Home UVB phototherapy for psoriasis

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Home UVB phototherapy for psoriasis

UVB thuisbelichting voor psoriasis
(met een samenvatting in het Nederlands)

Proefschrift

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door

Mayke Bernadette Gerdine Koek
geboren op 17 maart 1975 te Borculo

Promotoren

Prof. dr. C.A.F.M. Bruijnzeel-Koomen

Prof. dr. E. Buskens

Co-promotor

Dr. V. Sigurdsson

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To live is the rarest thing in the world.
Most people exist, that is all.

Oscar Wilde

Voor papa

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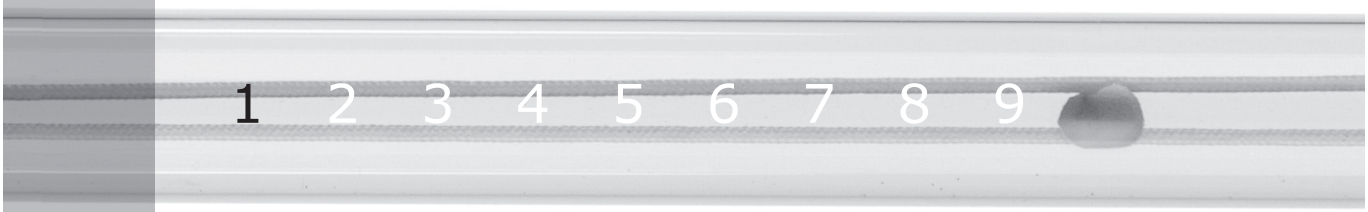
General introduction



1.1 Background

Psoriasis is a chronic recurrent skin disorder, affecting 2% to 4% of the population in western Europe and the USA.[1] The disease is characterised by red scaly lesions, so-called plaques, which may develop anywhere on the skin. As such, visible parts of the body may also be involved. Due to its potentially cosmetically disfiguring consequences and the often involved severe flaking of the affected skin, the disease may have a considerable impact on patients' quality of life.

Psoriasis can be treated symptomatically in several ways, depending on severity and extent. First line therapy usually consists of topical application of creams and ointments,[2] often containing corticosteroids or vitamin D derivatives. In some patients, however, the skin lesions may no longer respond to topical treatment. Also, occasionally the disease is too generalised; for those patients the area of skin involved is so extensive that topical treatment is not feasible. When the psoriasis cannot be managed adequately with topical medications, irradiation with ultraviolet (UV) light or systemic medication is indicated.[3;4]

Irradiation of the skin with UV light is called phototherapy, and for psoriasis it is mostly performed with ultraviolet B light (UVB) or the use of a psoralen in combination with ultraviolet A light (PUVA). For psoriasis, UVB has been the phototherapy of choice because it is less carcinogenic than PUVA.[5] In particular, since a highly efficacious UVB lamp emitting so-called 'narrowband UVB' became available (TL-01 lamp, Philips, Eindhoven, Netherlands) this has become the standard.[6]

In general, guidelines and consensus agree that (narrowband) UVB phototherapy is the primary treatment option after failure of topical therapies.[3;4;7] After that, PUVA or systemic treatment with methotrexate or ciclosporin may be considered, finally followed by the so-called biologicals.

UVB phototherapy, however, has considerable consequences for the patient because it is nearly always carried out in an outpatient setting. The UVB irradiation itself normally takes only a few minutes, but patients attend their local outpatient department during working hours two to three times a week for several months. In the Netherlands, a densely populated country, distances from the patient's home to the hospital are in general relatively short. Nevertheless, UVB treatment in an outpatient setting is considered time-consuming, also for the hospital personnel. Thus it imposes a substantial burden on patients and society. In contrast to the Netherlands, in most other developed countries dermatology clinics typically

cover a large geographical area, making UVB phototherapy only available for those patients living locally to a phototherapy unit.[8]
To treat patients living far from their local hospital, home UVB phototherapy was introduced in the late 1970s.[9-12] Since then, several positive reports on the successes in treatment of psoriasis have appeared,[13-15] but at the same time few dermatologists have embraced home phototherapy. Varying opinions exist as to the advisability of prescribing home UVB phototherapy. A number of dermatologists have raised concerns in particular about its safety and effectiveness. In addition, patient compliance with home UVB treatment is questioned.[14;16-22] Surprisingly, very little research on home UVB phototherapy has been conducted to support or refute these assumptions. As such, the use of home UVB phototherapy for psoriasis has since its introduction remained debated. Despite all discussions, however, home UVB is being prescribed by several dermatologists,[13;14] especially when patients live far from the clinic. When finally, in 1998, a Dutch health care insurance company decided to cover the costs of home UVB treatment, dermatologists once more expressed their concerns. The Dutch Health Care Inspectorate (IGZ) subsequently advised the Dutch Society of Dermatologists (NVDV) to develop professional standards on administering UVB phototherapy at home.

1.2 Organisation of home UVB phototherapy in the Netherlands

In most countries, home UVB phototherapy is based on patients buying a UVB device on prescription of a physician. After buying the device patients therefore potentially have year-round access to UVB irradiation, every day of the week. Accordingly, clinicians may be concerned about possible misuse—that is, unsupervised continuation or unsupervised re-start of home UVB phototherapy.[16] In the Netherlands, however, a very different system for home UVB phototherapy has been implemented: rental of home UVB equipment with involvement of a specialised nurse.[13] Since the 1990s, two Dutch home care organisations have set up a lease-service, supplying total body home UVB equipment to patients on a temporary base. They also provide care and supervision through involvement of a specialised nurse. Both companies supply to patients all over the country.

In general, this is the procedure: the dermatologist fills out an application form for home UVB phototherapy and sends it to one of the home care services. After approval of reimbursement by the patient's insurance company (in the Netherlands reimbursement of home UVB phototherapy has to be specifically requested and authorised prior to the treatment), the equipment will be placed in the patient's home on a rental base for a fixed period. The specialised nurse provides a brief instruction at the patient's home, and explains how to use the equipment. Patients receive a treatment schedule based on treatment-times, and sign a contract restricting use of the UVB equipment to themselves. At intervals, the nurse may contact the patients by telephone. Patients can also contact the nurse in case of questions or problems. Throughout the total treatment, the medical responsibility stays with the prescribing dermatologist, who examines the patient during routine consultations. If extension of the rental period is needed, this can only be arranged with approval of the dermatologist. The current commercial invoice prices for this service are approximately € 650 per patient for 12 weeks, and include delivery and collection of the phototherapy unit as well as the costs for the nurses' services. Most Dutch insurance companies will cover the costs of home UVB therapy when it is specifically requested. However, some insurance companies will not finance the total costs and require a co-payment from the patient. Few companies will not reimburse the costs at all. Due to the existence of this rental-service very few Dutch dermatologists support a request to privately purchase home UVB equipment, resulting in almost negligible private possession of home UVB equipment in the Netherlands (information obtained from personal communications with the manufacturers of home UVB equipment and with the home care companies).

1.3 Aims and outline of this thesis

The aim of this thesis is to settle the long lasting discussion concerning the advisability of home UVB phototherapy for psoriasis. To do so, we first searched for evidence and guidelines concerning home UVB phototherapy for psoriasis, and investigated the opinions and actual use of this therapy among dermatologists (chapter 2). Since we found there was a lack of randomised research on home UVB treatment, we initiated a randomised clinical trial (RCT) comparing home UVB phototherapy with the standard outpatient UVB phototherapy for psoriasis.

With this trial we aimed to demonstrate that treatment effect, safety, quality of life and cost-effectiveness of home UVB phototherapy do not differ substantially from that of conventional UVB phototherapy in an outpatient clinic. Additionally, with home treatment we expected a lower burden from treatment and higher patients' satisfaction. We focussed on narrowband (TL-01) UVB phototherapy. In chapter 3 we present the study protocol of this RCT; the methodological particulars of the study design are briefly clarified in chapter 4. The results concerning treatment effects, safety, burden of treatment and patient satisfaction are described in chapter 5, while the costs and cost-effectiveness analyses of the RCT are presented in chapter 8. Anticipating the use of Quality Adjusted Life Years (QALYs) as a measure of effectiveness in chapter 8, we examined the impact of psoriasis on quality of life and on QALYs (chapter 6). We also investigated two instruments that are used to calculate QALYs, the EuroQol 5D (EQ-5D) and the SF-6D, for their agreement and usefulness in psoriasis research. The results of this study are described in chapter 7. The results of chapters 6 and 7 comprise the basis upon which the economic evaluation as described in chapter 8 rests—that is, the balance between costs and effects. Finally, the implications of the studies described in this thesis are discussed in chapter 9, presenting a bird's-eye view of the evidence, practice and policy regarding home UVB phototherapy for psoriasis. This thesis ends with a summary in English and Dutch.

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No consensus on home UVB phototherapy

Home UVB phototherapy for psoriasis: Discrepancy between literature, guidelines, general opinions and actual use. Results of a literature review, a web search, and a questionnaire among dermatologists

Mayke BG Koek
Erik Buskens
Carla AFM Bruijnzeel-Koomen
Vigfús Sigurdsson

Br J Dermatol 2006; 154: 701-11
The definitive version is available at www.blackwell-synergy.com

2.1 Abstract

Background Home ultraviolet B (UVB) phototherapy is a debated treatment. It is currently being prescribed for patients with psoriasis whereas literature on the subject is scarce. Despite the apparent contradiction between clinical practice and literature, no systematic study of either has been conducted.

Objective To assess and compare the available publications and guidelines on home UVB phototherapy for psoriasis with the actual opinions and actual use of this therapy.

Methods Search of the literature and guidelines using databases, search engines and e-mail. A postal survey of 343 Dutch dermatologists and 142 dermatologists from 32 other countries. 255 and 102 dermatologists respectively responded. Outcome measures were the reported advantages, drawbacks and prescription rates of home UVB phototherapy.

Results Fourteen publications (non randomised) and six guidelines concerning home UVB phototherapy for psoriasis were identified. Most were reluctant about the use of this treatment. Publications not describing patient-based research (7/14) reported most drawbacks (24/31).

Home UVB phototherapy was prescribed to 5% (median) of all UVB requiring patients in the Netherlands. Yet 28% (68/244) of the Dutch dermatologists prescribed home UVB in 20% to 100% (n=4) of the cases. Dermatologists from other countries reported that between 0 and 10% of the UVB treatments were offered at home. For both Dutch and non-Dutch dermatologists, the most important reasons for prescribing home UVB concerned time and travel-distances (79.5%=163/205 and 75%=33/44). Therapy-related drawbacks (such as poor service & equipment) were the objections mentioned most often (55.4%=103/186 and 62.6%=57/91). Concerns about the medico-legal liability of home UVB were rarely expressed by individual respondents, but frequently mentioned in the various reports.

Conclusion A discrepancy exists between the actual use of home UVB phototherapy and the general opinions found in publications. The treatment is prescribed for a considerable number of patients despite the fact that literature and guidelines advice caution. Personal and non evidence-based opinions on this therapy are widespread while randomised clinical studies have thus far not been conducted.

2.2 Introduction

Home ultraviolet B (UVB) phototherapy was introduced in the late 1970s.[1-4] Since then it has been successfully used primarily for the treatment of psoriasis.[3-10] A number of dermatologists, however, have raised concerns in particular about its safety and effectiveness, as well as patient compliance with this form of therapy.[5;6;10-15] Surprisingly, very little research on home UVB phototherapy has been conducted to justify or dismiss these concerns. As such, the use of home UVB phototherapy for psoriasis remains debated in dermatology.

In the Netherlands too, varying opinions exist as to the advisability of prescribing home UVB phototherapy. In 2005, the Netherlands Society for Dermatology and Venereology published an official national guideline on the use of photo(chemo) therapy in patients with severe psoriasis, in which prescription of home UVB phototherapy is explicitly discouraged.[11;16] Many Dutch dermatologists, however, do prescribe home UVB phototherapy. Informal evidence indicates that two home care organisations are successfully providing equipment and supervision for about 1400 Dutch psoriasis patients annually (unpublished registry data from the home care organisations and one published magazine article).[9] Likewise, it has been estimated for the U.S.A. and Germany that respectively at least 5000 and 3000 home UV phototherapy machines (full body length panels) have been sold to date (unpublished sales figures from 4 manufacturers in Europe and 4 in the U.S.A.). It appears that home UVB phototherapy for psoriasis may be prescribed more often than is generally recognised. The opinions of dermatologists who use this therapy may diverge from the more cautionary messages encountered in the scarce literature on this subject. Despite the apparent contradiction between clinical practice and the general tenor of the literature, neither has been the subject of a systematic study. As such, it may be useful to compare the actual opinions of dermatologists on this treatment with those postulated in the literature. Therefore the aim of this study was to assess and compare the available publications and guidelines on home UVB phototherapy for psoriasis with the opinions and actual use of this therapy among dermatologists.

2.3 Methods

Literature and guidelines

The literature and guideline search, on the subject of home UV(B) phototherapy for psoriasis, was performed using PubMed/Medline, Embase, Cochrane, a web browser (Google), and cross-reference searches. The following search terms were used: phototherapy, home, home care, psoriasis, ultraviolet therapy, UV, UVB, treatment, guidelines, protocol, clinical protocols, and treatment protocol. Both single search terms and combinations of terms were used. In addition, the national dermatological societies of 25 countries were contacted by e-mail in order to inquire whether national guidelines on (home) phototherapy or on psoriasis were available.

Questionnaires

The Netherlands

All Dutch dermatologists (n=343) received a questionnaire concerning home UVB phototherapy for psoriasis. In order to achieve a high response rate, we developed a short one-page form with open questions. One question addressed the respondent's frequency of prescription of home UVB phototherapy (as a percentage of his/her total number of prescriptions of UVB phototherapy for psoriasis). Other questions related to the advantages and drawbacks of this therapy as perceived by the respondent. Where respondents indicated that they did prescribe home UVB phototherapy, we asked them to state their most important reasons for doing so. All questions concerned only total body home UVB phototherapy for patients with psoriasis, thus excluding UVA therapy, small or hand-held devices, and indications other than psoriasis.

Other countries

To discover the extent of home UVB phototherapy use for psoriasis in other countries, a comparable questionnaire was sent to a selection of dermatologists from around the world. For this purpose, the original Dutch questionnaire was translated into English. Note however, that we did not ask our foreign respondents to describe their own practice, but rather to estimate the prescription frequencies for their country and to give their country's view of home UVB phototherapy. A list of recipients was compiled using several sources: the European Society for PhotoDermatology (ESPD), the Photomedicine Society, several national dermatological societies, the American Academy of Dermatology (AAD), and the internet. Whenever possible,

we selected dermatologists specialised in psoriasis or in ultraviolet therapy. In total, questionnaires were posted to 142 dermatologists from 32 countries. The appendix presents the number of recipients and respondents per country.

Analysis

The results of the questions concerning the prescription rate of home UVB phototherapy are presented as percentages of the total number of UVB phototherapy prescriptions for psoriasis. The answers to the other open questions were recorded and coded. We used summary terms such as 'therapy-related advantages', 'dermatologists' objections', and 'convenience' to reflect the different categories of reported advantages, drawbacks and reasons for prescribing home UVB. Results are presented as percentages—that is, the number shown is equal to the percentage of the respondents mentioning this specific reason, advantage or drawback. Differences between the Netherlands and the other countries with regard to the response categories were estimated by calculating the differences in proportions with a 95% confidence interval (95% CI). To establish whether differences between the Netherlands and other countries can be accounted for by differences in experience, we calculated the differences between 'experienced' dermatologists and 'inexperienced' dermatologists for both groups. Experienced dermatologists were those prescribing home UVB (or reporting the use of home UVB in their country), and 'inexperienced' dermatologists were those not prescribing (or reporting) home UVB.

2.4 Results

Literature

The literature search revealed a total of 25 articles relating to home phototherapy, of which only 14 specifically concerned home UVB treatment for psoriasis. The most important features of these 14 publications are shown in table 1. Interestingly, only 7 of these articles describe patient-based research, of which only 2 compare two groups of patients. Neither were randomised studies.[8;15] Twelve publications mention drawbacks of home UVB phototherapy, and all but one report advantages. Drawbacks are mentioned more often in comments, reports and position papers, and less so in patient-based studies. Important objections include the lack of medical supervision, higher risks -including phototoxicity-, and uncontrolled use

Table 1 – Characteristics and outcome of studies on home UVB phototherapy for psoriasis

	Study and Therapy specifications					
Author, year	**Study type**	**Type of UV**	**N**	**Study group**	**N**	**Control group**
Cameron[8], 2002	Prospective study with historic controls	UVB (TL-01)	33	(a) 3x weekly, at home (n=23) (b) 3x weekly in hospital (n=10)	NR	Departmental audit data.
van Vloten[7], 1993	Prospective study	UVB (TL-01)	100	3-4x weekly, at home, by Home Care Organisations	-	-
Paul[15], 1983	Prospective study	UVB	20	3x weekly, in hospital, start Jan-March 1981, LISUP	20	3x weekly, in hospital, start Oct-Nov 1980, UVB
Jordan[4], 1981	Prospective study	UVB + tar	56	6-9x weekly, at home. Goeckerman regimen	-	-
Larkö[3], 1979	Prospective study	UVB (solarium)	28	7x weekly, at home	-	-
Feldman[6], 1996	Retrospective study	UVB	22	2-7x weekly, at home	-	-
Biella[29], 1985	Prevalence survey	UVB (solarium)	-	self-treatment	-	-
Matto[9], 2003	Magazine article, describing	UVB (TL-01)	-	-	-	-
Gerritsen[11], 2000	Review	UVB	-	-	-	-
Sarkany[12], 1999	Report on workshop Review	UVB	-	-	-	-
Prince[13], 1994	Comment	UVB	-	-	-	-
Lowe[5], 1992	Position paper	UVB	-	-	-	-
NPF[10], 1991	Position paper, survey	UVB	-	-	-	-
Abel[14], 1985	Position paper	UVB	-	-	-	-

Used abbreviations: NR = Not reported NA = Not applicable LISUP = Low-Intensity Selective UV Phototherapy MRA = Minimal Residual Activity

DRAWBACKS Code: A = Abuse by relatives, AM = Adequate maintenance of equipment necessary, HC = Higher Costs, HR = Higher attendant risks, ID = Inaccurate Dosimetry (also: higher cumulative doses), LSC = Loss of social contacts with healthcare professionals, ML = Medico-legal liability, MS = Medical supervision is crucial for treatment effect (also: lack of control by dermatologists), PT = Phototoxicity, SO = Suboptimality, UC = Unsupervised Continuation of irradiations after treatment course.

