last treatment session

4 or 5 treatments - administer 60% of the last treatment dose

2 or 3 weeks - administer 50% of the last treatment dose

More than 3 weeks - the patient has to be reviewed by a research nurse to discuss the issues of non-compliance and by a clinician who will decide on a reduced dose, if the patient still wishes to continue the treatment.

Section 7: What to do if the patient took/ was prescribed a new medication during the trial?

Step 1: Complete the New Medication CRF and establish if the new drug is **photosensitive or not**

If not photosensitive, no actions need to be taken

Step 2: If photosensitive, establish for how long the patient is likely to be taking this medication.

- *If it is a one off*

e.g. has taken ibuprofen because of headache, advice to the patient NOT to have treatment on that day. Continue the treatment the next day and repeat the same treatment dose as previously e.g. Monday: treatment time=17 sec

Taken ibuprofen on Wednesday

Advice Not to have treatment on Wednesday, but carry on Thursday and repeat the same dose i.e. 17 sec (rather than 21 sec).

- *If up to 2 weeks*

Stop the treatment for the time period that the patient will be taking the photosensitive drug and restart the treatment after the course has been completed.

The re-starting dose will be reduced by 50% from the last dose i.e. as per "missing sessions" guidance (4 or 5 missing treatments)

- *If up to 3 weeks*

Stop the treatment for the time period that the patient will be taking the photosensitive drug and restart the treatment after the course has been completed.

The re-starting dose will be reduced by 60% from the last dose i.e. as per "missing sessions" guidance (2-3 weeks missing treatments)

- *If more than 3 weeks*

Please withdraw the patient from the trial and complete the withdrawal form.

Step 3 Take accurate details of the exact dose and the advice that the patient received according to the above in the patient's notes

Section 8: CRFs and consent forms

Researcher / CRFs	Co-ordinating centre	Dermatologist	Research nurse
Pre-trial contact/ telephone pre-screening	✓		
Screening/educational visit		✓ (Part C)	✓ Part A,B and MED)
Baseline visit (MED test reading)			✓
Follow up telephone calls (1 week, 2 weeks, 6 weeks and 12 weeks)	✓		
Follow up face to face visit at 8 weeks			✓
Final trial visit (16 weeks)		✓ (Part C)	✓ (Part A, B) Part C if blinded
Unscheduled visits/calls	✓	✓	✓
Withdrawal			✓

Each patient/carer will have to sign 2 consent forms:

1) At the beginning of the screening visit: to consent for the information to be gathered

2) After the educational session: to ensure that he/she has understood the educational material

Final visit (16 weeks) Part C- to be completed by a dermatologist or a research nurse who **has not seen** the patient during the trial (e.g. for side effects or trial hospital visits)

Section 9: Digital images

When should I take an image?

A maximum of **3 lesions** will be chosen for each participant and images are taken:

- Baseline
- 2 Months
- 4 Months

How should I take an image?

You will have been provided with a camera from the co-ordinating centre. This has been set-up with the required settings - please **do not** alter these.

You do need to ensure the Macro setting is **ON** each time (it automatically turns off each time). To do this, press the button that looks like a flower.

The following points should be noted when taking an image:

Image Size

- Try to make the lesion and some surrounding skin fills the image as much as possible
- As previously mentioned, try and avoid glare from the flash by moving the camera away from the subject and using the optical zoom to fill the viewfinder

How many images should I take per visit?

Four in total – two with flash, two without.

Only 2 need to be sent to Viktoria.

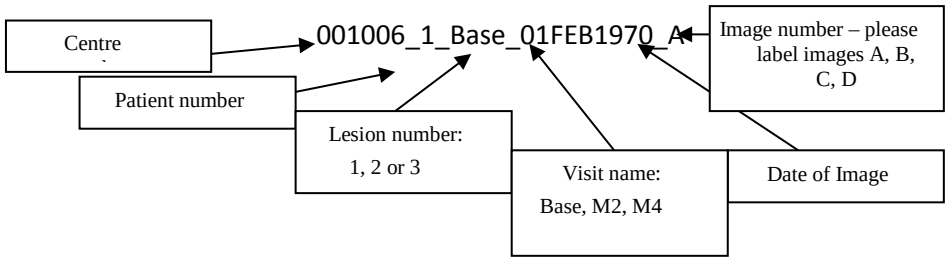
How do I upload the images I have taken?

Connect the camera to your computer using the USB connection cable. Save them to a local place on your computer (e.g. your desktop) as a temporary measure.

How should images be labeled?

Once you have uploaded the images to your local computer, you should rename them, giving each image the following file name:

Centre number_Participant number_lesion number_Date of Image (DDMMMYYYY)_Image letter. For example;



How do I send the image to the co-ordinating centre?

Save a copy of the image locally (i.e. to the computer you are working from) and email the images as an attachment to: viktoria.eleftheriadou@nottingham.ac.uk

You will receive an email shortly afterwards telling you the image has been received.

When can I delete the images from the camera?

You **must** delete images from the camera once you have received confirmation from the co-ordinating centre that the images have been received. To do this, open the image on the camera and press the green button which looks like a dustbin.

It is wise to keep a file of images locally on your computer or local network so you can review before appointments or for someone new to review to ensure consistent lesions are measured each visit.

Section 10: Withdrawing a participant

This section relates only to those participants who are being withdrawn entirely from the trial. If you are stopping a participant's randomized treatment, this does not mean they are being withdrawn.

It may be necessary to withdraw a participant for a number of reasons:

- Death
- The participant becomes lost to follow-up
- The participant no longer wishes to have any part in the trial and withdraws their consent
- The participant no longer meets the eligibility criteria. For example, photosensitive medication was prescribed.

If a participant is withdrawn from the trial, if possible a final visit CRF should be completed.

Section 11: FAQs

11.1 Do I have to write to the participant's GP?

You should write to the GP as per your normal care. The coordinating centre sends a letter to the GP to inform them that your participant is in the trial. This letter has been approved by the Ethics Committee and your Trust R&D department.

11.2 How many lesions does the patient allow to treat?

It is up to the patient how many and which lesions (s)he wants to treat. The patient has the liberty to choose and discuss what lesion (s)he wants or doesn't want to treat, as long as these discussed during the screening visit and documented in the relevant section of baseline CRF. It is possible for the patient to treat only one or two of her/his lesions if (s)he wishes to.