Therapy effect		Expressed opinions on home UVB phototherapy:		
Study group	**Control group**	**Drawbacks**	**Advantages**	**Eligibility-criteria#**
(a) 18/23 reached clearance or MRA in 22.5 exposures and 9.84 J cm^{-2} (b) 7/10 reached clearance or MRA in 18 exposures and 10.38 J cm^{-2}	median 18 exposures and 9.33 J cm^{-2} to reach clearance or MRA	ML	CE, LA, S, TS	Reliable, competent and compliant. Understand the therapy
PASI at start 4.8-41.9, PASI at end 0.0-4.8	-	LSC	DM, LA, TS	-
8/20 reached clearance, 5/20 improved	18/20 reached clearance, 1/20 improved	PT	CV, HF	-
51/56 reached clearance	-	-	CE, HF	Conscientious and motivated
20/28 reached clearance, 6/28 improved	-	-	LC, TS	-
NA *	-	AM, ID, UC	LC, GC	-
NA	-	MS	CV, TS	-
-	-	AM, MS	CV, LA, TS	Motivation and discipline. Able to perform self-treatment
-	-	A, HR, ID, ML, MS, PT, SO, UC	-	Intelligent enough to bear responsibility. Sufficient comprehension of therapy
-	-	AM, HR, ML, MS, PT, SO	DM	Understand and accept responsibility
-	-	HC	DM, LA, TS	
-	-	HR, ML, UC	DM, LC	Reliable and compliant. Willing to be examined regularly
-	-	ML, UC	CE, CV	-
-	-	ML, MS	CE, CV	Reliable, conscientious and motivated

ADVANTAGES Code: CE = Cost-effective, CV = convenient, DM = Demedicalisation (also: less sense of invalidism), GC = Good compliance, HF = Higher treatment frequency possible, LA = Less absenteeism (work/school), LC = Lower costs, S = Safe, TS = Time saving

Eligibility criteria: only criteria concerning the patient's personality

* This study reported use of home UVB equipment in the past 2 years, but reported SAPASI scores (Self Administered Psoriasis Area and Severity Index) at the time of the questionnaire.

of the equipment after the treatment period. Benefits related to time & travel (less absenteeism, time-saving) and related to convenience & demedicalisation are the most frequently mentioned advantages of home UVB. Potential benefits related to costs are also mentioned many times.
Of the additional 11 publications on home phototherapy, 5 investigated the use of commercial sunbeds.[17-21] Another 6 publications dealt with home phototherapy for diseases other than psoriasis.[1;2;22-25]

Guidelines

Despite a very extensive search, we found only one national guideline explicitly dealing with home UVB phototherapy. This guideline is the report of the British Photodermatology Group (BPG)'s 1996 workshop on home phototherapy.[12]
Several official national guidelines on psoriasis or phototherapy were found, but only four of these contained some information on home UVB phototherapy.[16;26-28]
From Germany we obtained a copy of a consensus-letter written on behalf of two German dermatological societies and the German psoriasis confederation on February 18, 1999.[29] This mutual statement concerns home UV phototherapy for patients with psoriasis and was addressed to the cooperation of German health insurance companies (not published, copy can be obtained from first author).
In general, all the guidelines are very reserved towards home UV phototherapy, and recommend restricting its use as well as a careful selection of patients.
Only 4 guidelines specify what they presume are the hazards of home UVB. Three of them suggest that the medical supervision is insufficient, that the treatment gives suboptimal results and has higher attendant risks, and mention medico-legal liability as a point of concern. A summary of the most important issues contained in these guidelines is displayed in table 2.

Questionnaires

Response

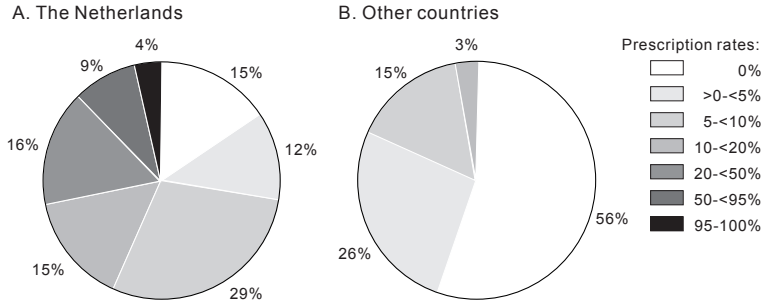
From September 9th 2003 through January 31st 2004, 255 Dutch dermatologists (74%) completed and returned the questionnaire. Of the 255 respondents, 19% were working in a University hospital, 77% in a non-university hospital, and 2% in private practice. Comparable percentages for the original population (n=343) were 23%, 72% and 3% respectively.
Regarding the worldwide survey, a total of 102 questionnaires (72%) were completed and returned between November 13th 2003 and March 9th 2004.

From each selected country at least one completed questionnaire was obtained (100% response for the countries).

Home UVB prescription rates

Of the 255 responding Dutch dermatologists, 38 (15%) never prescribed home UVB phototherapy for patients with psoriasis, and 211 (83%) prescribed this treatment to a variable extent. Six respondents (2%) did not prescribe UVB treatment at all. 244 Dutch respondents calculated their prescription rate of home UVB as a percentage of their total number of UVB prescriptions for psoriasis. Likewise, 98 of the 102 respondents from abroad estimated the home UVB prescription frequency for their country. A graphical representation of the distribution of these prescription rates is presented in figure 1. The median prescription rate of home UVB phototherapy in the Netherlands was 5% of all UVB treatments for psoriasis. Yet 28% (68/244) of the Dutch dermatologists prescribed home UVB for at least 20% of their UVB-treated psoriasis patients, and nearly 1 out of 8 Dutch dermatologists (12%, 30/244) prescribed home UVB in 50% or more of their cases. Nine Dutch dermatologists (4%, 9/244) prescribed home UVB phototherapy to 95-100% of their patients requiring UVB treatment. Concerning the other countries (figure 1b), the majority of the respondents (56%, 55/98) reported that home UVB phototherapy was not prescribed in their country at all. Another 18% (15/98) estimated that home UVB in their country is prescribed to 5% or more of the patients receiving UVB treatment. The maximum estimated prescription rate was 10% (n=3).

Figure 1 – Home UVB phototherapy prescription rates for psoriasis



The figure presents home UVB prescription rates in the Netherlands and in other countries. Dutch dermatologists estimated to what extent they prescribed home UVB phototherapy for their psoriasis patients requiring UVB. Dermatologists from other countries estimated the prescription rate for their country.

Table 2 – Characteristics of guidelines concerning home UVB phototherapy for psoriasis and advice given

Publication:		**Advice concerning home UVB treatment**
Country, type, year	**Subject**	
United Kingdom[12], Report on workshop BPG, 1999	Home phototherapy	… should be discouraged unless departments are prepared to invest time and effort to make home treatment as safe and effective as hospital treatment ... should be restricted to those with overwhelming difficulties in attending hospital therapy
The Netherlands[16], Guideline, 2003		… should be restricted to patients with overwhelming difficulties in attending hospital therapy.
Ireland[26], Guideline, 1997	Photo(chemo) therapy	… is not recommended as patient safety and optimisation of therapeutic regimens would not be possible
The U.S.A.[27], Guideline, 1994	Photo(chemo) therapy	… should be restricted mainly to patients who have difficulty in attending on-site therapy
The U.S.A.[28], Guideline, 1993	Psoriasis	… is inappropriate … should only be used with great caution under the direction of the patient's physician
Germany[29], Consensus-letter, 1999	Home UV phototherapy for psoriasis	1 Invariably, UV phototherapy under direct supervision of a dermatologist (i.e. in an outpatient setting, MK) remains preferable 2 Insurance companies should reimburse the costs of home UV phototherapy in exceptional cases like immobility, long travel distances, occupational reasons and being indispensable at home

Opinions

The different categories of reasons for, and advantages and drawbacks of prescribing home UVB phototherapy mentioned by both groups and their distribution (%) are displayed in table 3. The flowchart in figure 2 shows the different numbers of respondents for all items.

We found that the most important reasons to prescribe home UVB concerned 'time, travelling and obligations': 79.5% (163/205, Dutch respondents) versus 75.0% (33/44, respondents from other countries). Although these figures appear almost identical, a different distribution across the subcategories was observed. For 63.9% (131/205) of the Dutch dermatologists 'work/study/school' was the most important subcategory, but for dermatologists from other countries the main subcategory was 'long travel distance/long travel time' (63.6%, 28/44).

Expressed opinions home UVB phototherapy		
General drawbacks	**Medico-legal liability***	**Eligibility criteria**
HR, MS, PT, SO, UC	Yes	understand and accept the responsibility
AM, HR, ID, MS, PT, SO	Yes	1 motivated with sufficient comprehension of the therapy, 2 intelligent enough to bear responsibility, 3 willing to be regularly examined
AM, HR, SO	-	-
MS	-	1 intelligent, motivated and reliable 2 attend for regular evaluations
-	-	-
-	Yes	intellect and compliance

Used Abbreviations:

BPG = British Photodermatology Group

DRAWBACKS Code:

AM = Adequate maintenance of equipment necessary,

HR = Higher attendant risks,

ID = Inaccurate Dosimetry,

MS = Medical Supervision is crucial for treatment effect (also: lack of direct control by dermatologists),

PT = Phototoxicity,

SO = Suboptimality,

UC = Unsupervised Continuation of irradiations after treatment course

* Medico-legal liability was mentioned as a point of concern

Likewise, analysing the objection of 'poor/suboptimal service and equipment' (The Netherlands 34.9% vs. other countries 37.4%), we found that Dutch dermatologists ascribed this objection mainly to human error: 'poor service/ supervision/feedback' (30.1% vs. 17.6%), while foreign dermatologists saw more hazards in the equipment ('poor/inadequate dosimetry', 8.6% vs. 24.2%). When Dutch dermatologists mentioned some issues significantly more or less often than their colleagues from other countries, the difference is shown with a 95% CI. For instance, non-Dutch dermatologists assumed higher risks of complications and higher costs of treatment, respectively 22.2% and 19.5% more frequently than did their Dutch colleagues.

Table 3 – Reasons for prescribing home UVB phototherapy, perceived advantages and drawbacks

Response categories	The Netherlands %	Other countries %	Differences (95% CI)
Reasons for prescribing	**(N=205)**	**(N=44)**	
Convenience	30.2	20.5	
Time, travelling and obligations - Long travel-distances/long travel-time - Work, study, school - Home bound / no transportation - Time-saving and saving travel costs	79.5 23.9 63.9 22.0 9.8	75.0 63.6 25.0 11.4 4.5	 -39.7 (-24.7 to -54.8) 38.9 (22.8 to 55.0)
Therapy-related reasons	3.9	2.3	
Dermatologists' reasons	8.3	0.0	8.3 (0.1 to 16.5)
Other reasons	16.6	27.3	
Advantages	**(N=140)**	**(N=72)**	
Convenience	68.6	54.2	14.4 (0.7 to 28.1)
Time and travelling - Less travelling (distances / time) - Less absenteeism (work/school/study) - Time-saving and saving travel costs	41.4 17.1 17.1 17.9	43.1 29.2 8.3 17.1	 -12.0 (-23.6 to -0.4)
Therapy-related advantages - Good effectiveness - Good service & supervision / good care - High patient compliance	28.6 17.1 13.6 4.3	11.1 8.3 0.0 4.2	17.5 (5.6 to 29.4) 13.6 (5.5 to 21.7)
Other advantages	11.4	18.1	
Drawbacks	**(N=186)**	**(N=91)**	
Therapy-related drawbacks - Poor effectiveness - Poor/suboptimal service & equipment - No confidence in capability of patients	55.4 9.1 34.9 30.1	62.6 8.8 37.4 34.1	
Dermatologists' objections - (Fear of) losing control - Loss of earnings, labour-intensive	54.3 50.5 8.1	44.0 41.8 6.6	
Time-related drawbacks	11.3	0.0	11.3 (4.7 to 17.9)
Higher risks	10.8	33.0	-22.2 (-31.9 to -12.6)
Financial drawbacks	12.4	31.9	-19.5 (-29.3 to -9.7)
Other drawbacks	8.1	14.3	

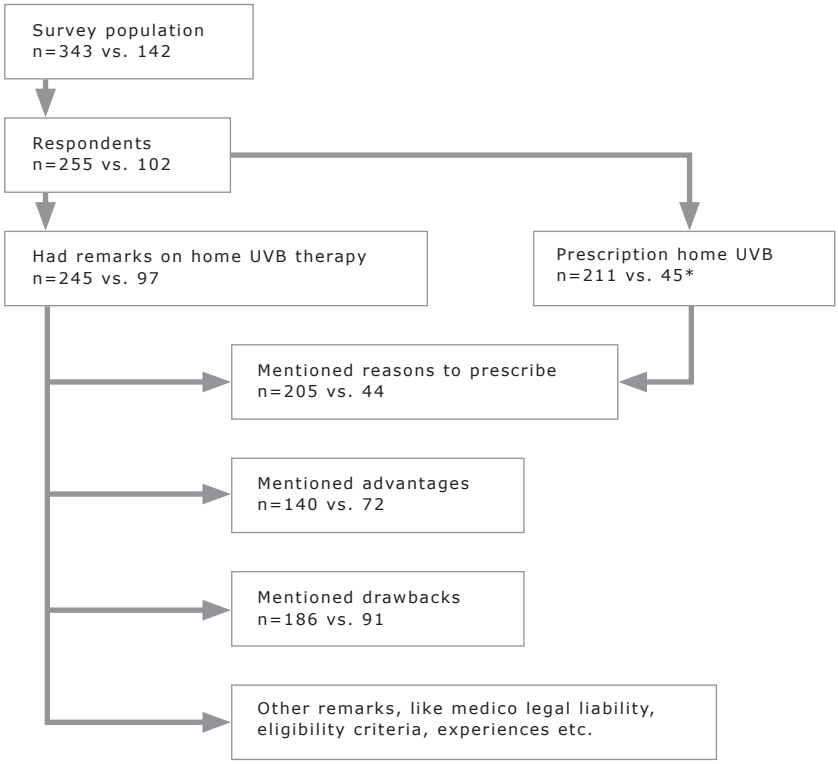
The different response categories and subcategories are shown. The numbers shown are percentages* of respondents who gave an answer in (one of) the categories. Significant differences between the Netherlands

	Explanations & Examples
	Convenience, flexibility, freedom, demedicalisation
	- …… to the clinic - Difficult or impossible to take time off. - Immobility, also because of small children/family etc. -
	Good effectiveness, good service, high patient compliance, higher treatment frequency possible
	No UVB equipment available, not enough personnel
	e.g. patient's request
	Convenience, flexibility, freedom, demedicalisation
	- Including: higher treatment frequency possible - -
	e.g. cheaper than therapy in the clinic, less work for personnel in the clinic
	- - Poor service/supervision/feedback, poor or inaccurate dosimetry due to equipment - Incorrect use (underdosage, overdosage, too frequent, etc), poor patient compliance, unsupervised continuation of irradiations after the treatment
	- No control of therapy and (side-)effects, loss of follow-up, no influence on quality of UVB devices - also: difficult to arrange, a lot of paperwork
	Waiting times for home UVB equipment, delay before a certain effect is accomplished
	e.g. burns, side effects, carcinogenesis, photo-aging
	Home UVB more expensive for patients, for society and/or insurance companies than UVB in the clinic
	e.g. lack of space at home, abuse of UVB equipment by relatives

and the other countries are shown with a 95% confidence interval (95% CI)

* Some respondents gave more than one comment, so percentages may add up to more than 100%

Figure 2 – Flowchart



Numbers of respondents from the Netherlands versus respondents from other countries.

* The Netherlands: number of respondent prescribing home UVB phototherapy

Other countries: number of respondents reporting the use of home UVB treatment in their country

Of all the statistically significant differences between both groups, only 3 are possibly attributable to differences in experience: the advantage of 'convenience', 'therapy-related advantages', and the fear of 'higher risks'. The first two were mentioned significantly more frequently by experienced Dutch dermatologists than by their inexperienced Dutch colleagues, while the fear of higher risks was mentioned less often by experienced Dutch dermatologists. Within the group of respondents from other countries, no statistically significant differences were shown between dermatologists reporting the use of home UVB in their country and those reporting no use of this therapy.

Eligibility criteria

Some respondents indicated that, when prescribing home UVB, they impose some eligibility criteria upon their patients, such as intelligence, compliance, motivation, and experience. Of the Dutch dermatologists, 18.0% (44/245) reported using such eligibility criteria (95% CI=13.2-22.8), compared to 14.4% (14/97) of the respondents from other countries (95% CI=7.4-21.4).

Medico-legal liability

Since the medico-legal liability of home UVB phototherapy was mentioned both as a possible drawback as well as a question posed to the investigator, this aspect was analysed separately. Only 22/245 Dutch dermatologists (9.0%, 95% CI=5.4-12.6), and 14/97 respondents from other countries (14.4 %, 95% CI=7.4-21.4) expressed concerns about this aspect.

2.5 Discussion

A discrepancy exists between the actual use of home UVB treatment and the opinions found in the literature and guidelines. Home UVB is prescribed for a considerable number of patients while the literature and guidelines suggest that it should be used with caution. In reality, very little is known about this therapy. No randomised research has yet been conducted, and only 2 observational studies comparing 2 groups of patients have been performed.[8] Nevertheless, home UVB is currently being prescribed in appreciable frequencies and personal and non-evidence based opinions on this therapy are widespread.

Strengths and weaknesses of the study

In this study of home UVB phototherapy we included and analysed all available literature on the topic and every relevant guideline found or brought to our attention. Therefore, to the best of our knowledge, the review of literature and guidelines is complete. The questionnaire survey allowed for an exploration of the actual use of home UVB phototherapy for psoriasis as well as the personal opinions of dermatologists. Neither had been investigated previously. The response rates to the questionnaire were high, 74% and 72% respectively. On the other hand, the questionnaire was not standardised and validated. Also, categorising the answers to the open questions left room for interpretation. Another point of consideration is that the questionnaire was sent to all Dutch dermatologists (343),

but to only a relatively small selection of dermatologists from other countries (142). Consequently, dermatologists from other countries were asked to give answers concerning their country as a whole, while the answers given by the Dutch dermatologists reflect their personal situation and opinion. It is not unlikely that some of the differences shown between both groups of dermatologists were caused by this difference in selection.

Literature and guidelines

All guidelines and the majority of the literature are reserved about the use of home UVB phototherapy. Interestingly, the non patient-based publications[5;9-14] report far more drawbacks of home UVB than do the patient-based studies.[3;4;6-8;15;30] For both the non patient-based publications and the guidelines we conclude that the expressed opinions are largely negative and mostly repeat the statements made in earlier publications. To a large extent these are personal views based on opinion and belief rather than on evidence from patient-based research. The patient-based studies seem to generate more positive conclusions, mentioning more advantages than drawbacks. Still, these authors as well offer mostly personal opinions rather than evidence-based conclusions.

Individual opinions

Almost all of the objections raised by our respondents are related to fear (poor dosimetry, lack of confidence in patients, fear of losing control, fear of more and/or more serious complications etc.), while only a few objections have been verified through experience or medical evidence. This is consistent with the results from our study of the literature and guidelines. The opinions on home UVB reported by individual dermatologists however only partially agreed with those cited in the literature and guidelines. For instance, financial advantages were frequently mentioned in the literature,[3-6;8;10;14] but were reported by only a minority of our respondents. On the other hand, therapy-related benefits were quite frequently mentioned by the individual respondents (mainly Dutch), but not at all in the literature. Also, the presumed higher risks of home UVB were an important objection in both the literature and the guidelines,[5;11;12;15;16;26] but only one out of 10 Dutch dermatologists considered home UVB to carry a higher risk of complications. While the first of these three differences (the question of costs) may be explained by the somewhat wider perspective taken in the literature compared to individual opinions, the other two differences (therapy-related

benefits, higher risks) may be attributed to the relatively broad experience of present-day (Dutch) dermatologists compared to the authors of most of the publications at the time of publication.
Last but not least, the question of medico-legal liability regarding home UVB phototherapy was an important concern expressed in almost half of the literature and guidelines,[5;8;10-12;14;16;29] but only a minority of the respondents mentioned it. We conclude that whereas the medico-legal liability with regard to home UVB phototherapy seems important in theory, in practice it is not perceived as such.

Actual use

In spite of the differing opinions, the results of the questionnaires showed that a considerable number of dermatologists prescribe home UVB phototherapy, especially in the Netherlands. This is probably due to the easily accessible system in the Netherlands: home UVB phototherapy equipment can, on prescription from a dermatologist, be rented from home care companies. In addition to the high prescription rates that we found, four previous studies revealed that 25-50% of the psoriasis patients apply self-treatment with commercial sunbeds.[19;20;30;31] Based on these facts we conclude that home (UVB) phototherapy is an important therapy for many psoriasis patients, despite the more guarded opinions of professionals.

Conclusion

Despite the scarcity of literature and guidelines on home UVB phototherapy, personal and non evidence-based opinions on this therapy are widespread. Moreover, a considerable proportion of (particularly Dutch) dermatologists prescribe home UVB phototherapy to many of their patients. According to the official opinion, however, home UVB phototherapy should still be used with caution. Home UVB phototherapy remains a contentious and debated treatment, especially with regard to issues like effectiveness, side effects, quality of life and cost-effectiveness. Only randomised research into the benefits and drawbacks of home UVB phototherapy as compared to UVB phototherapy administered in an outpatient setting will resolve the issue.

Acknowledgements

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Appendix

Number of dermatologists addressed and number responding per country.

Country (n recipients/n respondents):

Argentina (5/1), Australia (4/2), Austria (3/3), Belgium (7/4), Canada (5/4), China (2/1), the Czech Republic (2/2), Denmark (4/2), Egypt (3/3), Finland (3/2), France (12/10), Germany (10/6), Greece (3/1), Hungary (6/1), Iceland (3/2), Ireland (3/3), Israel (4/4), Italy (7/5), Japan (3/2), Korea (3/2), The Netherlands (343/255), New Zealand (3/3), Norway (3/2), Philippines (3/1), Portugal (3/2), South Africa (3/2), Spain (6/5), Sweden (4/4), Switzerland (3/3), Thailand (3/2), Turkey (3/2), United Kingdom (6/6), the U.S.A. (10/10)

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Design of a randomised clinical trial

UVB phototherapy in an outpatient setting or at home: a pragmatic randomised single blind trial designed to settle the discussion (PLUTO study)

Mayke BG Koek
Erik Buskens
Paul HA Steegmans
Huib van Weelden
Carla AFM Bruijnzeel-Koomen
Vigfús Sigurdsson

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3.1 Abstract

Background Home ultraviolet B (UVB) treatment is a much-debated treatment, especially with regard to effectiveness, safety and side effects. It is, however, increasingly being prescribed, especially in the Netherlands. Despite ongoing discussions, no randomised research has been performed, and only two studies actually compare two groups of patients. Thus, firm evidence to support or discourage the use of home UVB phototherapy has not yet been obtained. The goal of the present study, the PLUTO study (Dutch acronym for "national trial on home UVB phototherapy for psoriasis"), is to provide this evidence.

Methods We designed a pragmatic randomised single blind multicentre trial comparing home UVB treatment with UVB phototherapy in a hospital outpatient department. This trial is designed to evaluate the effectiveness, quality of life and cost-effectiveness of both interventions in a setting reflecting routine practice. In total 196 patients with psoriasis who were clinically eligible for UVB phototherapy were included. Normally 85% of the patients treated with UVB show a relevant clinical response. With a power of 80% and a 0.05 significance level it will be possible to detect a reduction in effectiveness of 15%. Effectiveness will be determined by calculating differences in the Psoriasis Area and Severity Index (PASI) and the Self Administered PASI (SAPASI) scores. Quality of life is measured using several validated generic questionnaires and a disease-specific questionnaire. Other outcome measures include costs, side effects, dosimetry, concomitant use of medication and patient satisfaction. Patients are followed throughout the therapy and for 12 months thereafter. The study is no longer recruiting patients.

Discussion In the field of home UVB phototherapy this trial is the first randomised parallel group study. As such, this trial addresses the weaknesses encountered in previous studies. The pragmatic design ensures that the results can be well generalised to the target population. Because in addition to effectiveness, aspects such as quality of life and cost-effectiveness are also taken into consideration, this study will produce valuable evidence to either support or discourage prescription of home UVB phototherapy.

Trial registration Current controlled trials/Nederlands Trialregister: ISRCTN83025173. ClinicalTrials.gov: NCT00150930.

3.2 Background

About 2% to 4% of the Dutch population suffer from psoriasis. Psoriasis is a chronic recurrent skin disorder characterised by erythematosquamous lesions (plaques). Usually the affected areas are few, but occasionally the disease is more generalised. Psoriasis can be treated topically by application of creams and ointments, for instance corticosteroids and vitamin D3. For most patients topical therapy will suffice, but for some patients the area involved is so extensive that local treatment is not feasible. In other cases the skin lesions no longer respond to topical treatment. In that case the dermatologist may start irradiation with ultraviolet (UV) light or prescribe systemic medication. UV irradiation of the skin can be performed with different types of UV light: e.g. UVA, broadband UVB, or narrowband UVB. UVB irradiation is usually prescribed as a single therapy. However, adjuvant use of topical therapy may be continued.

UVB therapy has considerable consequences for the patient because it is nearly always carried out in a hospital outpatient department. The UVB irradiation itself normally takes only a few minutes, but to receive the irradiation patients have to travel to the outpatient department during working hours two to three times a week. In general it is a relatively time-consuming treatment. For hospital personnel as well, this mode of therapy demands a considerable investment of time. They have to determine the dosage, set the machine to the proper dosage, and fill out the medical records for each patient visit.

To overcome the drawbacks of UVB treatment in the outpatient department, home UVB phototherapy was introduced over 25 years ago.[1-4] Ever since, however, the safety and effectiveness of home UVB have been the subject of debate.[5-13] Despite all discussion, increasing numbers of dermatologists seem to be prescribing home UVB phototherapy to their patients.

In an earlier study we listed all known publications and studies on home UVB phototherapy, and conducted a survey among dermatologists.[14] We found that in the Netherlands home UVB is currently prescribed to approximately 5% of the UVB-treated patients, with some dermatologists prescribing it in 100% of the cases. We also demonstrated that there is no firm evidence that would either support or dissuade from prescribing home UVB phototherapy. Glaringly absent is any randomised research in this area. This lack of research has resulted in ongoing discussions and the dissemination of personal, non-evidence based opinions, especially with regard to issues like effectiveness, side effects and cost.[14]

Thus, in general, home UVB phototherapy remains a debated treatment. We concluded that only randomised research on home UVB phototherapy as compared to UVB treatment in an outpatient setting could resolve the issue.[14] In this paper, we describe a randomised pragmatic trial that we are currently conducting, a national trial on home UVB phototherapy for psoriasis. The Dutch acronym for this trial is PLUTO (Psoriasis: Landelijk UVB Thuisbelichtings Onderzoek). The trial is designed to evaluate the impact of home UVB phototherapy versus conventional outpatient UVB phototherapy on effectiveness, quality of life and cost-effectiveness. The focus is on narrowband UVB treatment (TL-01 lamps). The study tests the hypothesis that home UVB phototherapy is as effective as outpatient UVB phototherapy. We further expect a better quality of life when patients are treated at home, and we hypothesise that home treatment will have similar or reduced total costs. This article presents the design of this trial.

3.3 Methods

Objective

The aim of this study is to compare home UVB (TL-01) phototherapy with the current outpatient UVB (TL-01) phototherapy for patients with psoriasis. This objective was specified by the following research questions. Compared to UVB phototherapy in an outpatient setting:

1 Is home UVB phototherapy for patients with psoriasis equally effective?
2 Does home UVB phototherapy yield a better quality of life?
3 Are costs for home UVB phototherapy higher, lower or similar?
4 Is home UVB phototherapy cost-effective?

Design

We conducted a pragmatic randomised parallel group single blind multicentre trial among psoriasis patients eligible for narrowband UVB (TL-01) phototherapy. Patients were randomly allocated to two groups, thus obtaining two treatment groups of equivalent prognosis. One group was given home UVB phototherapy and the other UVB phototherapy in the outpatient department of the participating hospitals.

The design was chosen to be 'pragmatic' in order to compare the two treatments under the conditions in which they would be applied in daily practice.[15] Accordingly,

in our pragmatic trial we randomised the patients into two treatment groups, but we did not impose a prespecified treatment regimen on the participants. Instead, we urged dermatologists to carry out the assigned UVB treatments as they would normally, and thus to act in accordance with their own views. Consequently, all of the implicit differences in the two treatments were compared, including factors such as frequency of irradiations, dosage, compliance, concomitant medication, support and equipment. We did not control for these and other possible differences relating to the treatment, because they cannot be controlled for in a real life situation.
The locations of the two treatments (at home versus in the outpatient department) of course made blinding of the participants impossible. Because of the pragmatic design of the study it was not desirable to blind the dermatologist. We, however, arranged for the extent and severity of the psoriasis to be assessed by an independent research nurse blinded to treatment arm.

Study population

Psoriasis patients who were clinically eligible for narrowband UVB (TL-01) phototherapy ànd who had had this therapy prescribed by their own dermatologist were invited to participate in the study. All inclusion and exclusion criteria are displayed in table 1.
The main selection criterion of being 'clinically eligible for narrowband UVB treatment' was purely pragmatic and was left to the discretion of the participating dermatologist. Dermatologists were, however, explicitly discouraged from increasing the number of their prescriptions on behalf of the study. No financial benefit or other compensation was offered to participating dermatologists for their efforts; this to avoid any conflict of interest and to include only those patients who would otherwise have received narrowband UVB treatment. Likewise, the patients also received no material compensation for their participation in the study.

Sample size

The sample size could not be calculated on the basis of presumed differences in effectiveness as there is no clear data available on the possible differences in treatment effects. Based on the data available from a 1993 pilot study[16] and recent experience with home UVB phototherapy, however, we in fact expected the effectiveness of both therapies to be similar. The sample size was therefore calculated in accordance with a negative trial approach.[17] We considered a 50%

Table 1 – Eligibility criteria

Inclusion criteria:
1 Guttate or plaque psoriasis, clinically eligible for narrowband UVB (TL-01) phototherapy;
2 Willing to undergo treatment according to randomisation.
Exclusion criteria:
1 No informed consent: – age below 18 years; – not willing to accept one of the two treatments offered.
2 Practical reasons: – not able to receive one of the two treatments offered (e.g. lack of space at home / living too far from hospital etc.); – analphabetism (unable to read the patient information and the questionnaires, unable to provide written answers and written informed consent); – lack of command of the Dutch language; – not in possession of a telephone.
3 Expected non-compliance: – lack of understanding of what the study / treatment is about, and its potential consequences.
4 Medical contraindications: – Malignancy of the skin in the past / at present; – known UVB-allergy or chronic polymorphic photodermatosis; – use (at time of inclusion) of medication with known phototoxic or photoallergic properties; – use (at time of inclusion) of systemic antipsoriatic medication (ciclosporin, methotrexate, neotigason, fumaric acid); – history of exposure to ionising radiation.

Study participants were subject to the inclusion and exclusion criteria mentioned above.

or greater improvement in the psoriasis severity from baseline to be a relevant clinical response. A systematic review by Spuls et al. indicates that approximately 85% of the patients treated with UVB show at least a 50% improvement in their psoriasis.[18] Thus, with N=90 per treatment group and at $\alpha=0.05$ and $\beta=0.20$ (power 80%), we would be able to show a difference in effectiveness of 15% or more—that is, a reduction in effectiveness from 85% to 70% or less should be distinguishable. To allow for missing data and losses to follow-up (i.e. withdrawals, incomplete case register forms) we aimed at 100 patients per group, 200 in total. To obtain accurate estimates of the cumulative costs of UVB treatment a consecutive sample of 100 patients (50 per group) was considered to be sufficient, because little variation was expected in treatment duration, number of UVB irradiations, and use of concomitant medication.

Recruitment

Hospitals

We planned to include two hundred patients in approximately 2 years' time, starting October 2002. To achieve this, several hospitals were invited to join the study. Initially five university hospitals and one closely related non-university hospital agreed to participate. Later on, when inclusion of patients fell short of expectations, another eight hospitals were recruited from the same districts or nearby. In total 14 hospitals took part in the trial; 5 university hospitals and 9 non-university hospitals.

Patients

When the dermatologists of the collaborating hospitals prescribed UVB phototherapy to a patient, they checked eligibility for the trial using the list of inclusion and exclusion criteria displayed in table 1. If all criteria were met, patients were informed about the possibility to participate. If the patient was interested, he/she received written information to take home. The same day the central co-ordination centre (UMC Utrecht) was provided with the name and phone number of the patient. After 1-2 days the investigators at the central co-ordination centre contacted the patient by telephone and provided additional information. During this conversation the principle of randomisation (no choice of treatment) was explained at length, and eligibility criteria were checked again. If after reading and hearing the information and being allowed to ask additional questions patients were still interested in participating, a visit for inclusion and informed consent was scheduled as soon as possible. Patients not included in the trial were allowed to start their UVB therapy of choice without any further delay.

Randomisation procedure

Every patient eligible for UVB phototherapy who was willing to participate in the study was registered at the central co-ordination centre. After providing informed consent and registration of baseline data a randomisation number corresponding with either home or outpatient phototherapy was drawn from a computer-generated list. Randomisation took place using stratified randomisation, in particular the minimisation method described by Pocock.[19] This method assigned the two treatments taking into account the recruiting hospital and possible previous experiences with UV phototherapy. After randomisation, both the patient and the dermatologist were informed of the assigned treatment, and this treatment was started according to standard procedures.

UVB therapy and equipment

In the outpatient department

Patients randomised to the group treated in the outpatient department received the UVB treatment in their own hospital. The type of irradiation was restricted to narrowband UVB (TL-01 tubes).[20] All hospitals used their own treatment schedules and their own (full circle) cabins. Some types of cabins had UV indicators measuring irradiation intensity (mW/cm^2); others did not and measured only treatment time. For cabins with intensity indicators, treatment schedules were formulated in dosage (J/cm^2). For cabins without intensity indicators, treatments were prescribed in units of time (seconds). Neither equipment nor schedules were modified for the trial. The frequency of irradiation was 2-3 times a week, depending on the hospital.

At home

When patients were assigned to have home UVB phototherapy, the investigator placed an order with one of the two home care organisations that provide the vast majority of home UV phototherapy in the Netherlands.[14] Orders were divided equally between the two organisations, taking into account equal distributions per hospital and the preferences of the patient's insurance company (reimbursement). The UVB treatment was administered in the patient's home, using equipment provided by one of the home care organisations. The home phototherapy units used were Waldmann UV-100 units with TL-01 lamps. This device comprises a semi-circular arrangement of lamps. These units do not have an irradiation intensity indicator; therefore treatments were prescribed in units of time.
The patients were instructed and supervised in the use of the equipment by the nursing staff of the home care organisations. The treatment schedules were the schedules normally used by those organisations. Neither equipment nor schedules were modified for the trial. The frequency of irradiation was at least 3-4 times a week (i.e. once every 2 days, sometimes starting daily).

In general

In all cases the initial treatment plan was narrowband UVB phototherapy according to randomisation. No prespecified treatment regimen was imposed on the participants and adjuvant use of topical therapy was allowed to continue throughout the trial. No other additional treatments or changes to the original treatment plan were intended. However, in order to compare the two UVB treatments under practical conditions and to reflect clinical reality, alterations to the initial treatment plan were allowed if the dermatologist decided they

were necessary. As such, all treatment changes originating after inclusion and randomisation were permitted. For instance, starting any type of medication after inclusion, even systemic medication, was not considered a reason for exclusion if the dermatologist considered this treatment change necessary. Also, temporarily starting phototherapy in an outpatient setting while waiting for placement of a home phototherapy unit was allowed.

Outcome assessment

To answer the separate research questions, several outcome assessments had to be performed during the trial. The majority of the outcomes were measured using questionnaires or were assessed by an independent, blinded research nurse.