Please note that lesions on genitalia are not to be treated.

11.3 How are the representative lesions decided upon?

Out of the lesions that the patient wishes to treat, the research nurse will make the decision to choose three "representative" lesions. Only these will be measured during the trial i.e. photographed and assessed.

Please try and choose 3 lesions on 3 different anatomical sites if possible i.e. face, hand, leg, abdomen, back.

If the number of lesions that the patient wants to treat is less than 3 then all the treated lesions will be representative.

APPENDIX 4

TRAINING MANUAL FOR PATIENTS

Instructions on how to use hand-held devices at home

and deal with side effects

Introduction

What is phototherapy?

Phototherapy is the use of light for the treatment of some skin disorders including vitiligo. It reproduces the action of sunlight in a scientific and controlled manner.

NB-UVB light means narrow band ultraviolet B light. These specific wave lengths of light are the same as some of those we expose our skin to when we are outdoors.

What is a hand held phototherapy unit?

This is a hand held device fitted with a NB-UVB lamp. It is used to treat skin conditions such as vitiligo.

You have been selected to use a hand held unit at home following a training programme, which will be held in your local hospital.

Light therapy is almost exclusively available at hospitals, usually involves exposing the whole body and requires regular visits to the hospital at least three times a week.

Hand held light therapy units use the same NB-UVB light as the hospital ones but are suitable for the treatment of small white patches such as on the face, hands, ears and lips. The uninvolved skin is therefore not exposed to the light.

What happens before I start my treatment?

First of all a member of the research staff will show you the lamp and will explain to you all the procedures involved in the treatment.

Before you begin light treatment, you will receive a small test dose, called MED (Minimal Erythema Dose). A number of doses of ultraviolet light B will be shone on small squares on your vitiligo skin or on your normal skin if your vitiligo patch is not big enough. This takes about 15 minutes and the result will be read the next day (24 hours later).

This reading will help decide the start dose your light treatment should be. Even if you have had UVB treatment in the past, MED test will normally be required because your skin’s sensitivity to UVB can change. The MED not

only makes sure that you are treated at a safe UVB dose, but also makes sure you are started at a high enough dose for you.

How long will I have UVB treatment?

Usually, this varies from person to person, but an average course lasts from 2 to 6 months.

For the purpose of this trial you will receive phototherapy for 4 months.

Before you start UVB treatment the research staff will check the medicines that you are taking. If your tablets (including anything you have bought form a pharmacist) are changed during the trial, *please let the research staff know before you start your next treatment. This is because some tablets can affect the way treatment works.*

What should I do if I start taking new drugs during the trial, including over the counter drugs?

Some drugs could make your skin more sensitive to the light therapy. This means that even with small doses of light you might get sunburn. These are called photosensitive drugs.

Please remember that NOT all individuals who use or take these medications will experience a photosensitive reaction.

- *If you are prescribed a new drug* during the trial, including antibiotics, you should let your doctor know that you are receiving light therapy and ask if this drug is ok to take. If your doctor says that the new drug is photosensitive, you should stop your light treatment and contact your phototherapy nurse for further advice.
- *If you are buying a drug over the counter* please see the following list of photosensitive drugs. If you are not sure please call your phototherapy nurse or if out of hours please call your hospital and ask them to connect you to the on-call dermatology Registrar and ask them for advice.
- ***The following list is not exhaustive and therefore please call us BEFORE your next session if you have taken ANY new drugs***

List of photosensitive drugs

Over the counter drugs: 1. **Painkillers such** as Ibuprofen, Diclofenac 2. **Antihistamines such as** Benadryl
Prescription drugs: 3. **Antibiotics** such as Ciprofloxacin, Tetracycline, Doxycycline, Trimethoprim 4. **Cardiac drugs** such as Amiodarone, Diltiazem 5. **Diuretics** such as Furosemide 6. **Diabetic drugs** such as chlorpropamide 7. **Acne medications** such as isotretinoin

When and how often should I use my hand held phototherapy lamp?

You should treat your vitiligo patches every other day (2nd) e.g. Monday, Wednesday, Friday etc. This means you would do at least 3 and a maximum of 4 treatments per week. *Please do not treat your vitiligo every day, as you have to give your skin a break to recover from the light therapy.*

You can do your treatments at *any time of the day suitable for you.*

What about my creams?

For the purpose of this trial you have agreed to stop any current treatment for vitiligo, including creams.

Please continue to use **regular moisturisers** during your course of treatment.

Important things to remember

Before the treatment

- *Cosmetics and perfumes*: On the days of treatment, please avoid using perfumed products such as cosmetics, perfumes or aftershaves *on the treated areas* as these can make your skin more sensitive to the light.

- *Moisturisers:* Please do not use any moisturisers on your vitiligo patches any moisturiser for at least 2 hours before treatment as this can act like a sunscreen and stop the treatment working.

- *Medication changes:* Please inform your research team or your nurse of any medication changes during the treatment.

During the treatment

- *Sunbeds and sunbathing* should be avoided throughout the course of treatment. Please apply high SPF sun creams before going out in the sun.

When using the hand held units, always wear the *protective goggles* supplied. If another person is administering the treatment he/she should also wear protective goggles or glasses.

- Please wear the cotton gloves provided during the treatment in order to protect your hands from overexposure.
- *Attach the comb:* Only use the unit with the comb on. If the comb gets dusty, it can be removed and washed in soapy water. Ensure that it is thoroughly dried before reattaching it.
- If other people are also present in the room during the treatment, they all have to wear protective glasses to protect their eyes.
- The unit is provided for the treatment of your vitiligo and only for the patches discussed with your doctor. Do not use it on other areas

of your skin or allow anyone else to use it as they may develop a severe burn reaction.

After the treatment

- When the equipment is not in use you should ensure that it is switched off and unplugged from the main supply. It should be stored in a safe place in its case or box, out of reach of children.

Side effects

A sunburn like reaction may occur at some point during your treatment or you may find your skin becomes dry. Occasionally you may develop an itchy rash. If you experience any of these reactions, your moisturiser will help to soothe your skin. If you are very uncomfortable please contact the research team. You may need to see a doctor.

If you develop a cold sore on the face, please stop the light treatment **in that area** until the cold sore has healed. You can continue treating vitiligo patches on other areas of the skin as normal.

Premature ageing of the skin (e.g., dryness, freckling and wrinkling) can occur in patients who have had UVB therapy for many years and such individuals may be at an increased risk of developing skin cancer. The increased risk of skin cancer is related to the total lifetime UVB exposure from sunlight as well as treatment.

Please remember, it is extremely important to check your skin in order to identify the side effects that may occur as a result of phototherapy. You should examine your skin regularly throughout the treatment course e.g.

before going to bed on the evening of your treatment, the next day and before your next treatment.

What side effects could occur?

The side effects that could occur on the skin following light therapy are the following:

- Erythema (Redness)
- Blisters
- Rash
- Itching
- Dry skin
- Cold sores
- Tan (brown) around the edges of vitiligo patches

The most common side effect that could occur is red skin like sunburn. There are four different grades of redness, called grades 1-4. Each grade of erythema has different symptoms e.g. the colours are different and some are painful while others are not.

What should I do if I develop redness of the skin (erythema)?

Should you develop redness of your skin, you should carry out the following steps:

1. Decide upon the grade of your erythema. Think about how the erythema feels, when it first appeared, its colour and how long it last for. Please refer to the table below for help.
2. Apply moisturiser after the treatment on your red skin.

3. Always complete your diary!

4. Report your side effects to us as advised in the table below.

5. If you are not sure about what grade your erythema is and would like to double-check you are always welcome to call us on (to be inserted). Or if out of hours please call your local hospital and speak to the oncall dermatology registrar.

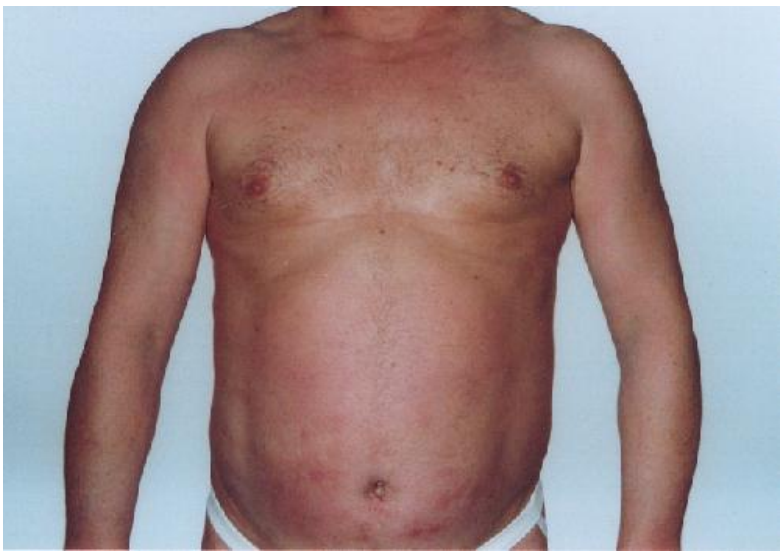
Please remember – Redness of your skin, no matter what grade, will be visible approximately 4 hours after treatment.

Grade 1 erythema: skin is slightly pink / red in colour. It will develop on the day of treatment, and settle within a day. This means that on your next session your skin will look normal again. This burn does not feel hot and is **NOT painful**.

Action:

- *Apply moisturiser on the affected areas after the treatment*
- *Decrease your treatment time on your next session (please see the treatment schedule summary on page 17)*
- *This reaction is normal. You don't have to call us to let us know, but please make a note of it in your diary.*

GRADE 1 ERYTHEMA



Grade 2 erythema: skin is obviously red in colour. It will develop on the day of treatment and will still be there approximately two days after

the treatment. This burn does not feel hot, might feel slightly uncomfortable but is **NOT painful.**

Action:

- *Apply moisturiser on the affected areas after the treatment*
- *Skip one next treatment session until your skin settles and return to normal.*
- *After your skin looks normal again you should restart treatment but will have to decrease your treatment time (please see the treatment schedule summary on page 17).*
- *This is not an emergency as this is also an expected reaction of the skin.*
- *However if you are not sure or would like to confirm your actions please call us BEFORE you restart treatment on (tel: xxxxx name of phototherapy nurse) or on 0115 8468629 (co-ordinating centre). Inform us of the area of the skin affected, along with the colour and symptoms of the burn. State the action you plan to take. Once we confirm the correct action to take for your next treatment, carry this out on the correct treatment day as per your schedule. If your next session is at the weekend, SKIP it and call us on Monday between 9 and 5 o'clock.*

E.g. if you developed grade 2 erythema on Monday (treatment time=21 sec), you will skip your Wednesday treatment session and restart again on Friday (decreased treatment time=18 sec).

If you have developed redness of your skin and your skin feels

HOT and PAINFUL - this is at least a grade 3 erythema.

Grade 3 and grade 4 erythemas are serious, so please contact the research team as soon as possible

Grade 3: skin is very red and feels **like sunburn**. Your skin will feel hot, uncomfortable and **PAINFUL.** This will last for two to three days. The symptoms will reduce in severity as the days pass.

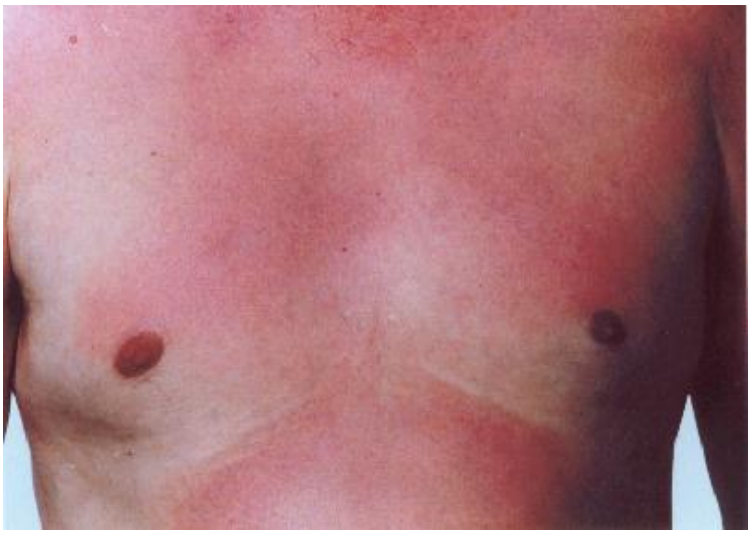
Action:

- *Stop treatment*
- *Apply moisturiser to the affected areas*
- *Contact your phototherapy nurse (tel:xxxxx) or research team (tel:xxxxx) ASAP. You will need to stop treatment until your skin settles. If this happens at the weekend or out of hours, please call your local hospital (insert name and number) and ask them*

to connect you to the oncall dermatology SpR for advice.