Effectiveness

We assessed the effectiveness of both treatments using the Psoriasis Area and Severity Index (PASI)[21] and the Self Administered PASI (SAPASI).[22] Both indices combine the severity of the psoriatic lesions with the area of psoriatic involvement. Their scores vary from 0.0 (no lesions at all) to 72.0 (complete erythroderma of the severest possible degree).[21] An independent and blinded research nurse administered the PASI during several patient visits to the outpatient department. The SAPASI was easier to collect using a questionnaire and was used as an equivalent of the PASI as well as an indicator of the patient's own impression of the extent of the psoriasis lesions.[22;23] Both the PASI and the SAPASI were assessed for the whole body, including the lower legs and the scalp. We also determined skin type according to Fitzpatrick's classification of skin phototypes[24;25] and collected data on concomitant use of medication, side effects, demographics and past medical history.

Dosimetry

We routinely measured the light intensity (J/cm^2) of all UVB equipment from the hospitals with a small portable Waldmann UV meter, type 585 100 (Villingen, Schwenningen, Germany), referred to as meter A. If the cabin had an irradiation intensity indicator, we compared its reading with our own measurements. To collect information about calculated treatment doses (mW/cm^2), we made copies of the treatment charts of the participants treated in the outpatient departments.
The home care organisations measured the light intensity of every unit before the first irradiation and after the last irradiation, using their own small Waldmann UV meters, all type 585 100, referred to as meters B. At the end of the trial we collected these measurements and compared their meters (B) with our

Table 2 – Calculation of standardised cumulative doses

Situation	Treatment location	UVB equipment	Treatment schedule	Cumulative Dose (CD)	Standardisation factor F
1	In the hospital	With intensity indicator	in J/cm²	$CD = CD_h \times F$	$F = \frac{I_A}{I_h} \times \frac{I_{sr}}{I_{cA}}$
2	In the hospital	Without intensity indicator	in time (seconds)	$CD = CTT \times I_A \times F$	$F = \frac{I_{sr}}{I_{cA}}$
3	At home	Without intensity indicator	in time (seconds)	$CD = CTT \times \frac{I_{B1} + I_{B2}}{2} \times F$	$F = \frac{I_{cA}}{I_{cB}} \times \frac{I_{sr}}{I_{cA}}$

CD = Cumulative Dose (J/cm²) standardised for the study

CD_h = Cumulative Dose (J/cm²) as calculated by the hospital (retrieved from treatment chart)

CTT = Cumulative Treatment Time (s) as retrieved from the diary and/or treatment chart

F = correction factor for standardisation

Measurements on location:

I_A = Intensity (mW/cm²) measured by the investigators for each hospital UVB unit with portable intensity meter A

I_h = Intensity (mW/cm²) as simultaneously measured by the hospitals' UVB unit irradiation intensity indicator

I_{B1} = Intensity (mW/cm²) measured by the home care organisations before first treatment, using their meters (B)

I_{B2} = Intensity (mW/cm²) measured by the home care organisations after last treatment, using their meters (B)

Measurements during calibration:

I_{cA} = Intensity (mW/cm²) as measured during calibration by the investigators' portable intensity meter A

I_{cB} = Intensity (mW/cm²) as measured during calibration by the intensity meters (B) of the home care organisations

I_{sr} = Intensity (mW/cm²) as measured during calibration with the High Accuracy Spectroradiometer type OL 752

own Waldmann UV-meter (A), calibrated with the High Accuracy UV-Visible Spectroradiometer, type OL 752 (Orlando, Florida, U.S.A.).
Both groups of participants kept a record of their treatment times in their diary.
For all patients we calculated standardised cumulative doses using the intensity measurements together with the individual treatment charts and/or diaries.
The way cumulative doses were standardised in this trial is described in table 2.

Quality of life (QoL)

To assess quality of life we used one disease-specific questionnaire and several universal questionnaires. The standard questionnaires that were used were:

- Psoriasis Disability Index (PDI)[26;27]
- Short Form-36 (SF-36),[28;29] and
- EuroQol (EQ-5D)[30;31]

The PDI is a short questionnaire consisting of 15 questions regarding disability due to psoriasis. Answers are recorded on a seven point linear scale with 1 indicating no disability and 7 indicating maximum disability. Therefore the maximum potential PDI score is 105, with a minimum of 15.[27]

One of the generic QoL questionnaires used in the study is the SF-36, a 36-item questionnaire yielding a profile of 8 dimensions. All dimensions range in score from 0 to 100, with higher scores indicating a higher level of health status. By adding weighted combinations, the 8 scales can be combined into a physical and a mental component summary score.

The EQ-5D is also a generic quality of life questionnaire. It was developed to assess the impact of a disease in terms of multi-attribute value judgements yielding one overall value judgement, a so-called utility score ranging between -0.594 (the pits) and 1 (optimal health).[30;31] When utility scores are plotted against time, the Area Under the Curve (AUC) reflects the Quality Adjusted Life time usually expressed in Years (QALYs). Thus QALYs will be calculated as follows: utility scores from two time points will be linearly interpolated (i.e. summed and divided by two). This outcome will be multiplied by the time difference. This procedure will be repeated for all parts of the curve; the outcomes of all parts of the curve will be summed and ultimately yield an estimate of the entire AUC. In this way QALYs will be calculated for all patients, and a mean and standard error of the mean (SEM) will be determined.

Besides these standard questionnaires, we designed a brief 'Burden of Treatment' (BoT) questionnaire with 4 questions on the perceived burden of the UVB treatment (especially the specific burden of the treatment method and the burden of the time lost to treatment), and we developed a questionnaire on patient satisfaction. The patient satisfaction questionnaire collected information about:

- waiting times,
- perceived improvement of the psoriasis lesions,
- satisfaction with the treatment as a whole,
- satisfaction with the final treatment result,
- satisfaction with the rate of improvement,
- satisfaction with the nurses' supervision,
- perceived extent of side effects,
- perceived safety of the treatment,
- perceived advantages and drawbacks of both modes of therapy, and
- preferences with regard to future UVB treatment, if necessary (home UVB phototherapy versus UVB treatment in the hospital).

Costs

Estimation of costs will be based partially on the actual cost of the resources used, for instance the rental price of home UVB light panels, the cost of using hospital equipment, and travel expenses among others. Some indirect costs -such as the loss of work time due to decreased efficiency or absenteeism- will be assessed using the 'Health and Labour Questionnaire',[32] a general introductory questionnaire and the previously mentioned diary. These two questionnaires will supply information on time lost or expenses incurred for the treatment of the psoriasis, for instance the cost of transportation to a dermatologist or general practitioner. The diary on the other hand provides information on the frequency of these types of expenses during the treatment period. From the patients' pharmacists we will obtain data on the use of medications and their prices. The friction cost method[33] will be applied to assess the losses to society due to sick leave.

Cost-effectiveness

A direct comparison will be made between the effectiveness of the two therapeutic modalities and their associated cost. Incremental cost per additional patient treated successfully and costs per QALY gained will be estimated. Cost-effectiveness will be calculated at the end of phototherapy and for a time horizon of 12 (11-13) months after inclusion. The quality of life (QoL) questionnaires were no longer administered after cessation of irradiation. Based on the association between clinical symptoms and QoL, the impact in terms of QoL for the remaining follow-up—that is, up to 12 months, will be extrapolated using regression models. Subsequently, cost per QALY can be calculated. In case the difference in effectiveness is less than 15%, we will consider this as equal effectiveness and will limit the economic evaluation to a cost minimisation analysis.

Measurement planning

Outcome measurement was planned according to time points specified in the timetable in figure 1. Briefly, the procedure was as follows: When patients were willing to participate, we arranged a visit with an independent research nurse. During this visit, patients signed a consent form, baseline data were recorded and instructions were given on the use of the diary and questionnaires. Immediately after this first visit, patients were randomised using the baseline data (information on the recruiting hospital and any previous experience of the patient with UV therapy were used to determine the randomisation strata). Both the patient and the attending dermatologist were informed about the type of treatment

Figure 1 – Timetable

	Baseline (inclusion, n=196)	Therapy (n=196)			Follow-up (FU) (n=105)[c]					
		Start of therapy	23 irradiations[a]	End of therapy[b]	2-month FU	4-month FU	6-month FU	8-month FU	10-month FU	12-month FU
Visits to research nurse	visit 1		visit 2	visit 3						
t=	0	1	2	3	4	5	6	7	8	9
Introductory questionnaire	x									
Skin type	x									
SAPASI	x	x	x	x	x	x	x	x	x	x
PASI	x		x	x						
PDI	x		x	x						
EQ-5D	x		x	x						
SF-36	x		x	x						
Health and Labour	x		x	x						
Medication	x		x	x						x
Burden of Treatment			x	x						
Patient Satisfaction				x						
Follow-up information					x	x	x	x	x	x
Dosimetry –> treatment chart	x	x	continuous	x						
Diary: Side effects	x	x	continuous	x						
Diary: Treatment times	x	x	continuous	x						

Schematic representation of successive time points for data collection, reported for all outcome measures and questionnaires.

a 23 irradiations: outcome measurement was planned at approximately 23 irradiations, with a minimum of 20 and a maximum of 26 irradiations.

b End of therapy: measurement was planned at the end of the treatment. When more than 46 irradiations were needed, measurement was planned at 46 irradiations.

c Follow-up: Starting at the end of the therapy (or at the 46th irradiation, see b), follow-up measurements were planned bimonthly for up to 1 year after the last irradiation.

assigned, and the treatment was started accordingly. When (sometimes after a waiting period) the therapy was started, the patients did a SAPASI-assessment and began using the study diary. At approximately 23 (20-26) UVB treatments ànd at the end of phototherapy (or 46 treatments) the patients received a series of questionnaires at home. Visits to the previously mentioned research nurse were scheduled for the same time points. Throughout the whole trial, the independent research nurse was not informed about the randomisation results and therefore remained blinded.

For all UVB therapies lasting longer than 46 treatments, a cut-off point of maximally 46 treatments was used to establish effectiveness. The choice of 46 as the maximum number of treatments was derived from unpublished data from the home care organisations about the treatment duration of their patients.

At the end of the therapy (or 46 treatments), 105 patients were followed for 12 more months to monitor long term effectiveness and cost. The patients received a short questionnaire at home every 2 months and returned this questionnaire by mail. At the end of the follow-up, information on medication use during the trial period was retrieved retrospectively for each patient from his/her pharmacist.

Ethics & informed consent

The final protocol was approved by the Medical Ethics Committees of all participating hospitals. Patients were able to quit the study at any time. Informed consent was obtained after the study objectives, types of therapy, benefits and risks, and the concept of randomisation had been explained extensively. The study was performed according to the principles of Good Clinical Practice.[34]

Statistical analysis

All data will be analysed according to the intention to treat principle, meaning all included patients will be analysed according to the group they were randomised to. This includes patients who dropped out or changed therapy. The statistical methods that will be used are chosen in accordance with the type of data that is available. For continuous data, differences and their 95% Confidence Intervals (95% CIs) will be presented. In case of binary outcomes, differences in proportion with 95% CIs will be calculated. Whether randomisation was successful will be determined by assessing comparability of baseline characteristics. No formal statistical tests are foreseen. In the event apparent differences are noted, a multivariate analysis will be performed to adjust for potential confounding.

Effectiveness

Assessment of effectiveness of both UVB treatments will take place through calculation of the PASI and SAPASI scores for both treatment modalities at regular points in time, and subsequently calculating differences in (SA)PASI scores over time. Possible differences in effectiveness between the two therapies will be established through comparison of differences in (SA)PASI scores inclusive of 95% CIs. The side effects of the therapy were reported for each irradiation as being present ("yes") or not being present ("no"). For each type of side effect the answers will be compared on a group level and presented with their 95% CIs.

Dosimetry

Cumulative dosimetry will be determined as formulated in table 2. Comparison of cumulative doses between the treatment groups will be done by calculating the difference in mean dose with its 95% CI.

Quality of life (QoL)

Continuous sum-scores of the QoL questionnaires will be compared by calculating differences in QoL and their 95% CIs. Changes in QoL will also be compared across groups.

Costs

Both costs as reimbursed by the health insurance companies and actual costs as calculated by including all expenses (direct and indirect) will be compared for the two treatments as difference in costs with a 95% CI. The uncertainty associated with the point estimates will be evaluated using bootstrapping.[35]

Cost-Effectiveness

Initially the trial estimate of the incremental cost per additional patient with successful outcome will be assessed. Similarly, the costs per QALY gained will be estimated. To assess uncertainty with regard to incremental cost-effectiveness a standard bootstrap technique will be applied.[35] The trial data will be randomly sampled with replacement from the original dataset 1000 times. For each bootstrap sample the incremental costs and effects will be calculated and plotted (costs on the y-axis and effects on the x-axis). Thus an integrated presentation of the mutually dependent cost and effect differences is obtained that may be interpreted as a direct reflection of the uncertainty, i.e. a two dimensional dispersion, with regard to the incremental cost-effectiveness ratio. Using this so-called CEA Plane (Cost-effectiveness Analysis Plane), an inference regarding the likelihood of one treatment being more cost-effective than the other can be made.[36]

Other data

These include concomitant use of medication, data on patient satisfaction and on the burden of both treatments. These data will also be compared across groups and be presented with their differences and 95% CIs.

3.4 Results

Recruitment of patients was stopped after 2 years and 2½ months. Initially 252 possible participants were recruited by the participating hospitals. Of these 252 patients, 56 were excluded from starting the trial for a variety of reasons. Thirty-three (33) patients had a clear preference for either home or hospital-based therapy and refused to submit to being randomised. Another 11 patients did not want to participate in a study, 6 patients did not fulfil the inclusion criteria or met one of the exclusion criteria, 2 had already started UVB therapy, 2 persons decided not to be treated with UVB, and 2 patients were excluded for other practical reasons.

Thus, in total 196 patients (252-56) were included in the study. A consecutive sample of 105 patients was followed for 12 months after the end of the UVB treatment in order to gain sufficient data about the costs incurred after the treatment. Randomisation according to the minimisation method[19] was successful. The two factors accounted for, their levels and the number of assigned therapies are shown in table 3.

The therapy took place according to randomisation for 184 patients. Five (5) patients switched therapy (protocol violators), of which four patients switched to home UVB phototherapy. Another seven (7) patients never started therapy. Of those seven patients, four (4) had their lesions improved during the waiting period before treatment could be started and did not need UVB treatment after all (three of them were randomised to the group receiving home UVB treatment). The other three (3) that did not receive therapy withdrew respectively because of agoraphobia, not wanting to participate in the study, and not wanting any treatment during pregnancy. Two of them were assigned to have phototherapy in an outpatient setting.

Table 3 – Results of the randomisation procedure

Factor	Level	Number of patients		
		Hospital	Home	Total
Hospital	UMC Utrecht	24	25	49
	Hilversum Hospital	14	15	29
	Academic Hospital Maastricht	9	9	18
	Diakonessen Hospital Utrecht	9	8	17
	Meander Hospital Amersfoort	7	8	15
	Groene Hart Hospital Gouda	6	5	11
	AMC Amsterdam	5	5	10
	Erasmus MC Rotterdam	5	4	9
	VUmc Amsterdam	4	5	9
	Gelre Hospital Apeldoorn	5	3	8
	Diakonessen Hospital Zeist	3	4	7
	Reinier de Graaf Hospital Delft/Voorburg	4	3	7
	AntoniusMesosGroup Hospitals Nieuwegein/Utrecht	2	2	4
	Lucas Andreas Hospital Amsterdam	1	2	3
Previous UV phototherapy	Yes	50	50	100
	No	48	48	96

Stratified randomisation, in particular the minimisation method described by Pocock[19] was used, which took into account (1) the recruiting hospital, and (2) possible previous experience of the patient with UV therapy. This table shows the results of the treatment assignment by the two factors for 196 patients.

3.5 Discussion

This article presents the design of the first randomised controlled trial of home UVB phototherapy for psoriasis. The design of this trial was 'pragmatic', which means that we did not adapt daily practice to conform to a specific protocol: the two treatments were compared under the conditions in which they would be applied in daily practice.[15] In contrast to a pragmatic trial, an 'explanatory' trial studies treatments under controlled idealised or equalised conditions, preferably by means of a double-blind placebo-controlled study design and a rigid research protocol.[15] Thus, explanatory trials aim at providing information on the effects of a single

difference in treatment, while a pragmatic trial compares two treatment strategies as a whole.[15] Consequently, in a pragmatic trial the treatments will be carried out just as they would have been without the trial, and therefore the advantage of a pragmatic design is the assurance that the results can easily be generalised to the target population. As a result, this trial will make a valuable and important contribution to the evidence base for the use of home UVB phototherapy for patients with psoriasis. It will produce a solid estimate of the effectiveness of home UVB treatment compared to UVB phototherapy in an outpatient setting.

Of the five previously conducted studies on home UVB treatment, only two compare two groups of patients.[14] Our study addresses two weaknesses encountered in those earlier studies. First of all, our trial has a parallel group design in order to compare the two treatments during the same seasons of the year. Secondly, to obtain two similar groups of patients and thus prevent selection bias, assignment of treatments is by randomisation. As such, this study is the first to perform a parallel group randomised comparison of home UVB phototherapy with UVB treatment in an outpatient setting.
Another strength of the study is that it is designed to compare the two treatments as they are carried out in daily practise (pragmatic design), guaranteeing a good generalisability of the results. A further substantial difference with other trials in this field is that in addition to the effectiveness of the two therapies, the impact of each treatment on quality of life and on its associated costs is assessed.
A cost-effectiveness analysis will be conducted to investigate the aspects of expense and effectiveness together. The trial will also provide information about patient satisfaction, travel time, side effects, cumulative dosimetry, concomitant use of medication, waiting periods and total treatment duration. The manner in which data collection was planned throughout the trial ensures that both groups can be compared during the treatment period without important differences in the number of irradiations. During the follow-up the measurements are all comparable with regard to the time interval since the last irradiation.

There are, however, also some weak points which bear discussion. For instance, because the measurement planning does not use fixed time points starting from inclusion, for most patients the outcome at 12 months after inclusion (used to calculate cost-effectiveness) will have to be interpolated from the two adjacent measurements. These two adjacent measurements are only two months apart,

thus providing a solid basis for interpolation. Also, the EQ-5D questionnaire was only administered until the end of the treatment and not during the remaining follow-up period, making direct calculation of QALYs for this period impossible. We will have to rely on extrapolation from the treatment period. Another issue for discussion is that during the trial it was impossible to keep a record of all patients with psoriasis who were prescribed TL-01 UVB treatment but who were nòt referred to the central co-ordination centre. We therefore do not know the reasons for non-referral.