GRADE 2/3 ERYTHEMA

(can be similar in colour, but have different symptoms)

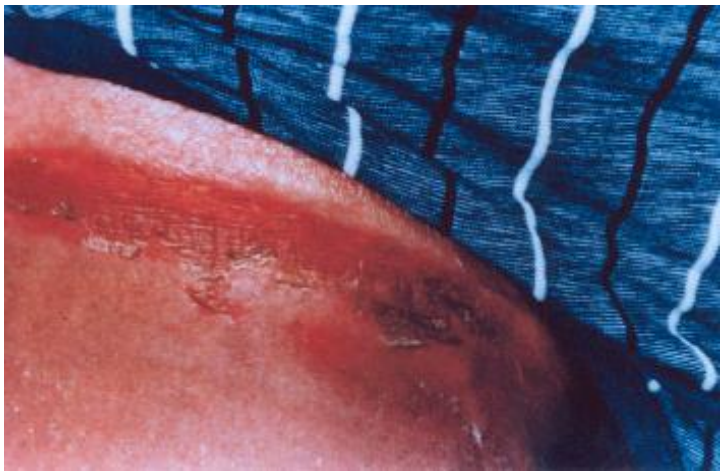


Grade 4: skin is very red and hot and has **blisters**. This reaction is **VERY PAINFUL** and may make you feel unwell. This burn can last for four to five days. The symptoms will reduce as the days pass.

Action:

- *Stop treatment and*
- *Contact your phototherapy nurse (tel:xxxx) or research team (co-ordinating centre tel:xxxx). If this happens at the weekend or out of hours, please call your local hospital(name and phone number) and ask them to connect you to the oncall dermatology SpR. You will be seen by a doctor in your local hospital.*
- *The research nurse will contact you regarding how and when restarting your treatment.*

GRADE 4 ERYTHEMA



Please remember

If you develop grade 3 or 4 erythema of your skin, always contact our research team BEFORE your next treatment in order to confirm your assessment. By failing to do this, you may cause a more severe burn reaction, e.g. if you have assessed your skin wrongly or take the wrong action for your next treatment

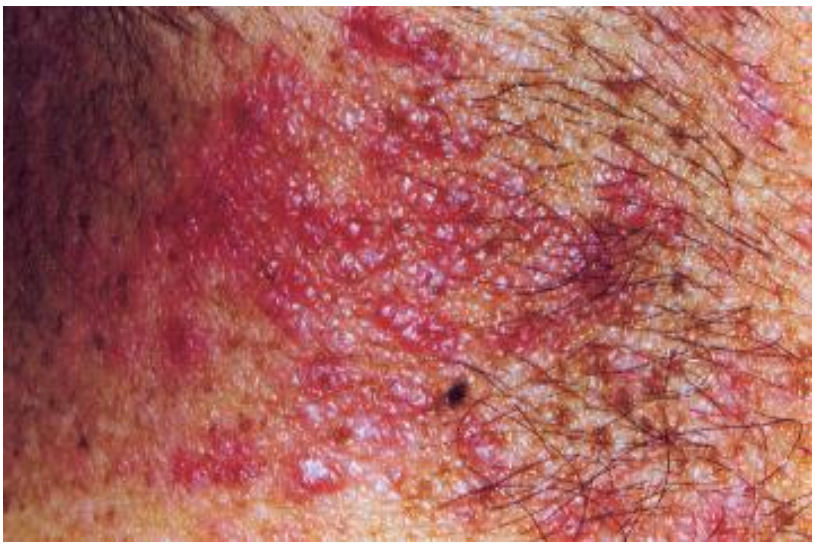
What should I do if I develop side effects other than redness of the skin?

- If the treated skin **is itchy and begins to feel dry**, apply your moisturiser at least three to four times a day throughout the treatment course. Please do not apply moisturiser BEFORE the treatment session.

- If you develop **tan (brown) around the edges of vitiligo patches**, this is normal reaction of the skin. You don't have to do anything and therefore continue your treatment as normal.

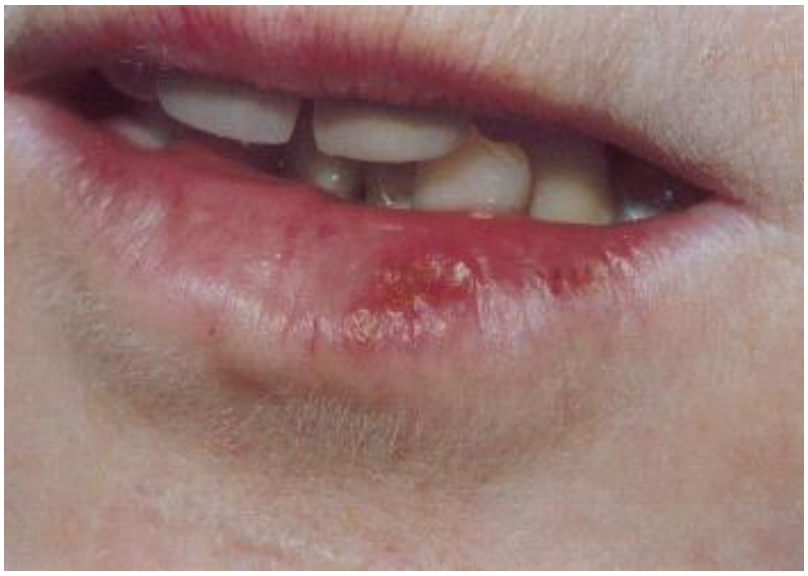
- If you develop a **rash, stop the treatment immediately. Please call our research team as soon as possible on (co-ordinating centre tel:xxxx) or if out of hours please call your local hospital** (Name of the hospital and telephone to be inserted) **and ask to speak to the on-call dermatology SpR.**

RASH



- If you develop cold sores **stop the treatment until the cold sore has healed. Call us on 0115 84 68629 or on (tel of research nurse) to let us know that you have cold sores as well as after they have healed. You research nurse will let you know how to correctly restart the treatment on that area.**
- **This is not an emergency and therefore please call us during day time or wait unitl the next morning. However if you are worried and out of hours please call your local hospital** (Name of the hospital and telephone to be inserted) **and ask to speak to the on-call dermatology SpR.**

COLD SORE



- If you have any **other questions about side effects,** please call your research team (co-ordinating centre Tel to be inserted) for advice before your next treatment!

What should I do if I have mechanical problems with the lamp?

If you need advice regarding **mechanical problems with the lamp,** please call your research team on **0115 84 68629**

About the device

When will I receive my device?

You will receive your unit on the day of your baseline hospital visit or in a few days after your first hospital visit. It will arrive by post as a signed for delivery. If you do not receive your device within 5 working days of your educational session please contact our research team on **0115 84 68629** or email vitiligostudy@nottingham.ac.uk.

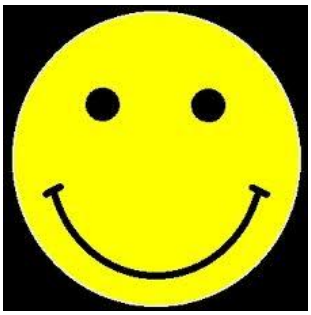
What to do when I receive my device?

After receiving your package, please check that all the following are in the box:

- Hand held lamp
- Safety goggles
- Safety glasses
- A pair or cotton gloves
- Comb (plastic teeth)

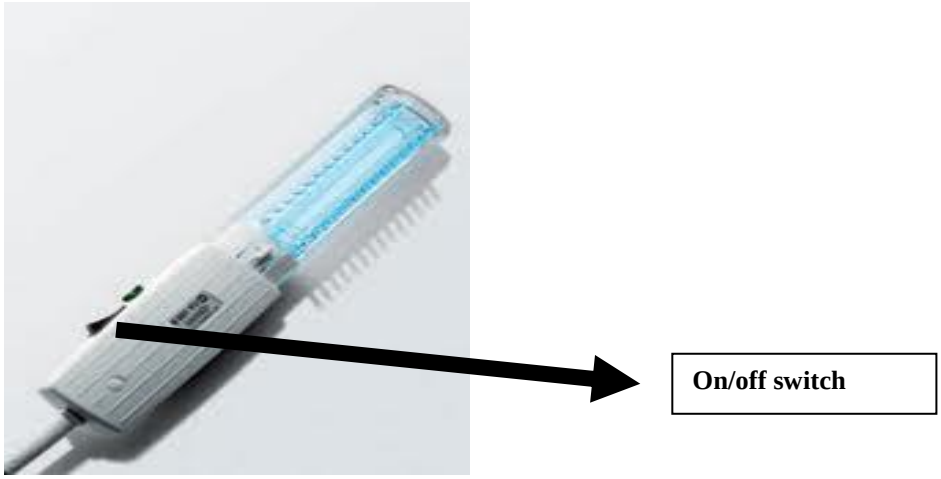
Please call us on (phone number to be inserted) to let us know that you have received all the above.

And now you are ready to start your treatment!



Treatment guidance

How the device works



Before switching on the device:

- Ensure you are wearing your protective glasses or goggles
- Ensure you are wearing the cotton gloves provided

Please follow the following simple steps to start your treatment:

1. Make sure you have calculated and recorded your treatment times in your diary **before** you start!
2. Set up the alarm clock
3. Connect the lamp to the main supplier
4. Turn the lamp on
5. Please remember that during the treatment the device will warm up. This is normal. Please continue the treatment

Trouble shooting

	Problem	**Reason**	**Solution**
1	The device won't switch on	The device is not connected to the socket	Make sure you have pressed the lamp entirely into the socket.

Your treatment schedule

As prescribed by your doctor, you should do your treatment every other day. This means that you will treat your white patches 3 to 4 times a week.

Please remember NOT to treat your skin every day.

Your treatment schedule depends on your skin type. Each session you will be increasing your treatment time i.e. if you have skin type 1 and you did 21 seconds on Monday, you will do 24 seconds on Wednesday providing you did not experience any redness of your skin in the meantime. You

should continue increasing your treatment time until you reach the MAXIMUM TREATMENT TIME as recorded in your diary.

Please remember to calculate your treatment times and write them down in your diary BEFORE starting you session!

Please see the following table for more details.

Treatment Schedule summary

Skin Type	Starting time	Time increase	Exposure time decrease	Maximum treatment time	Overall duration of treatment
I	15 sec	+ 3 seconds	-3 seconds	3 min	4 months
II	20 sec	+ 4 seconds	-4 seconds	4 min	4 months
III	25 sec	+ 5 seconds	-5 seconds	5 min	4 months
IV	30 sec	+ 6 seconds	-6 seconds	6 min	4 months
V	30 sec	+ 6 seconds	-6 seconds	6 min	4 months
VI	30 sec	+ 6 seconds	-6 seconds	6 min	4 months

In summary:

- Follow the starting time as in your personalised treatment schedule.
- If you are not experiencing any redness: on each treatment session i.e. every other day, increase your treatment according to your personal schedule.
- **If you develop redness please refer to the table on page 8 of this manual first and always contact the research team if appropriate BEFORE your next treatment!**
- If you develop grade 1 erythema: decrease your treatment time as above.

  i.e. if your skin type is 1 and after session 3 (21 seconds) you develop erythema, which is resolved by the next treatment day, you will receive 18 seconds on your session 4 instead of 24 seconds.
- If you develop grade 2 erythema or above: You should skip one treatment session and decrease your treatment time on the next one. E.g. if after your treatment on Monday (=21 seconds) you have developed grade 2 erythema, you will skip your session on Wednesday. On Friday, you will receive 18 seconds of light.