Overall, we feel that this trial has many benefits and will prove to be a very valuable addition to the current literature in the field. It is the first trial to compare these two commonly used treatments directly in a randomised parallel group design. Moreover, the study design allows for more than one objective. Besides clinical effectiveness, it also evaluates quality of life and cost-effectiveness. Being a pragmatic trial, it will be easy to generalise the results of this study to the target population. With 196 participants, the study is adequately powered to detect a 15% reduction in effectiveness, and the other outcome parameters can also be determined adequately.

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Pragmatic and non-inferiority study designs

Understanding and interpreting pragmatic trials and non-inferiority trials

Mayke BG Koek
Vigfús Sigurdsson
Carla AFM Bruijnzeel-Koomen
Erik Buskens

In preparation

4.1 Background

The randomised clinical trial described in this thesis is a pragmatic trial, designed to demonstrate that home UVB treatment is not inferior to the standard outpatient UVB treatment for psoriasis (non-inferiority trial). During writing and submitting our papers, we noticed that the principles of a pragmatic design as well as those of a non-inferiority approach are foreign to many general readers. Therefore we consider it desirable to introduce and explain both features in more detail.

4.2 Pragmatic design

Though the lamps most frequently used for home UVB treatment and outpatient UVB treatment are of the same type (TL-01 lamps), both treatments are not applied in exactly the same way. Although it is theoretically possible to do so, this is not current practice in the Netherlands. Differences in treatment schedules simply do exist, and consequently also differences in irradiation frequency and dosage occur. Because we were interested in determining whether home UVB treatment works in daily practice, we aimed to investigate the routine application of both treatments. Thus both treatments as they are currently being administered including their differences were compared. This approach is called a 'pragmatic' design, which is a recognised methodology to address questions on effectiveness (rather than efficacy in a 'controlled' setting).[1-4]

A pragmatic design has methodological features that differ from the -more frequently applied- explanatory design for randomised clinical trials. An explanatory trial aims to answer the question why and how an intervention works by investigating whether the intervention works under ideal or selected conditions (efficacy).[3]

A pragmatic trial, by contrast, investigates whether an intervention works in daily practice (effectiveness).[2] It is especially useful in answering questions about how effective a (new) therapy is when compared to a standard or accepted treatment,[5] and therefore it is very valuable in deciding whether a treatment should become available to a wide variety of patients.[1;3]

In line with the above, a pragmatic study should be designed to reflect the variations between patients and between treatments that occur in real life. Thus in contrast to the preferred homogeneous population in explanatory trials, patients selected to participate in a pragmatic trial should be representative of patients to whom the

treatment will normally be applied.[2;5] Also, the interventions should be applied routinely, left to the discretion of the clinician. Additional treatments and treatment changes are allowed, because it is the 'package of care' that is under investigation. Accordingly, it is not necessary for participants to complete the trial in the group to which they were allocated. Statistical analyses, however, needs to be on an intention to treat (ITT) basis—that is, participants have to be analysed in the group they were initially randomised to.[2;5]

As described above, the major advantage of a pragmatic design is that it facilitates optimal generalisation of the findings of the study, and hence is very useful for making policy decisions. Due to investigating a package of care, however, the exact health benefit for each aspect of the treatment cannot be determined separately.[5] Also, the results of a study evaluating a large heterogeneous group may tell the clinician little about how to manage individual patients.[6]

4.3 Non-inferiority design

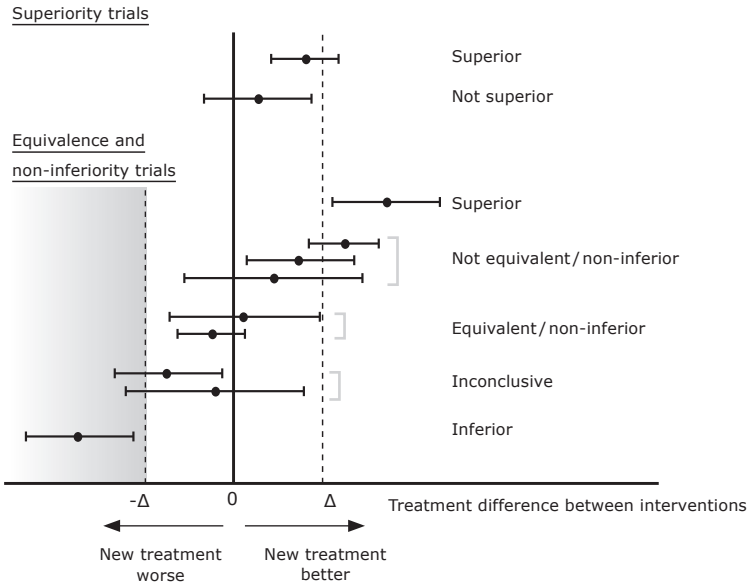
A further aspect of the design, or rather analysis, possibly requiring elaboration is the fact that we hypothesised a priori that home UVB treatment would not be inferior to UVB treatment in the outpatient department. We felt that that the use of the same type of lamps (TL-01) at home and in the hospital, would probably result in similar effects. Therefore, besides choosing a pragmatic design, we also designed our trial as a non-inferiority trial—that is, to establish that home UVB treatment is at least equally effective as (or: not inferior to) outpatient UVB treatment.

Our presumption and the corresponding choice of design contrasts with those of most other trials, which in general have a design appropriate to test the hypothesis that that one treatment is more effective than another treatment (superiority trial). However, often the aim of a superiority trial is not primarily to establish that one treatment is superior to the other, but mainly that a new treatment is equally effective as, or not inferior to, a reference treatment. If such is the case, the trial should be designed as an equivalence trial or non-inferiority trial respectively.[7;8]

Non-inferiority trials and equivalence trials should be distinguished from superiority trials, because they present particular challenges in interpretation.[8] Key factor is that observing no significant difference in treatment effects (as often happens in superiority trials), is not by itself sufficiently informative to claim equivalence or

non-inferiority. That is, the inability to prove superiority is no evidence that both treatments are therapeutically similar. Altman and Bland[8;9] formulated it as follows: "Absence of evidence is not evidence of absence". To demonstrate equivalence or non-inferiority, investigators in contrast have to prove that there is no pre-specified relevant difference (Δ, the so-called non-inferiority margin) in treatment effects.[7;8;10] The most important part of the analysis is therefore to assess whether the 95% CI for the difference in treatment effects excludes the (a priori determined) non-inferiority margin Δ. Any inferiority less than Δ is considered acceptable.[11] A selection of possible treatment outcomes and their interpretation for the various types of trials are shown in the figure.[7;11-13]
The choice of the appropriate margin depends largely on clinical judgement, and may be considered arbitrary. Also, Δ may be used two-sided (equivalence trial) or one sided (non-inferiority trial).

Figure – Possible scenarios for treatment differences in superiority trials and equivalence and non-inferiority trials



Bullets with error-bars represent the point-estimates of the treatment difference with 95% CIs.

The range -Δ to +Δ is the margin of equivalence. The tinted area indicates the zone of inferiority.

Non-inferiority and equivalence trials are especially advisable when comparison with a placebo or an untreated group of patients would be considered unethical. This may be the case in situations where a reference treatment is already commonly used, or when its effectiveness is known and beyond discussion.[8;14] Because both types of trials often require a larger sample size than superiority trials, they should be designed using an appropriate sample size calculation according to a negative trial approach.[15] Another consideration to take into account is that in non-inferiority and equivalence trials, intention to treat (ITT) analyses and per protocol analyses are considered equally important. This is because due to crossovers and dropouts, ITT analyses may be biased to finding no difference, which is the favoured outcome in non-inferiority studies.[14]

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Effectiveness, safety, burden of treatment and patient satisfaction of home UVB phototherapy

Home versus outpatient ultraviolet B phototherapy for mild to severe psoriasis: pragmatic multicentre randomised controlled non-inferiority trial (PLUTO study)

Mayke BG Koek
Erik Buskens
Huib van Weelden
Paul HA Steegmans
Carla AFM Bruijnzeel-Koomen
Vigfús Sigurdsson

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5.1 Abstract

Objectives To determine whether narrowband (TL-01) ultraviolet B (UVB) phototherapy at home, as studied in a context reflecting normal clinical practice, is equally safe and equally effective as the conventional outpatient UVB phototherapy for psoriasis. Furthermore Burden of Treatment (BoT) and patients' satisfaction are compared.

Methods 196 patients with psoriasis were included in a pragmatic multicentre single blind randomised clinical trial comparing home UVB phototherapy with outpatient UVB phototherapy. Both therapies were conducted in a setting reflecting routine daily practice in the Netherlands. The first 105 consecutive patients were also followed for one year after cessation of therapy. Main outcome measure was effectiveness as measured by the proportion of patients reaching a 50% or more reduction of the baseline Psoriasis Area and Severity Index (PASI) or Self Administered PASI (SAPASI), respectively called the PASI-50 and SAPASI-50 (relevant treatment effect). Secondary outcomes were the percentage reduction in median (SA)PASI scores, the (SA)PASI-75 (successful treatment effect), the (SA)PASI-90 (almost complete clearance), BoT, patient preferences and satisfaction, UVB dosimetry and short term side effects.

Results 82% of the patients treated at home compared with 79% of the patients treated in an outpatient setting reached the SAPASI-50 (95% CI of the difference -8.6% to 14.2%), while 70% compared with 73% reached the PASI-50 (95% CI -15.7% to 11.1%). Median SAPASI and PASI scores decreased 82% (6.7 to 1.2) and 74% (8.4 to 2.2) respectively for patients treated at home versus 79% (7.0 to 1.4) and 70% (7.0 to 2.1) for patients treated in an outpatient setting. The mean decline in (SA)PASI scores was significant (p=0.000) and similar across groups (p>0.3). Total cumulative doses of UVB were similar (51.5 versus 46.1 J/cm^2, difference 5.4, 95% CI -5.2 to 16.0), and the occurrence of short term side effects did also not differ. The burden of undergoing UVB treatment was significantly lower for patients treated at home (differences 1.23 to 3.01, all p-values <=0.001). Patients treated at home also more often rated their experience with the therapy as 'excellent' (42%, 38/90) than did patients treated in hospital (23%, 20/88, p=0.001).

Conclusion Home UVB phototherapy and outpatient phototherapy are equally safe and equally effective, both clinically and in terms of quality of life. Furthermore, UVB treatment at home results in a lower burden of treatment and leads to greater patients' satisfaction.

Trial registration Controlled-trials, ISRCTN83025173. Clinicaltrials, NCT00150930.

5.2 Introduction

Psoriasis is a chronic skin disorder which, regardless of extent, can affect patients' quality of life. The disease can be treated symptomatically in several ways.
An effective treatment that is often applied is ultraviolet B (UVB) phototherapy.[1-4] UVB phototherapy is indicated when topical treatment is insufficient. It is generally offered in an outpatient clinic, requiring patients to travel to the outpatient department during working hours two to three times a week. This makes it a relatively time-consuming treatment, also for the hospital personnel, imposing a substantial burden on patients and society.
To overcome the drawbacks of UVB treatment in the outpatient clinic, equipment for use at home was introduced in the late 1970s.[5-8] Although UVB phototherapy has been used at home ever since,[7-14] its safety and effectiveness and compliance with treatment have been debated. Non-evidence based fears are often expressed about higher attendant risks such as inaccurate dosimetry, phototoxicity, suboptimal treatment, and unsupervised continuation of irradiations after the treatment has finished.[11-24] It is generally thought that these risks influence the occurrence of acute side effects and lead to an increased cumulative dose, and hence promote photocarcinogenesis and photoageing.
We previously demonstrated that over 55% of the dermatologists consider home UVB treatment to be inferior to UVB therapy in the outpatient department. Moreover, about 30% think that home UVB carries higher risks than UVB used in a hospital, such as erythema, burns, carcinogenesis and photoageing.[25] This clearly demonstrates that discussions are ongoing. Research using randomised designs is non-existent, and literature on the subject remains scarce—that is, firm evidence supporting or discouraging the use of UVB phototherapy at home is simply lacking.[25]
Although many dermatologists hardly ever prescribe UVB phototherapy at home, in some settings home UVB treatment is common. We reported that 3000 panels for dispensing ultraviolet B light had been sold in Germany and 5000 in the United States, and that two Dutch home care organisations were successfully providing UVB equipment and supervision for 1400 psoriasis patients annually. We also showed that in the Netherlands about 5% of patients treated with UVB phototherapy are prescribed UVB phototherapy at home. Some dermatologists even reported prescribing home UVB to all of their patients treated with UVB.[25]

To summarise, firm evidence on which to base a considered policy decision about home UVB phototherapy is lacking.[25] In the absence of sound evidence based on randomised research, discussions on home UVB phototherapy will continue to result in the spread of non evidence-based opinions and opinion based medicine.[25] Notably, little attention has been paid to the possible positive effects of home treatment on quality of life, patients' satisfaction and on the burden of the UVB treatment.

On the basis of recent experience with home UVB treatment and data from a 1993 pilot we expected the effectiveness of home UVB phototherapy to be similar to that of current UVB phototherapy used in outpatient settings.[9] We aimed to establish that treatment effect, safety, quality of life and cost-effectiveness of home UVB phototherapy do not differ substantially from that of conventional UVB phototherapy in an outpatient clinic. Additionally, with home treatment we expected a lower burden from treatment and higher patients' satisfaction.

We compared both treatments in a setting reflecting routine daily practice in the Netherlands, and focused on narrowband (TL-01) UVB treatment for psoriasis.[26] The Dutch acronym for this trial is PLUTO. The cost effectiveness data will be published separately.

5.3 Methods

Design

From 2002 to 2005 we carried out a pragmatic multicentre single blind randomised trial comparing UVB treatment at home with UVB treatment in an outpatient setting. The participants and methods section has been described in detail elsewhere (www.biomedcentral.com/content/pdf/1471-2288-6-39.pdf).[26]

A pragmatic design is a recognised methodology for tackling questions on effectiveness in daily practice as opposed to efficacy in a 'controlled' setting.[27-29] Thus in our trial the interventions were administered as they would be routinely, with the management of the intervention left to the discretion of the prescribing clinician. That is, dermatologists were encouraged to carry out the assigned treatment as they would normally. Consequently, part of the comparison is possible variability in actual frequency of irradiations, dosage, compliance, support, and equipment used. We did not control for these and other possible differences related to treatment because they will occur in a real life situation.

Besides the treatment, the selection of patients also reflected routine practice. Blinding participants to treatment obviously was not possible, and because of the pragmatic design of the study it was undesirable to blind the dermatologists. The extent and severity of the psoriasis was, however, assessed by an independent research nurse blinded to treatment arm.[26]

Patients

Since patient selection should reflect routine clinical practice,[28-30] we invited patients with plaque or guttate psoriasis to participate if they were considered clinically eligible for narrowband (TL-01) UVB phototherapy. As a result, the severity of psoriasis was not a selection criterion. The UVB treatment had to be prescribed by the patient's own dermatologist, and patients provided written informed consent to undergo treatment according to randomisation. Exclusion criteria included an age below 18 years, expected non compliance, medical contraindications and practical reasons. Further details are described elsewhere.[26] The main selection criterion of being 'clinically eligible for narrowband UVB treatment' was purely pragmatic and was left to the discretion of the patients' own dermatologists. Dermatologists were, however, explicitly discouraged from increasing their prescriptions on behalf of the study. No financial benefit or other compensation was offered to participating dermatologists for their efforts. Likewise, patients also received no compensation for their participation in the study.

Sample size

On the basis of recent experience with home UVB treatment and data from a 1993 pilot we expected the treatments to be equally effective.[9] The sample size was therefore calculated in accordance with a negative trial approach.[31] We considered a 50% or greater improvement in the psoriasis severity from baseline to be a relevant clinical response. From literature we expected about 85% of the patients treated with UVB to show at least a 50% improvement of their psoriasis.[32] We determined that with an α of 0.05, β of 0.20 (power 80%), and a distinguishable decline (Δ) in proportion of patients of -15% (from 85% to 70%) we would need N=90 per treatment group.[26] To allow for missing data and losses to follow-up we aimed to recruit 100 patients per group, 200 in total. From the end of the treatment onwards, we considered a consecutive sample of 100 patients (50 per group) to be sufficient to obtain accurate estimates of cumulative costs.[26]

Randomisation procedure

After providing informed consent and collection of baseline data, a randomisation number corresponding to UVB treatment either at home or in an outpatient department was drawn from a computer generated list. Randomisation was done using stratified randomisation, in particular the minimisation method described by Pocock.[26;33] This method takes into account the recruiting hospital and possible previous experiences with UV phototherapy. After randomisation both the patient and dermatologist were informed of the assigned treatment, and this treatment was started according to standard practice.

Therapy

Patients randomised to outpatient UVB phototherapy received narrowband UVB (TL-01) treatment in their local hospital. All hospitals used their own treatment schedules and their own (full circle) cabins. Some types of cabins had UV indicators measuring intensity of irradiations (mW/cm^2); others did not and measured only treatment time. Accordingly, treatments were prescribed either in dose (J/cm^2) or in units of time (seconds).[26] Determination of the Minimal Erythema Dose (MED) before treatment was only done if that was routine practice for that particular hospital. Patients were treated two or three times per week, also depending on the hospital.

Patients randomised to receive home UVB phototherapy, were temporarily provided with a TL-01 home phototherapy unit (Waldmann UV 100; Waldmann, Villingen-Schwenningen, Germany) in their homes. This device comprises a semi-circular arrangement of lamps without an intensity indicator. Therefore treatments are prescribed in units of time (seconds). The Waldmann-100 unit was rented out by the home care organisations, which also delivered the unit to the patients' home and collected it at the end of the treatment period.