- If you develop grade, 3 or 4 erythema: please stop your treatment and contact the research team as soon as possible.

What to do if I miss a treatment?

If for any reason **other than side effects**, you have missed one or more treatment sessions e.g. you were busy or away and didn't take your lamp with you please do the followings:

1. **One or 2 missed treatment sessions:** administer decreased time on your next session i.e. if on Monday you administered 21 seconds but you have missed both your Wednesday and Friday treatment, you would administer 18 seconds on Saturday.
2. **Three or more missing treatments:** please contact your research team for advice.

Treatment time schedule

Your nurse will give you your personalised treatment schedule suitable for your skin type following the results of your MED test.

Please remember to use this treatment plan as a guide only and if you are not experiencing any side effects.

APPENDIX 5

Patient’s diary for home phototherapy

Instructions on how to complete this diary

Step	Column	Information required	Example
1	Session	Session number	e.g. 2
2	Date	The date you perform your treatment	e.g. 02/03/2011
3	Area(s) treated	Write down what areas are you treating. If you didn't have any side effects on all patches since your last session please insert ALL (patches) If one or some areas has at least one side effect please insert in a separate line	e.g. face, left hand or all in separate line e.g. face and in separate line e.g. left hand
4	**Time(sec)**	Write down the time of treatment session. Remember to insert before starting your session	e.g. 25 sec
5	Problems? (Y/N)	Did you have any side effects from you previous session? If no- insert N and leave the rest of the line empty. If yes-continue	Yes or No
6	Redness or other side effects	If you had any of the side effects mentioned in your diary or your manual please specify accordingly	Redness: e.g. 1 Other side effects: e.g. D
7	**Contacted research team**	If you had side effects, please tell us if you had called the research team by replying *yes or no* in the column	Yes or No
8	**if yes, was advised**	If you have replied yes to the above question, please tell us what were you advised to do e.g. reduce dose= 1 and complete the **if yes, was advised** column accordingly.	1 or 2 or 3
9	**Comments**	If missed a treatment for ANY reason please insert here Or any other comments	e.g. session 4, date 11/11/2011 comments: missed treatment reason…

Research team contact details:

If you have any questions or need advice please contact us during office working hours:

- **Jo Perdue (administrator, co-ordinating centre):**
- **Lisa Charlesworth (administrator, co-ordinating centre)**

Telephone: 0115 84 68629

RESEARCH NURSE:
(Sue Davies-Jones, 0115 82 31041/07945 420508 or Jo Llewellyn 07407 154580)

EMERGENCY OR OUT OF HOURS:
If out of hours **AND** in case of **EMERGENCY** please call your local hospital, Queens Medical Centre on 0115 9249924 and ask to speak to the on-call dermatology registrar.

Please remember to fill your diary BEFORE every treatment session.

Skin type treatment plan: Start time:

Maximum treatment time:

Participant's MED:

Name of person administering the treatment (if applicable):

***if you develop redness of your skin, please describe:**
Grade 1 redness-pink/red skin, settles within a day. NOT painful
Grade 2 redness- red skin, lasts for around 2 days. NOT painful.
Grade 3 redness-very red, like sunburn, lasts for 2-3days. HOT and PAINFUL
Grade 4 redness-very red skin and BLISTERS. VERY PAINFUL

Patient's Diary for Home phototherapy

Session	**Date (dd/mm/yyyy)**	**Area(s) treated**	**Time (sec)**	**Problems? Yes/No**	**Redness Please record accordingly *:** Grade 1=1 Grade 2=2 Grade 3=2 Grade 4=4	**Other side effects. Please record all applicable:** Dry skin=D Rash=R Itch=I Blister=B Cold sores=C Brown at the edges=H	**Contacted research team? Yes/No** (only complete if any side effects)	**If yes, was advised to...** Reduce the dose=1 Skip a treatment=2 See a doctor=3	**Comments (e.g. take a note here if you have missed a session)**
1									

APPENDIX 6

END OF STUDY QUESTIONNAIRE

HI-LIGHT TRIAL

Final hospital visit

Week 16

Date of completion:	_ _ / _ _ / _ _ _ _

If completed by co-ordinating centre over the phone please tick ☐

Your opinion on the success of the treatment

1. How satisfied are you with the treatment? (please tick one option)				
Very dissatisfied ☐	somewhat dissatisfied ☐	Neutral ☐	Somewhat satisfied ☐	Very satisfied ☐

2. Please rate the colour match of your vitiligo patches following light treatment (please tick one option)					
Lesion name	Bad	Fair	Good	Excellent	Darkening of the skin around the lesion is present (Y/N)
	☐	☐	☐	☐	
	☐	☐	☐	☐	
	☐	☐	☐	☐	

Now have a look at the photographs of your representative patches before starting the treatment.

Looking at the photographs of before treatment and comparing to your patches today:

3. How would you rate the overall changes in your vitiligo? (Please tick one option)				
Much worse	A bit worse	No change	A bit better	Much better
☐	☐	☐	☐	☐

Your opinion on the hand held phototherapy lamp and the training session

	Waldmann	**Dermfix 1000**
4. Which device did you have?	☐	☐

	Yes	**No**	**Unsure**

5. Please say what you liked the most about this lamp?

6. Please say what you liked the least about this lamp?

	Yes	No	Unsure
7. Do you think the training session at the beginning of the trial was sufficient for you to operate the device at home with limited medical supervision?	☐	☐	☐

8. If you answered no or unsure on the previous question please tell us how the training session could be improved?

	Yes	No	Unsure
9. Did you find it difficult when deciding on the grade of erythema (redness)?	☐	☐	☐
10. If you replied yes or unsure on the following question please explain.			

	Yes	**No**	**Unsure**
11. Did you have any difficulties with operating the lamp?	☐	☐	☐

12. If you replied yes or unsure on the following question please explain.

	Never	**Some of the time**	**Most of the time**	**Always**
13. Did you follow your treatment schedule as prescribed by your doctor i.e. light therapy 3 times a week?	☐	☐	☐	☐

14. If you did NOT use the treatment as recommended, why not?

	Active	Dummy
15. Do you think you have had an active device or a dummy device in this trial?	☐	☐

	Yes	No	Maybe
16. Would you use the lamp again?	☐	☐	☐
17. Would you recommend the lamp to others?	☐	☐	☐

Your opinion on this trial and future research into vitiligo

18. What did you like the most about this trial?

19. How do you think the trial could be improved?

Would you be willing to take part in future clinical trials for vitiligo comparing:	**Yes**	**No**	**Unsure**
20. Ultraviolet light to dummy lamp?	☐	☐	☐
21. Ultraviolet light to steroid cream?	☐	☐	☐
22. Combination of ultraviolet light and steroid creams to steroid cream alone and to light therapy alone	☐	☐	☐

23. Please tell us the reasons for your answers above

	Yes	**No**
24. Would you be happy for us to contact you about the results of this trial and our future research work on vitiligo?	☐	☐

APPENDIX 7

HI-LIGHT TRIAL

TREATMENT PLANS AND ADULT CONSENT FORMS

The University of Nottingham

HI-Light for vitiligo trial

Skin type I-very white	
Treatment session number	Treatment time
1.	15 seconds
2.	18 seconds
3.	21 seconds
4.	24 seconds
5.	27 seconds
6.	30 seconds
7.	33 seconds
8.	36 seconds
9.	39 seconds
10.	42 seconds
11.	45 seconds
12.	48 seconds
13.	51 seconds
14.	54 seconds
15.	57 seconds
16.	1 minute
17.	1 minute 3 seconds
18.	1 minute 6 seconds
19.	1 minute 9 seconds
20.	1 minute 12 seconds
21.	1 minute 15 seconds
22.	1 minute 18 seconds
23.	1 minute 21 seconds
24.	1 minute 24 seconds
25.	1 minute 27 seconds
26.	1 minute 30 seconds
27.	1 minute 33 seconds
28.	1 minute 36 seconds
29.	1 minute 39 seconds
30.	1 minute 42 seconds
31.	1 minute 45 seconds
32.	1 minute 48 seconds
33.	1 minute 51 seconds
34.	1 minute 54 seconds
35.	1 minute 57 seconds
36.	2 minutes
37.	2 minutes 3 seconds
38.	2 minutes 6 seconds
39.	2 minutes 9 seconds
40.	2 minutes 12 seconds
41.	2 minutes 15 seconds
42.	2 minutes 18 seconds

43.	2 minutes	21 seconds
44.	2 minutes	24 seconds
45.	2 minutes	27 seconds
46.	2 minutes	30 seconds
47.	2 minutes	33 seconds
48.	2 minutes	36 seconds
49.	2 minutes	39 seconds
50.	2 minutes	42 seconds
51.	2 minutes	45 seconds
52.	2 minutes	48 seconds
53.	2 minutes	51 seconds
54.	2 minutes	54 seconds
55.	2 minutes	57 seconds
56.	3 minutes	Maximum exposure time
57.	3 minutes	Maximum exposure time
58.	3 minutes	Maximum exposure time
59.	3 minutes	Maximum exposure time
60.	3 minutes	Maximum exposure time

The University of Nottingham

HI-Light for vitiligo trial

Skin type II- white	
Treatment session number	Treatment time in seconds
1.	20 seconds
2.	24 seconds
3.	28 seconds
4.	32 seconds
5.	36 seconds
6.	40 seconds
7.	44 seconds
8.	48 seconds
9.	52 seconds
10.	56 seconds
11.	1 minute
12.	1 minute 4 seconds
13.	1 minute 8 seconds
14.	1 minute 12 seconds
15.	1 minute 16 seconds
16.	1 minute 20 seconds
17.	1 minute 24 seconds
18.	1 minute 28 seconds
19.	1 minute 32 seconds
20.	1 minute 36 seconds
21.	1 minute 40 seconds
22.	1 minute 44 seconds
23.	1 minute 48 seconds
24.	1 minute 52 seconds
25.	1 minute 56 seconds
26.	2 minutes
27.	2 minutes 4 seconds
28.	2 minutes 8 seconds
29.	2 minutes 12 seconds
30.	2 minutes 16 seconds
31.	2 minutes 20 seconds
32.	2 minutes 24 seconds
33.	2 minutes 28 seconds
34.	2 minutes 32 seconds
35.	2 minutes 36 seconds
36.	2 minutes 40 seconds
37.	2 minutes 44 seconds
38.	2 minutes 48 seconds
39.	2 minutes 52 seconds
40.	2 minutes 56 seconds
41.	3 minutes
42.	3 minutes 4 seconds
43.	3 minutes 8 seconds
44.	3 minutes 12 seconds

45.	3 minutes 16 seconds
46.	3 minutes 20 seconds
47.	3 minutes 24 seconds
48.	3 minutes 28 seconds
49.	3 minutes 32 seconds
50.	3 minutes 36 seconds
51.	3 minutes 40 seconds
52.	3 minutes 44 seconds
53.	3 minutes 48 seconds
54.	3 minutes 52 seconds
55.	3 minutes 56 seconds
56.	4 minutes Maximum exposure time
57.	4 minutes Maximum exposure time
58.	4 minutes Maximum exposure time
59.	4 minutes Maximum exposure time
60.	4 minutes Maximum exposure time

The University of Nottingham

HI-Light for vitiligo trial

Skin type III- olive	
Treatment session number	Treatment time in seconds
1.	25 seconds
2.	30 seconds
3.	35 seconds
4.	40 seconds
5.	45 seconds
6.	50 seconds
7.	55 seconds
8.	1 minute
9.	1 minute 5 seconds
10.	1 minute 10 seconds
11.	1 minute 15 seconds
12.	1 minute 20 seconds
13.	1 minute 25 seconds
14.	1 minute 30 seconds
15.	1 minute 35 seconds
16.	1 minute 40 seconds
17.	1 minute 45 seconds
18.	1 minute 50 seconds
19.	1 minute 55 seconds
20.	2 minutes
21.	2 minutes 5 seconds
22.	2 minutes 10 seconds
23.	2 minutes 15 seconds
24.	2 minutes 20 seconds
25.	2 minutes 25 seconds
26.	2 minutes 30 seconds
27.	2 minutes 35 seconds
28.	2 minutes 40 seconds
29.	2 minutes 45 seconds
30.	2 minutes 50 seconds
31.	2 minutes 55 seconds
32.	3 minutes
33.	3 minutes 5 seconds
34.	3 minutes 10 seconds
35.	3 minutes 15 seconds
36.	3 minutes 20 seconds
37.	3 minutes 25 seconds
38.	3 minutes 30 seconds
39.	3 minutes 35 seconds
40.	3 minutes 40 seconds
41.	3 minutes 45 seconds
42.	3 minutes 50 seconds
43.	3 minutes 55 seconds
44.	4 minutes