On delivery, a nurse from the home care organisation provided 30-60 minutes' training in use of the unit. Patients signed a contract restricting use of the unit to themselves. Finally the patients received a treatment schedule, set in time (seconds). No MED was tested. Irradiation took place three or four times per week (every other day), sometimes starting with daily irradiations. The choice of subsequent steps in the treatment schedule depended on the extent of side effects experienced, i.e. erythema and/or burning sensation of the skin. If deemed necessary by the patient, the nursing staff of the home care organisations could be contacted for supervision. The cost for the nurses' services, delivery and

collection of the phototherapy unit was included in the rental price.[26]
Summarising, the irradiation schedules for both treatment groups were those normally used by the hospitals and home care organisations. Neither equipment nor schedules were modified for the trial. We observed standard practice, and therefore did not impose a pre-specified treatment regimen on the participants. And as with daily practice we allowed adjuvant use of topical therapy to continue throughout UVB therapy. No other additional treatments or changes to the original treatment plan were intended. However, to compare the two UVB treatments under practical conditions and to reflect clinical reality, alterations to the initial treatment plan were allowed if the dermatologist decided they were necessary. As such, all changes to the treatment originating after inclusion and randomisation were permitted and were no reason for exclusion.[26]

Outcome measures

We determined the severity of disease using the Psoriasis Area and Severity Index (PASI),[34] and the Self Administered PASI (SAPASI).[35-37] Both scales range from 0 (no lesions at all) to 72 (complete erythroderma of the severest degree).
The main outcome measure was effectiveness as measured by the proportion of patients with a 50% or more improvement of the baseline PASI or SAPASI (respectively PASI-50 and SAPASI-50), which is considered a relevant treatment effect. The secondary outcome measures were the percentage reduction in median (SA)PASI scores, the (SA)PASI-75 (proportion of patients reaching a 75% improvement of the (SA)PASI, a so-called successful treatment effect), the (SA)PASI-90 (almost complete clearance), and a patient assessed visual severity assessment scale ranging from 0 (= no psoriasis) to 100 (= most severe psoriasis imaginable).
To verify whether both treatments were equally safe, we assessed the incidence of acute side effects and measured the total cumulative dose of UVB. The patients recorded any short term side effects for every irradiation in a diary. We considered four short term side effects of interest: mild erythema and burning sensation (mild and expected side effects) and severe erythema and blistering (serious side effects).
To calculate cumulative doses of UVB, we routinely measured light intensity (J/cm^2) of all UVB equipment from the hospitals with a small portable Waldmann UV meter, type 585 100 (Villingen, Schwenningen, Germany). If the UVB unit from the hospital had an irradiation intensity indicator, we compared its reading with our own measurements. The home care organisations measured the light intensity

of every UVB unit before the first irradiation and after the last irradiation, using their own Waldmann UV meters (all type 585 100). At the end of the trial we collected these measurements and also compared their Waldmann UV meters with our own Waldman UV meter, which was calibrated with the High Accuracy UV-Visible Spectroradiometer, type OL 752 (Orlando, Florida, U.S.A.). Participants in both groups recorded treatment times in their diary. We also took copies of the treatment charts of the patients treated in the hospital. At the end of the trial, we calculated standardised cumulative doses (mW/cm^2) for all patients using the intensity measurements together with the individual treatment charts and/or diaries. The calculation of standardised cumulative doses is described elsewhere.[26]

To measure the perceived 'Burden of Treatment' (BoT), we designed a short four item BoT questionnaire using visual analogue scales ranging from 0 to 10 (available from first author). The questionnaire was drawn up to capture the perceived burden of the UVB treatment, especially the burden of the treatment method and the burden associated with time lost as a result of the treatment.

We assessed health-related Quality of Life (QoL) using a generic and a disease-specific questionnaire,[26] respectively the Short Form 36 general health survey (SF-36),[38;39] and the Psoriasis Disability Index (PDI).[40;41] The SF-36 questionnaire yields eight domain-scores ranging from 0 (lowest imaginable QoL) to 100 (perfect health).[38;39] The PDI on the other hand is a disability index ranging from 15 (no disability, highest QoL) to 105 (lowest QoL).[40;41]

Furthermore we developed and used a questionnaire on patients' satisfaction and preferences,[26] and collected data on concomitant use of medication and demographics.[26] More details on outcome measures are published elsewhere.[26]

Planning of measurements

For all included participants (n=196), we planned measurements coinciding with inclusion in the study (t=0), actual start of the therapy (t=1), around the 23rd irradiation (t=2), and the end of therapy (t=3). When UVB treatments exceeded 46 irradiations, we defined 46 irradiations as the end of the therapy.[26] To obtain accurate estimates of cumulative costs, some measurements continued every two months for one year after the end of therapy (measurements 4-9). For this objective, only 100 participants were needed. Therefore not all 196 participants but only the first consecutive 105 participants were followed for these measurements. Figure 1 schematically represents the measurement planning.

Figure 1 – Timetable

	Baseline (inclusion, n=196)	Therapy (n=196)			Follow-up (n=105)					
		Start of therapy	23 irradiations	End of therapy	2-month FU	4-month FU	6-month FU	8-month FU	10-month FU	12-month FU
Visit to research nurse	Visit 1		Visit 2	Visit 3						
t=	0	1	2	3	4	5	6	7	8	9
PASI, QoL, medication	x		x	x						
SAPASI	x	x	x	x	x	x	x	x	x	x
Burden of Treatment			x	x						
Dosimetry, treatment times, side effects		x	continuous	x						
Patient satisfaction, preferences				x						

Schematic representation of the measurement planning.

Statistical analysis

The main principle of our analysis was non-inferiority—that is, we hypothesised that there would be no differences between treatments in clinical outcome, QoL and safety. Effectiveness of both UVB treatments was assessed using the outcome measures as described in the outcome measures-section. The non-inferiority margin (Δ) for the primary outcome measures SAPASI-50 and PASI-50 was set at -15%. Non-inferiority of home UVB phototherapy was accepted if the lower bound of the 2-sided 95% confidence interval (95% CI) around the estimated difference in proportion of patients reaching the (SA)PASI-50 was above -15%. We also analysed the secondary outcome measures for non-inferiority, using evaluation of the lower bounds of the 95% CIs for clinical relevance. The differences at group level are presented with their 95% CIs.

We used statistical methods in accordance with the type of data to analyse the superiority of patients' satisfaction and BoT. For normally distributed continuous data from independent samples we carried out the unpaired t test. For ordinal data and data with a skewed distribution we used the Mann-Whitney U test.

All analyses were done according to the intention to treat principle.

5.4 Results

Patients

Overall, 196 patients were randomised: 98 to home UVB phototherapy and 98 to outpatient UVB phototherapy, see figure 2. We followed all included patients during therapy. The first 105 consecutive patients were also followed over one year after the end of therapy.[26]

Table 1 summarises the baseline characteristics of the 196 included patients. The severity of psoriasis at baseline between those patients who completed the study and those who dropped out did not differ. Baseline severity of psoriasis ranged from mild to severe, with individual PASI scores up to 48.6. One hundred (100) patients had previous experience with UV treatment, 8 of whom had previous experience with home UVB phototherapy. Three of these were allocated to home UVB treatment, and five to outpatient UVB treatment.

Table 1 – Baseline characteristics of both treatment groups[a]

	Home UVB (n=98)	**Outpatient UVB (n=98)**
Male gender, n (%)	66 (67%)	66 (67%)
Age, years	41.2 ± 1.38	45.0 ± 1.37
Duration of the disease, years	16.1 ± 1.37	16.0 ± 1.36
SAPASI[b]	7.2 ± 0.38	7.3 ± 0.32
PASI[c]	9.7 ± 0.71	8.6 ± 0.56
Previous experience with UV treatment, n (%)	50 (51%)	50 (51%)

a Data are presented as mean ± SEM (standard error of the mean), unless otherwise indicated

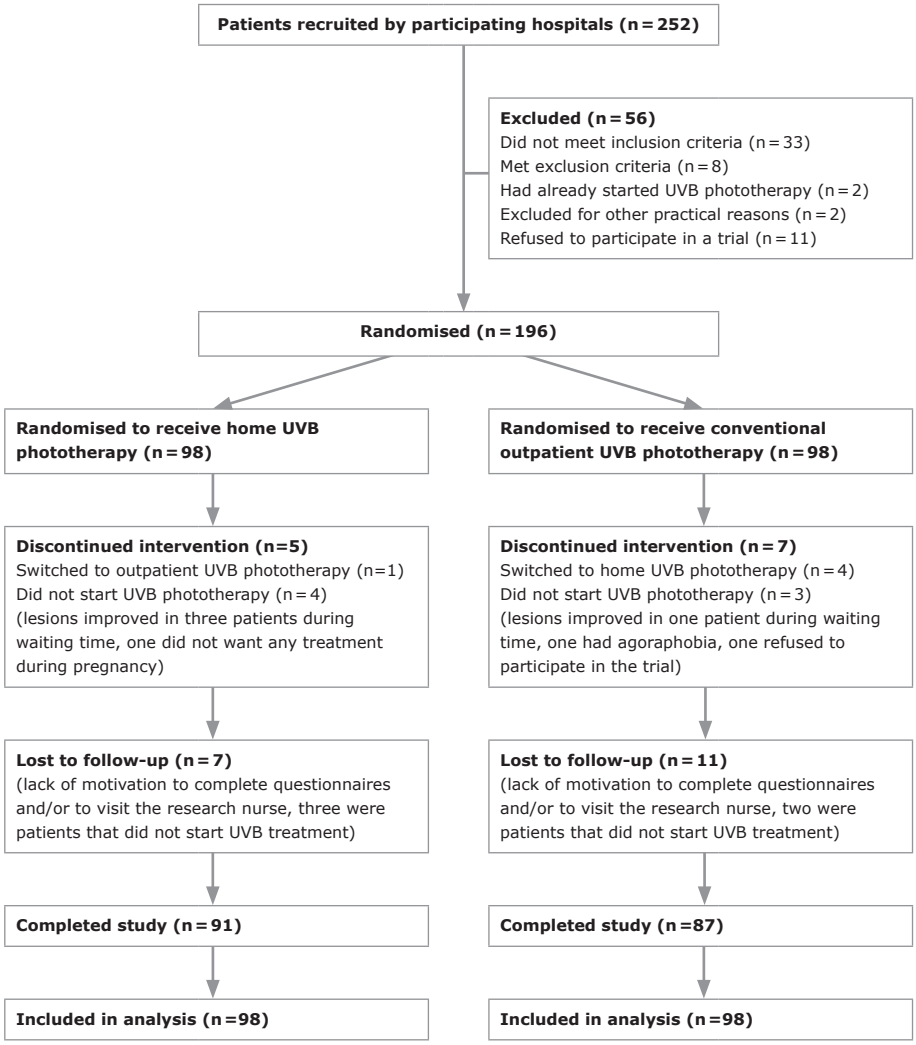
b The SAPASI was normally distributed at baseline, but showed a skewed distribution over the course of the trial

c The PASI was skewed during all measurements. Median values at baseline were 8.4 and 7.1 respectively

Treatment effect

Table 2 shows effectiveness as measured by the SAPASI-50, -75, and -90 and the PASI-50, -75, and -90. Four of these six outcome measures indicated that home UVB treatment is not inferior—that is, equally effective as (SAPASI-50 and PASI-90), at least equally effective as (SAPASI-75), or even superior to (SAPASI-90) outpatient UVB treatment for psoriasis. The remaining two measures

Figure 2 – Flow of patients



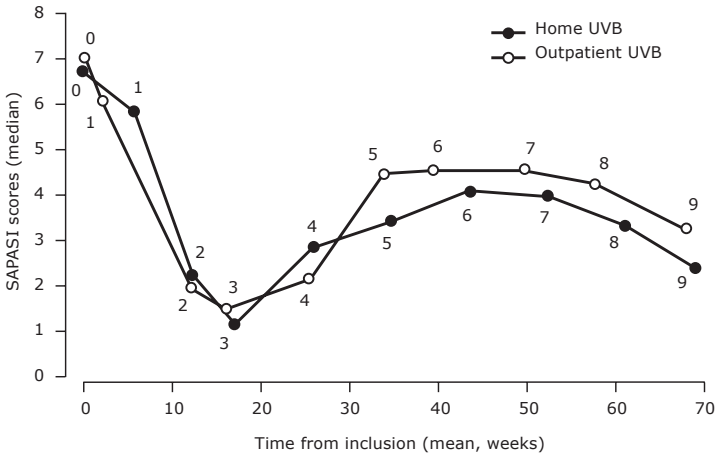
(PASI-50, and -75) had point estimates suggesting equal effectiveness, but non-inferiority could not be confirmed by the 95% CIs, of which the lower bounds were slightly lower than -15%. Supplemental analyses for both measures, however, showed that less than 5% of the distribution of the 95% CI fell below the margin of -15%.

The treatment effect as defined by the mean decline in SAPASI and PASI scores was statistically significant (all p-values <0.000) within and similar (p-values > 0.3) across both treatment groups.
Figure 3 illustrates changes in median psoriasis severity (SAPASI) over time. During therapy the median SAPASI score decreased from 6.7 to 1.2 for the home UVB group and from 7.0 to 1.4 for the outpatient UVB group; a decline of 82% and 79%, respectively. Essentially similar results were observed for decline in median PASI scores, from 8.4 to 2.2 for the home ultraviolet B group compared with 7.0 to 2.1 for the outpatient ultraviolet B group: a decline of 74% and 70%, respectively. Subgroup analyses for patients with more moderate to severe psoriasis (baseline SAPASI >=10) revealed that this subgroup reacted similarly to (home) UVB treatment as did the average participant. No differences were observed across both treatment groups.
PASI-values as measured during the 3 visits to the research nurse were comparable to the SAPASI-values (data not presented). Correlation coefficients for PASI and SAPASI scores varied between 0.48 and 0.52 (p=0.000). Mean psoriasis severity scores as assessed by the patients using a visual severity assessment scale (range 0-100) were 70.6 and 70.2 at inclusion and 18.1 versus 18.0 at the end of therapy (n=90 home vs. 88 outpatient).

Safety

To determine whether both treatments were equally safe, we assessed incidence of acute side effects and measured the total cumulative dose of UVB. Results are displayed in table 2.
Patients treated at home had a higher mean total number of irradiations than patients treated in the outpatient setting. Yet, the point estimate of the mean cumulative dose of narrowband UVB at the end of the therapy was only slightly higher for patients treated at home (difference 5.4 J/cm^2, 95% CI -5.2 to 16.0).
A total of 6180 irradiations were monitored. Complete information on side effects was available for 6111 irradiations in 185 patients. Regardless of treatment group, approximately 87% (n=161) of the patients had at least one occurrence of mild erythema, versus 58% (n=107) a burning sensation, 39% (n=73) severe erythema and 6% (n=11) blistering. No differences were observed across both treatment groups.
Besides the probability per patient to experience a particular side effect we also calculated the probability per irradiation for each patient by dividing the number

Figure 3 – Psoriasis severity (SAPASI) over time



Bullets are numbered according to the moments of measurement: 0=baseline (n=98 home vs. 98 outpatient), 1=start of therapy (n=93 vs. 94), 2=23 irradiations (n=90 vs. 74), 3=end of therapy (when UVB treatments exceeded 46 irradiations, the 46th irradiation was defined as end of the therapy; n=94 vs. 91), 4=2 months after therapy (n=51 vs. 43), 5=4 months after therapy (n=52 vs. 44), 6=6 months after therapy (n=50 vs. 44), 7=8 months after therapy (n=50 vs. 43), 8=10 months after therapy (n=49 vs. 42), 9=12 months after therapy (n=47 vs. 40). From measurements 0 to 3 all 196 participants were followed. From measurement 4 to 9 only a consecutive sample of 105 participants was followed.

of side effects during the treatment by the number of irradiations. No differences between both groups were observed in these outcomes (table 2).

Adjuvant medication, waiting time and duration of therapy

We divided the use of adjuvant medication during the trial into the use of topical medication (e.g. vitamin D derivatives, topical corticosteroids, dithranol) and systemic medication (methotrexate, acitretin, ciclosporin, fumarates). During UVB therapy a higher proportion of the patients treated in the outpatient department used topical steroids and vitamin D derivatives, whereas during waiting time (time between inclusion in the trial and start of the UVB treatment) a higher proportion of the patients treated at home used these two types of medication

Table 2 – Main results

		Home UVB	Outpatient UVB	Difference (95% CI)
Effectiveness				
	SAPASI-50, -75, and -90[a]	**(n=94)**	**(n=91)**	
	SAPASI-50	81.9 (77)	79.1 (72)	2.8 (-8.6 to 14.2)
	SAPASI-75	69.1 (65)	59.3 (54)	9.8 (-4.0 to 23.6)
	SAPASI-90	43.6 (41)	29.7 (27)	13.9 (0.002 to 27.8)
	PASI-50, -75, and -90[a]	**(n=91)**	**(n=84)**	
	PASI-50	70.3 (64)	72.6 (61)	-2.3 (-15.7 to 11.1)
	PASI-75	40.7 (37)	41.7 (35)	-1.0 (-15.6 to 13.6)
	PASI-90	19.8 (18)	19.0 (16)	0.8 (-10.9 to 12.5)
Safety				
	Irradiations (mean, n)	**(n=98)**	**(n=98)**	
	Total number of irradiations	34.4	28.6	5.8 (2.7 to 9.0)
	Cumulative dose (mean, J/cm^2)	**(n=85)**	**(n=68)**	
	At 23 irradiations	21.2	26.9	-5.7 (-10.3 to -1.1)
		(n=91)	**(n=93)**	
	At end of therapy	51.5	46.1	5.4 (-5.2 to 16.0)
	Side effects per irradiation (%)	**(n=93)**	**(n=92)**	
	Severe erythema	5.5%	3.6%	1.9% (-1.1 to 4.9)
	Blistering	0.3%	0.6%	-0.3% (-0.9 to 0.3)
	Burning sensation	7.1%	10.0%	-2.9% (-7.1 to 1.2)
	Mild erythema	28.8%	28.6%	0.3% (-7.4 to 8.0)
Use of adjuvant medication[b]				
	During waiting time[c]	**(n=94)**	**(n=95)**	
	Topical steroids	25.5 (24)	6.3 (6)	19.2 (8.8 to 29.6)
	Vitamin D derivates	18.1 (17)	6.3 (6)	11.8 (2.5 to 21.1)
	During UVB therapy	**(n=92)**	**(n=92)**	
	Topical steroids	31.5 (29)	52.2 (48)	-20.7 (-35.0 to -6.4)
	Vitamin D derivates	19.6 (18)	40.2 (37)	-20.6 (-33.8 to -7.4)
Waiting time and duration of therapy (mean, weeks)				
		(n=93)	**(n=95)**	
	Waiting time[c]	5.8	2.2	3.6 (2.9 to 4.4)
	Duration of therapy	11.4	14.1	-2.7 (-4.1 to -1.2)
	Time from inclusion until end of therapy	17.2	16.2	1.0 (-0.6 to 2.5)

Values are percentages (numbers) of patients unless stated otherwise. When treatments exceeded 46 irradiations, 46 irradiations is defined as the end of the therapy (cut off point). All values shown are calculated from data not exceeding 46 irradiations.

a Data are expressed as proportion of patients achieving at least a 50%, 75% or 90% decline of the baseline (SA)PASI at the end of therapy.

b Proportion of patients using adjuvant medication during the two consecutive phases of the trial.

c Time between inclusion in the trial and the actual start of UVB treatment.

(table 2). For patients using adjuvant medication, the amount of medication used per patient was similar for both groups. During waiting time and therapy, use of other topical medication and systemic medication was in fact negligible and not different across both treatment groups.
Waiting time (i.e. time between inclusion in the trial and the actual start of UVB-treatment) was longer for patients treated at home than for patients treated in the outpatient department (figure 3 and table 2). This, however, did not result in a clinically relevant difference in total duration until the end of treatment.

Burden of treatment

The BoT was measured after 23 irradiations and at the end of the therapy. Results for both time points were virtually identical; therefore the overall average values are presented. The BoT was significantly higher for patients treated in the outpatient department than for patients treated at home. Differences in mean scores for the four domains were 1.23 to 3.01 (all p-values <= 0.001, figure 4).

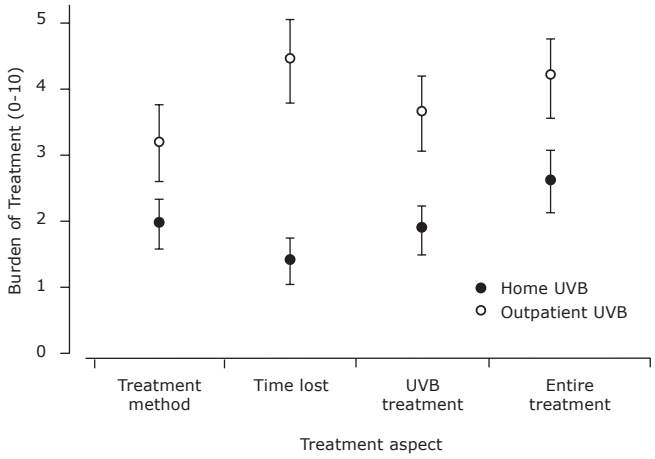
Quality of life

Both disease-specific QoL (PDI) and generic QoL (SF-36) improved during therapy. The PDI-values decreased from 32.8 in the home UVB group (n=98) and 34.3 in the outpatient UVB group (n=98) at inclusion to 20.9 and 22.0 (n=93 vs. 91) at the end of therapy. At all three time points of measurement, PDI-values were similar across groups (p-values >0.45). The eight SF-36 domain scores and the two component scores were also very similar across both groups. The values were, however, somewhat lower than the values observed in an unaffected population sample.[39]

Patients' satisfaction and preferences

Patients treated at home evaluated their therapy more positively than patients treated in the outpatient setting, p=0.001. For instance, the treatment was rated 'excellent' by 42% (38/90) of the group treated at home compared with 23% of the patients (20/88) treated in the outpatient department (figure 5).
Patients' satisfaction was categorised as satisfaction with the final treatment result (appearance of skin), the rate of improvement, and nursing care and supervision during treatment. Table 3 shows the distribution of the various degrees of satisfaction for the three dimensions.
As presented in the previous paragraph, patients experienced a -sometimes considerable- waiting time before UVB treatment could be started. However, 26%

Figure 4 – Burden of treatment



Mean burden of treatment values on a 0-10 VAS scale. Error bars indicate 95% Confidence Intervals (95% CI). The 4 treatment aspects correspond to the 4 item BoT-questionnaire.

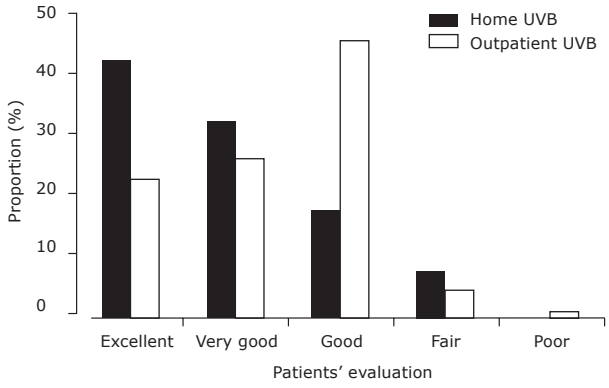
Treatment method: location of the UVB treatment (home versus hospital), positioning for irradiation, actions for the patient to perform etc. (n=92 home vs. 89 outpatient)

Time lost: time lost to the treatment, including travel time (n=92 vs. 89)

UVB treatment: all aspects of the UVB treatment (n=92 vs. 89)

Entire treatment: all aspects of the entire treatment plan—that is, the UVB treatment in combination with the use of creams/ointments and/or taking medications for psoriasis (n=87 vs. 83)

Figure 5 – Patients' evaluation of UVB treatment



Distribution of patients' self rated global experience of the UVB treatment they received during the trial.

(22/86) of the patients treated at home and 45% (26/58) of the patients treated in the hospital thought the waiting time was not a problem, and 48% (41/86) compared with 35% (20/58) thought the waiting time was acceptable. Only a minority thought it was too long (17%, 15/86 vs. 16%, 9/58) or far too long (9%, 8/86 vs. 5%, 3/58), p=0.038. Despite the experienced waiting times, the majority of the participants of both groups would prefer home UVB therapy in the future. For the patients treated at home this proportion was 92% (83/90), whereas it was only 60% (53/88) for the patients treated in the outpatient clinic (difference 32%, 95% CI 19.5 - 44.5). Most of the patients in both groups considered the therapy they received to be very safe (32% (29/90) vs. 21% (18/88)) or safe (52% (47/90) home, vs. 63% (55/88) outpatient). About 16% (29/178) reported being impartial, and none of the participants thought the therapy they received was unsafe (p=0.156).

Table 3 – Patients' satisfaction with the treatment: three dimensions

Dimensions and items	**Home UVB**	**Outpatient UVB**	
1) Final treatment result[a]	**(n=90)**	**(n=88)**	**P Value**[b]
Very satisfied	49 (44)	32 (28)	
Satisfied	32 (29)	47 (41)	
Somewhat satisfied	11 (10)	18 (16)	0.08
Unsatisfied	7 (6)	3 (3)	
Very unsatisfied	1 (1)	0 (0)	
2) Rate of improvement	**(n=90)**	**(n=88)**	**P Value**[b]
Very satisfied	36 (32)	27 (24)	
Satisfied	40 (36)	44 (39)	
Somewhat satisfied	18 (16)	25 (22)	0.34
Unsatisfied	4 (4)	2 (2)	
Very unsatisfied	2 (2)	1 (1)	
3) Nursing care and supervision	**(n=87)**	**(n=85)**	**P Value**[b]
Very satisfied	35 (30)	51 (43)	
Satisfied	49 (43)	41 (35)	
Somewhat satisfied	13 (11)	7 (6)	0.02
Unsatisfied	3 (3)	1 (1)	
Very unsatisfied	0 (0)	0 (0)	

Three dimensions to measure patients' satisfaction with UVB treatment at home or in an outpatient setting.

Values are percentages (numbers) of patients unless stated otherwise.

a The appearance of the psoriasis at the end of the treatment

b Mann-Whitney U test

5.5 Discussion

In contrast to prevailing opinion,[12-25] we proved that home UVB phototherapy is equally effective for treating psoriasis as UVB treatment administered in an outpatient setting and implies no additional safety hazards if applied in a setting precluding possible non-prescribed irradiations. Furthermore, UVB treatment at home poses a lower burden, is better appreciated and gives similar improvements in quality of life. Most of the patients said that they would prefer home UVB therapy over UVB treatment in an outpatient setting for future treatment.

Key findings

Four of six measures of the (SA)PASI-50, -75 and -90 indicated that home UVB treatment is (at least) equally effective as, or even superior to, outpatient UVB treatment for psoriasis. The remaining two measures had point estimates suggesting equal effectiveness, but from the 95% CIs possible inferiority of home UVB treatment could not be entirely excluded. Also the similar decrease in the (SA)PASI scores and the visual severity assessment score adds to the conclusion of similar effectiveness. The proportion of patients reaching the SAPASI-90 shows that home UVB treatment may be more effective than UVB therapy in the outpatient department. This was not, however, confirmed by the PASI-90 score. We think that possibly the patients' responses may have been somewhat biased resulting in optimistic assessment on (near) complete recovery.

Interestingly, in both groups the severity of the psoriasis had already improved during the waiting period, even before UVB treatment was started. This early improvement might result from patients being empowered and increasing their compliance with topical drugs after the recent visit to the dermatologist, hence leading to an initial improvement. The knowledge that UVB treatment would soon be started might also have reduced possible stress factors influencing the severity of psoriasis and its perception. Finally, the improvement may also be partly explained by regression to the mean.[42]

Besides being equally effective, both treatments were equally safe, as judged by the similar proportion of acute side effects experienced and the safety of the treatment as perceived by the patients. Therefore our results refute the widespread fear of more acute safety risks with ultraviolet B phototherapy used at home.[12;15;16;19-21;25]

The same conclusion can be drawn about the fear of higher cumulative doses and long term safety such as carcinogenicity and photoageing. In our trial the final

cumulative dose of UVB was not significantly different between the treatment groups. As the attributive long term risk for skin cancer caused by UVB treatment is believed to correlate directly with the experience of acute side effects and with the total cumulative dose of UVB,[43-45] we conclude that the risk of future skin cancer attributable to the UVB treatment would also be similar across both groups. Another argument is that a possible difference of 5.4 J/cm^2 in total cumulative dose (95% CI -5.2 to 16.0 J/cm^2) corresponds to a difference of approximately 9 MED (the 95% CI values correspond to -9 to 26 MED respectively). This was calculated using the action spectrum from Parrish,[46] the TL-01 emission spectrum,[47] and an average Erythemal Effective Dose for skin type II/III of 35 mJ/cm^2.[48;49] In The Netherlands the mean solar exposure is 75 MED annually for indoor workers and 170 MED annually for outdoor workers.[50] Therefore, a mean difference of 9 MED per year in our opinion seems insignificant and certainly not sufficient to favour outpatient UVB over home UVB treatment. Even the extreme of the 95% CI (26 MED) is in our opinion still not sufficient or relevant to favour one therapy over another.

Concerns about unsupervised continuation or restart of irradiations at home are not an issue in the Netherlands. In our country, home UVB phototherapy units are rented out by home care institutions only when prescribed by a dermatologist and the units are always collected at the end of treatment. Therefore in this setting multiple annual UVB treatments are only possible if prescribed. We are aware that this situation may not apply to other countries, such as in those where patients buy their own unit. On the basis of this trial, we cannot make any statements on the risk of non-prescribed irradiations in such settings. Recently however, Yelverton[51] described another measure that also provides additional safety through preventing long term use and misuse. The study used home UVB panels that were fitted with an electronic control to allow a preset number of irradiations. When this number had been used the patients had to contact their dermatologist for a new code to obtain additional irradiations.[51] This indicates that other ways to prevent non-prescribed use of home UVB panels do exist and are currently being used.

Because of the pragmatic design of our study, the use of concomitant medication was permitted and not restricted throughout the trial. We observed a higher proportion of the patients treated at home using topical steroids or vitamin D derivatives while awaiting phototherapy. We think this difference is attributable to the long waiting time for home UVB treatment, which is almost three times as long as the average wait for treatment in the outpatient clinic. The fact that during

the UVB treatment a higher proportion of the patients treated in the hospital used these two types of medication might be explained by the fact that treatment in the hospital is likely to be accompanied by closer supervision and more nursing care, resulting in more motivation to use adjuvant medication. Note, however, that differential use of medication during waiting time and during therapy had no effect on overall outcome.

The considerable waiting time before home UVB treatment could be started resulted from the national health insurance system and capacity problems at the home care organisations during winter. Duration of home ultraviolet B phototherapy was, however, shorter than outpatient treatment, supposedly due to the difference in irradiation frequency and the resulting difference in rate of improvement.[52;53] Thus, despite the longer waiting time for home UVB phototherapy, the mean time from inclusion up to the end of the treatment (waiting time plus treatment duration) was similar for both groups.

Our findings indicate that home UVB treatment results in a lower burden of treatment than UVB phototherapy in the outpatient department. The results of the BoT questionnaire show more comfort and a lower burden for patients treated at home. Improvement in quality of life, however, was similar for both treatment groups. This can be explained by the fact that the QoL-questionnaires used were not therapy-specific, but disease-specific (PDI) or even generic (SF-36). Disease severity decreased similarly in both treatment groups, hence it might be expected that general or disease-specific QoL would improve similarly in both groups.

An official therapy specific QoL-questionnaire does not exist however. We believe that the questionnaire we developed was suitable to report burden of treatment and can be considered a good predictor of therapy specific QoL.

Patients treated in the outpatient setting were in general slightly more satisfied with the nursing care and supervision. However, the longer waiting time for home UVB treatment was not an issue for most patients. In fact, most participants in both groups would prefer home UVB treatment over hospital based UVB therapy in the future. This finding was more explicit for patients treated at home (92%) than for patients treated in the outpatient department (60%). This difference probably results from a difference in experience with home UVB treatment, as this item was recorded after the treatment had finished. In our opinion most patients found home UVB phototherapy comfortable, flexible, and less time consuming than hospital based treatment. This led to higher reported satisfaction with home phototherapy than with outpatient phototherapy. Patients therefore apparently

prefer a comfortable treatment regimen over a rapid start of treatment. This would also explain why home UVB treatment was better appreciated by the patients.

Comparison with other studies

As our study is the first RCT on home UVB phototherapy, we have little with which to compare our results. We found only two previous observational parallel group studies.[11;19;25] In both, home UVB therapy equipment seemed to be effective. No information about baseline psoriasis severity was provided, however, and neither study had a randomised design.[11;19] Patients included in our trial had, judged by the baseline (SA)PASI scores, a severity of disease ranging from mild to severe. The average psoriasis severity was comparable to that of a non-selected group of 23 patients receiving UVB treatment in our hospital from August 2006 to July 2007 (median SAPASI 7.55). The mean baseline (SA)PASI scores in our trial were also similar to those of a trial where participants were said to be representative of patients receiving UVB treatment,[54] but were somewhat higher than those in a study where the same principle inclusion criterion of clinical eligibility had been used.[55] Effectiveness in terms of percentage decline in baseline (SA)PASI score was similar to that of three other trials studying the effect of narrowband UVB.[56-58] Effectiveness was also comparable to that of ciclosporin and etanercept (Enbrel®), but somewhat higher than that of methotrexate and efalizumab (Raptiva®) and lower than that of infliximab (Remicade®) and adalimumab (Humira®).[59-65] Overall we think our results may be considered representative, and can be extrapolated to many other settings.

With regard to safety, four out of six published guidelines that touch the subject of home UVB phototherapy for psoriasis presume that home UVB treatment leads to inaccurate dosimetry, suboptimal treatment, phototoxicity and higher attendant risks.[16;20-22;25] Also, three guidelines claim that medical supervision is crucial for the treatment effect.[16;20;22;25] Accordingly, the majority of the papers and guidelines about home UVB suggest being cautious when prescribing this treatment, and advise to use strict eligibility criteria in order to select patients.[8;11;12;15;16;18;20;22;25;66] In our study we however demonstrated that (1) home UVB treatment for psoriasis was equally effective and can be administered equally safe as UVB treatment in the outpatient department, and that (2) eligibility criteria for home UVB therapy can be broad. To provide an effective and safe treatment at home, we believe that there is no need to select patients based on their (presumed) higher intelligence, competence, responsibility, reliability or compliance.[11;12;15;16;18;20;22;25;66]

Strengths and weaknesses of the study

A major strength of this study is that it is the first randomised trial studying the effectiveness, quality of life and burden of treatment of home UVB phototherapy for psoriasis compared with the standard outpatient UVB treatment.[25] These issues have never before been properly investigated nor published.

As for generalisation, we used a pragmatic design in order to be able to compare the two treatments under the conditions in which they would be applied in daily practice. The design ensured broad inclusion of patients who were clinically eligible for UVB treatment. Altogether, we believe that our participants adequately represent patients with psoriasis receiving UVB treatment outside the trial. Additionally, the fact that treatments were similar to daily practice ensured that our results may be generalised to the target population. However, we recognise that in a setting lacking control and good maintenance of the home UVB units, the results of the treatment might be different.

A potential weakness may be the manner in which data collection was planned throughout the trial. This was organised such that both treatment groups could be compared without important differences in the number of irradiations. This aspect of the design, however, made it impossible to compare both treatment groups at fixed times -for example at 4 or 8 weeks after start of the treatment. Another point of consideration might be that during the trial 252 patients were referred to us, of which 196 actually consented to participate in the trial. Of the 56 (252-196) patients that were excluded, we know why they were excluded.[26] It was not possible, however, to keep a record of all patients with psoriasis who were prescribed TL-01 UVB treatment but were not referred to us for inclusion in the trial. We therefore do not know the reasons for non-referral and cannot entirely exclude that selection occurred. The latter would, however, be minimal since the patients included matched a consecutive sample of patients offered UVB therapy on our hospital at a later period.

Implications for practice

Our study provides proper evidence for dermatologists and dermatological societies, allowing definitive statements about effectiveness, safety, quality of life, and burden of treatment of home UVB phototherapy. Since the effectiveness of home UVB and outpatient UVB treatments is equal, future decisions should be based on the burden of treatment, patients' satisfaction and the economic burden for society. Now that we have provided the evidence and discussed the merits of

home UVB treatment, we feel that a considered policy decision and subsequent adaptation of guidelines would be possible.

Conclusion and recommendations:

In conclusion, we have shown that home UVB phototherapy is equally effective and also equally safe when applied in a setting that precludes non-prescribed irradiations. Home UVB therapy also led to a lower burden of treatment and greater patients' satisfaction than did outpatient UVB therapy, despite waiting times sometimes being considerably longer. We therefore regard home UVB treatment to be a worthy alternative to standard outpatient UVB phototherapy for patients with psoriasis. An economic evaluation comparing both treatments should follow in order to determine which treatment is economically preferred.