45.	4 minutes	5 seconds
46.	4 minutes	10 seconds
47.	4 minutes	15 seconds
48.	4 minutes	20 seconds
49.	4 minutes	25 seconds
50.	4 minutes	30seconds
51.	4 minutes	35 seconds
52.	4 minutes	40 seconds
53.	4 minutes	45 seconds
54.	4 minutes	50 seconds
55.	4 minutes	55 seconds
56.	5 minutes	Maximum exposure time
57.	5 minutes	Maximum exposure time
58.	5 minutes	Maximum exposure time
59.	5 minutes	Maximum exposure time
60.	5 minutes	Maximum exposure time

The University of Nottingham

HI-Light for vitiligo trial

Skin type IV, V, VI- brown, black	
Treatment session number	Treatment time in seconds
1.	30 seconds
2.	36 seconds
3.	42 seconds
4.	48 seconds
5.	54 seconds
6.	1 minute
7.	1 minute 6 seconds
8.	1 minute 12 seconds
9.	1 minute 18 seconds
10.	1 minute 24 seconds
11.	1 minute 30 seconds
12.	1 minute 36 seconds
13.	1 minute 42 seconds
14.	1 minute 48 seconds
15.	1 minute 54 seconds
16.	2 minutes
17.	2 minutes 6 seconds
18.	2 minutes 12 seconds
19.	2 minutes 18 seconds
20.	2 minutes 24 seconds
21.	2 minutes 30 seconds
22.	2 minutes 36 seconds
23.	2 minutes 42 seconds
24.	2 minutes 48 seconds
25.	2 minutes 54 seconds
26.	3 minutes
27.	3 minutes 6 seconds
28.	3 minutes 12 seconds
29.	3 minutes 18 seconds
30.	3 minutes 24 seconds
31.	3 minutes 30 seconds
32.	3 minutes 36 seconds
33.	3 minutes 42 seconds
34.	3 minutes 48 seconds
35.	3 minutes 54 seconds
36.	4 minutes
37.	4 minutes 6 seconds
38.	4 minutes 12 seconds
39.	4 minutes 18 seconds
40.	4 minutes 24 seconds
41.	4 minutes 30 seconds
42.	4 minutes 36 seconds

43.	4 minutes	42 seconds
44.	4 minutes	48 seconds
45.	4 minutes	54 seconds
46.	5 minutes	
47.	5 minutes	6 seconds
48.	5 minutes	12 seconds
49.	5 minutes	18 seconds
50.	5 minutes	24 seconds
51.	5 minutes	30 seconds
52.	5 minutes	36 seconds
53.	5 minutes	42 seconds
54.	5 minutes	48 seconds
55.	5 minutes	54 seconds
56.	6 minutes	Maximum exposure time
57.	6 minutes	Maximum exposure time
58.	6 minutes	Maximum exposure time
59.	6 minutes	Maximum exposure time
60.	6 minutes	Maximum exposure time

CONSENT FORM
ADULT WITH VITILIGO

Title of Study: HI-Light vitiligo trial (Home Intervention of light therapy for the treatment of vitiligo)

REC ref: 11/EM/0331

Name of Researcher: Professor Hywel Williams

Name of Participant: **Please initial box**

1. I confirm that I have read and understand the information sheet version number 3.0 10 November 2011 for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected. I understand that should I withdraw then the information collected so far cannot be erased and that this information may still be used in the project analysis. ☐

3. I understand that relevant sections of my medical notes and data collected in the study may be looked at by authorised individuals from the University of Nottingham, the research group and regulatory authorities where it is relevant to my taking part in this study. I give permission for these individuals to have access to these records and to collect, store, analyse and publish information obtained from my participation in this study. I understand that my personal details will be kept confidential. ☐

4. I agree to an MED test and a photograph of my skin being taken as part of the study procedures. ☐

5. I agree to follow the treatment regimen and to use the hand held device only for the purpose of this trial, and only for my treatment as discussed in the educational session. ☐

6. I agree to my GP being informed of my participation in this study. ☐

7. I agree for my personal contact details to be kept by the research team so that they can contact me after the end of the study *(optional)*. ☐

8. I agree to take part in the above study.

Name of Participant	Date	Signature

Name of Person taking consent	Date	Signature

REC ref: 11/EM/0331 Centre: Participant ID:

Title of the trial: **HI-Light vitiligo trial**

(Home Intervention of light therapy for the treatment of vitiligo)

Name of the participant:

_____

Consent form for person administering the NB-UVB home phototherapy

I _____ confirm that I have read and understand the instructions for using the hand held home phototherapy lamp, and possible side effects of this treatment. I also confirm that I am able to administer a course of such treatment to myself.

A trained member of research staff demonstrated the proper use of the unit, fully explained the nature and purpose of the treatment and answered any questions or doubts I may have regarding the treatment schedule and use of the lamp.

I confirm that I will use the treatment as I have been taught, and that I accept full responsibility for administering the treatment. I also understand that the hand held phototherapy lamp should not be used on areas other than the areas agreed with a member of the research team and that I should not use it on anyone else.

Signed: Date: dd/mm/yyyy

I understand that once the trial is over, the phototherapy lamp (including safety goggles and glasses) should be returned to the research team.

Signed: Date: dd/mm/yyyy .....

To be completed by research nurse:

I confirm that I have demonstrated the proper use of the hand held home phototherapy lamp. I have explained the nature and purpose of the therapy, including the possible side effects. I also confirm that _____ showed competence in using the equipment as per the treatment protocol.

Name: .....

Signed: Date: dd/mm/yyyy