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Impact of psoriasis on Quality of Life

The impact of psoriasis on Health Related Quality of Life quantified: a longitudinal study

Mayke BG Koek
Wendy J Post
Carla AFM Bruijnzeel-Koomen
Vigfús Sigurdsson
Erik Buskens

Submitted

6.1 Abstract

Background Most previous studies that investigated the relationship between psoriasis and Health Related Quality of Life (HRQoL) are restricted to the presentation of correlation coefficients or simply describe differences observed in both measures. Although providing some insight, those previous studies have not accurately quantified the impact of a specific increase of psoriasis severity on HRQoL. Also the impact of psoriasis on Quality Adjusted Life Years (QALYs) experienced has not been accurately quantified previously.

Objective and methods This study aimed to estimate the actual size of impact of self assessed psoriasis severity on HRQoL when adjusted for other determinants. Furthermore, we assessed the impact of psoriasis on QALYs experienced when compared with a national reference population. We used longitudinal data from a trial on UVB phototherapy for psoriasis in which HRQoL was measured using the PDI, SF-36, SF-6D and EQ-5D. Psoriasis severity was measured from a patient's perspective using the Self Administered Psoriasis Area and Severity Index (SAPASI). Multilevel models were used to optimally exploit the longitudinal nature of the data, aiming for more accurate estimates.

Results Decreasing SAPASI scores were associated with improved HRQoL on any scale, varying from 0.77 to 2.9 point improvement in HRQoL per point decrease of the SAPASI score. Male gender, older age, and being employed were also important determinants of better HRQoL. Participants experienced a loss of 0.033 QALY/year (16.000 QALYs nationally) when compared to the average Dutch population.

Conclusion HRQoL is inversely related to psoriasis severity, and is influenced by gender, age and employment status. Furthermore, psoriasis accounts for a considerable loss in terms of QALYs.

6.2 Introduction

Psoriasis is a chronic skin disorder that can have a major impact on the patients' quality of life,[1-3] which may in turn adversely affect the overall morbidity caused by psoriasis.[4] In recognition of the latter, Health Related Quality of Life (HRQoL) is becoming an important outcome measure in psoriasis research.[5-7] In addition to HRQoL, incremental health effects may also be expressed in terms of Quality Adjusted Life Years (QALYs). QALYs account for both a reduced HRQoL (due to morbidity) and -for diseases with a shorter life expectancy- a shorter duration of life (due to mortality).[8] QALYs are commonly used in economic evaluations as a measure of effectiveness, and as such they are pre-eminently suited to establish the impact of a disease when compared to an average (national) population or other patient categories.

To the best of our knowledge no previous study described the impact of psoriasis in terms of QALYs comparing to a national reference population. In contrast, there are many psoriasis studies showing a positive effect of treatment on psoriasis severity and HRQoL.[6;9;10] In most of these studies on HRQoL impairment due to psoriasis, psoriasis severity is reflected by the degree of so-called objective severity. Such as for instance the Psoriasis Area and Severity Index (PASI) and the percentage affected Body Surface Area (%BSA). In literature, however, it has been suggested that what is perceived to be severe psoriasis by the patient may not be perceived as severe by the physician and vice versa.[3;11] It has also been argued that subjective experience of psoriasis severity is a more powerful determinant of HRQoL than the degree of so-called objective severity.[12;13] This appears to be ample reason for clinical assessment of psoriasis severity to incorporate the patient's perspective.[11]

Another major limitation of most previous studies is that they are restricted to the presentation of correlation coefficients, or sometimes just simply describe a decreased psoriasis severity in combination with an increased HRQoL. Although providing some insight, those studies fail to quantify the impact of a specific increase of psoriasis severity on HRQoL. As such, they do not present the size of the loss of HRQoL for each unit increase in psoriasis severity when adjusted for other determinants.

The actual size of the impact of a single unit increase of psoriasis severity on HRQoL can be estimated by performing regression analyses. Only five previous studies have tried to quantify the impact of psoriasis and other determinants on

HRQoL accordingly.[9;10;14-16] Only two of those studies, however, used standardised measures of the patient's perspective on psoriasis such as a SAPASI score.[10;15] The magnitude of the impact of the SAPASI on HRQoL was not adequately specified by either of those two studies because of a correlation between predictors (collinearity)[15] and a lack of power.[10] Also, neither study incorporated a psoriasis-specific measure of HRQoL.[10;15] Furthermore, one of the other studies used a very infrequently applied measure of HRQoL only,[9] and none of the studies above measured the impact of psoriasis in terms of loss of QALYs. Finally, all five mentioned studies performed ordinary linear regression analysis, using data of only a single measurement in time per patient. None of the studies applied a repeated measures analysis (multilevel analysis) in order to optimally exploit the longitudinal recording of data.

Thus, accurate estimates of the exact size of change in HRQoL resulting from a one point increase or decrease in the self assessed psoriasis severity are lacking. Also, despite the chronic and recurring nature of psoriasis, to our knowledge no study has previously longitudinally assessed this impact in order to aim for more accurate estimates. In addition, the impact of psoriasis in terms of QALYs when compared to a national reference population has not been previously determined. Noting the above, we performed additional analyses on a prospective data-set originating from a randomised clinical trial on the effects of two UVB modalities. Specifically, the aim of this study was to more accurately assess the impact of psoriasis on HRQoL and additionally on (loss of) QALYs using multilevel analyses, while adopting the belief that the SAPASI is a better determinant and hence better predicts HRQoL than the PASI. Concerning HRQoL we were especially interested in commonly used measures such as the PDI, the 36-item Short-Form General Health Survey (SF-36), the EuroQoL EQ-5D and the SF-6D. In agreement with previous publications we furthermore estimated associations with other determinants. Additionally, we considered possible interactions (effect modification) between the various determinants.

6.3 Methods

Design and participants

We obtained data from patients with psoriasis who participated in a pragmatic single blind randomised clinical trial comparing home ultraviolet B (UVB) phototherapy with the current outpatient UVB treatment.[17;18] We grouped all data regardless of the randomisation, because there were no differences between both treatment groups in terms of clinical outcome or HRQoL.[18]

The protocol of this trial has been described in detail in a previous publication (open access on http://www.biomedcentral.com/content/pdf/1471-2288-6-39.pdf),[17] and has been registered in ClinicalTrials.gov (NCT00150930) and the ISRCTN register (ISRCTN83025173). The institutional review board of the University Medical Center Utrecht approved the study. We conducted the study according to declaration of Helsinki principles, and all participants provided written informed consent. Data was obtained from 2002 through 2005. The study had a pragmatic design, which is a recognised methodology used to address questions on effectiveness in daily practice.[19-21] Consequently, the results of this study will reflect (the impact of psoriasis in) a real life situation. Participants were clinically eligible for narrowband (TL-01) UVB phototherapy and had this therapy prescribed by the attending dermatologist. For both treatment groups, treatment was performed according to routine daily practice.[17]

Measurements

HRQoL

We measured HRQoL using two generic and one disease-specific questionnaire,[17] respectively the EQ-5D,[22] the SF-36[23;24] and the PDI.[25;26] The EQ-5D is a validated generic HRQoL instrument comprising five questions that were developed to assess the impact of a disease.[22;27] We applied the MVH A1 algorithm[28] to compute one overall value judgement, a so-called utility score. The EQ-5D utility score ranges from -0.594 (the pits) to 1 (optimal health). The SF-36 also is a generic HRQoL questionnaire, which has previously been used in several psoriasis studies.[29;30] It is a 36-item questionnaire yielding a profile of 8 domains: physical functioning (PF), role limitations physical (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitations emotional (RE), and mental health (MH).[23] All domains range in score from 0 to 100, with a higher score indicating a better health status. Recently, a utility score based on

several questions from the widely used SF-36 has been developed with the goal to maintain the richer descriptive set-up and still obtain a single utility score.[31] The so-called SF-6D was launched as an alternative to the EQ-5D utility score.[31;32] The SF-6D utility score ranges from 0.291 (worst possible health state) to 1 (optimal health). The PDI is a short disease-specific HRQoL questionnaire consisting of 15 questions regarding disability due to psoriasis. Answers are recorded on a seven point linear scale (1-7). The maximum achievable PDI score is 105 (maximum disability), with a minimum of 15 (no disability).[26] Thus, in contrast to the other HRQoL questionnaires where high scores stand for a high HRQoL, a high score on the PDI signifies a poor health state and thus a considerable decrease in HRQoL.

QALYs

Next to the use of EQ-5D utilities as a measure of HRQoL, the EQ-5D utility scores were also used to calculate impact in terms of mean quality adjusted time expressed in QALYs. A QALY is a generic measure of HRQoL that is commonly used in economic evaluations. It takes into account both the loss of quality of life and -if applicable- the loss of quantity of life due to a disease.[8] For chronic diseases that do not significantly affect life expectancy, however, the loss of quantity of life is not an issue. Therefore for a disease such as psoriasis, calculated QALYs merely reflect the integrated loss of HRQoL due to the disease.

QALYs are the arithmetic product of the time horizon (i.e. study duration) and the quality of life during this time horizon (i.e. EQ-5D utilities). As such, the mean QALYs for the study group can be visually conceptualised by plotting the mean utility scores against time. In such a plot the Area Under the Curve (AUC) reflects the quality adjusted time experienced (usually expressed in QALYs).

Psoriasis severity and other determinants

The instrument used to measure psoriasis severity from the patients perspective was the Self Administered Psoriasis Area and Severity Index (SAPASI) ranging from 0 (= no psoriasis) to 72 (= most severe psoriasis).[33-35] We avoided collinearity (correlation between predictors) by not including other psoriasis-specific variables (with overlapping domains). Besides the impact of psoriasis, HRQoL is known to be influenced by many other determinants in addition to psoriasis severity. For instance by factors associated with the treatment or general factors such as age, gender and employment status.[4;6;11;36] Information about demographics and other characteristics was collected using a general questionnaire as part of the trial design.[17]

Measurement planning

Psoriasis severity was determined at inclusion in the study (t=0, baseline), at start of the UVB treatment (t=1), after 23 irradiations (t=2), at the end of the UVB treatment (t=3), and bimonthly during one year after the end of the treatment (t=4 to t=9). Demographic characteristics were measured at baseline (t=0). The various HRQoL questionnaires were applied at t=0, t=2 and t=3.

Statistical analysis

We compared baseline and end-of-treatment data by determining their differences and calculating 95% Confidence Intervals (95% CIs).

To estimate the impact of psoriasis on HRQoL while taking advantage of our longitudinal design, we used linear multilevel models.[37] The expression 'multilevel model' is a technical terminology, used for modelling clustered data which is the case in longitudinal data and repeated measures. Patients represent the highest level. The repeated measures within each patient represent the lowest level. In this approach, it is assumed that missing data are missing at random (MAR).[38]

The interpretation of linear multilevel models is rather similar to that of linear regression models. Both types of models produce regression coefficients with accompanying standard errors. From a (multilevel) regression model, the variable of interest (dependent variable, Y) can subsequently be estimated from several predicting (explanatory) variables (X) using regression coefficients (β).

An example of a model is: $Y = intercept + \beta_1 * X_1 + \beta_2 * X_2 + \beta_3 * X_3 + \ldots etcetera$. As such, the regression coefficients describe the relationship between the dependent variable Y and the predicting variables X in terms of 'One point increase in variable X_1 gives a β_1 point increase in variable Y, given that all other predicting variables remain unchanged'. The $intercept$ is the value of the dependent variable Y when all X variables equal zero.

The major advantage of multilevel modelling as opposed to ordinary linear regression analysis is that linear multilevel models take an additional source of variability into account, namely the correlation between repeated measurements within one person. Therefore, linear multilevel models can be applied on data comprising several repeated measurements per person (longitudinal data), whereas linear regression models assume independent observations. People sometimes pool subsequent observations in effect assuming independence between subsequent measurements. Clearly the latter approach may yield overly optimistic model fit and should be avoided.

Using analysis with linear multilevel models we ascertained our assumption that a patient assessed psoriasis severity instrument (such as the SAPASI) better predicts HRQoL than a more 'objectively' assessed measure such as the PASI score. Therefore, to predict HRQoL in the best possible way, the SAPASI was preferred to the PASI.

For all dependent variables (PDI, SF-6D, EQ-5D and each domain of the SF-36), we created separate models. For each dependent variable we sequentially included several explanatory variables such as time since start of therapy and the SAPASI. In order to get easy-to-read effect estimates we multiplied the EQ-5D and SF-6D utility scores by 100 before creating the multilevel models. Fixed and random effects were considered. As starting point we used the model with random intercept and without other explanatory variables, only considering within patient variability and between patient variability.

The goodness of fit was evaluated by the change in deviance of the (nested) models. To estimate the effect of possible predictors, and to check for possible interactions, we added several demographic determinants, patient specific characteristics and interaction terms in the model. Interaction terms of the predicting variables are described when significant. We considered demographic variables such as gender, age, level of education, employment status, living alone, children living at home and age of the youngest child living at home. Patient characteristics comprised age at onset of psoriasis, concomitant use of medication, time passed since UVB therapy had started, treatment-arm and previous (home) UVB treatment. We used the MLwiN software package for fitting multilevel models (version 2.02; Center for multilevel Modelling, Institute of Education, University of London, UK).

After creating models for the outcomes of all HRQoL instruments, we used the regression model for the EQ-5D utilities to estimate mean EQ-5D values for the missing measurements at t=1 and t=4 to t=9. We subsequently plotted the observed and estimated EQ-5D utilities against time in order to calculate QALYs experienced. We compared the QALYs experienced by our study population with those experienced by the average Dutch population (calculated using the mean national Dutch population utility score).[39]

6.4 Results

Participants and characteristics

In total 196 patients were included in the study. Of these, 185 completed the questionnaires both at inclusion in the trial and at the end of the treatment.
A consecutive sample of (the first) 105 participants completed follow-up until one year after the end of therapy (measurements 4 to 9). Of the entire group (n=196), the mean age was 43.1 years (95% CI 41.1 to 45.1), and 67% (132) were men.
Baseline and end of treatment values of the SAPASI and the HRQoL measures are presented in table 1, inclusive of their differences and 95% CIs).
From baseline to the end of treatment, the SAPASI decreased significantly while simultaneously all HRQoL measures improved. Of the study population, half of the participants (50%, 98) were randomised to receive home UVB treatment, while 48% (94) had previous experience with UVB treatment. The mean age at onset of psoriasis was 27.1 years (95% CI 24.9 to 29.3). The majority of the participants (72%, 142) were employed, and only 6% (12) were not educated or educated at low level. Approximately 14% (28) lived alone, while 46% (90) had children living at home. Mean age of the youngest child living at home was 8.8 years (95% CI 7.2 to 10.4).

Table 1 – Clinical characteristics[a]

	Baseline	**End of treatment**	**Difference (95% CI)**
SAPASI	7.3	1.9	-5.4 (-4.9 to -5.9)
PDI	33.5	21.5[b]	-12.1 (-10.2 to -14.0)[b]
EQ-5D	0.81	0.90	0.08 (0.05 to 0.11)
SF-6D	0.74	0.83	0.08 (0.07 to 0.10)
SF-36 domains:			
PF (Physical Functioning)	84.6	88.6	3.8 (1.4 to 6.2)
RP (Role limitations Physical)	70.4	83.2	12.6 (7.4 to 17.7)
BP (Bodily Pain)	69.3	82.7	12.8 (9.6 to 16.0)
GH (General Health perception)	62.5	67.7	4.8 (2.6 to 7.0)
VT (Vitality)	58.9	64.9	5.5 (3.0 to 7.9)
SF (Social Functioning)	76.0	88.9	12.0 (8.6 to 15.3)
RE (Role limitations Emotional)	69.9	87.0	16.6 (10.4 to 22.7)
MH (Mental Health)	70.5	76.8	5.8 (3.6 to 7.9)

a Presented values are mean values. Baseline values n=196. End of treatment values and differences n=185.

b n=184

Impact on HRQoL

The SAPASI score, gender, employment status, age, level of education, time passed since UV therapy had started, and children living at home appeared to be significant predictors of HRQoL. In none of the models age at onset of psoriasis, living alone, age of the youngest child living at home, concomitant use of medication, treatment-arm and previous (home) UVB treatment had predictive value.

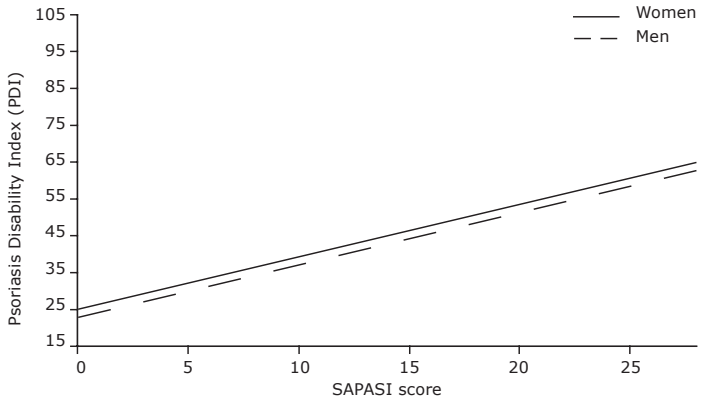
The results of the fixed effects of the models of the various HRQoL measures are presented in table 2 (see page 114-115). When the interaction term (product) of two determinants was a significant predictor, we also presented the main effects for the separate determinants, regardless of their significance. For the sake of simple representation, we did not show the random effects.

Using the results of table 2, the models for all HRQoL measures can be described using their own separate regression coefficients. Each regression coefficient represents the change in mean HRQoL for 1 point increase in the corresponding predictor, given that all other predictors remain unchanged. In general, negative regression coefficients stand for an impairment of the HRQoL measure. Note however that for the PDI, negative regression coefficients signify a decrease in the disability score, and hence an improvement in HRQoL instead of a worsening. For a clear comprehension of all models, we will discuss the results of the PDI model.

In table 2 the PDI model is presented as: *Mean PDI = 23.676 + (2.333 x SAPASI) + 2.643 (only for women) + (-0.053 x Age) + (-14.393 x Time from start therapy) + (-0.02 x Age x SAPASI)*. As shown in this model, we found a clear association between the PDI and the SAPASI, but gender, age, and time from start of the therapy were also of influence. For instance, for each point increase of the SAPASI score the PDI worsened by 2.33 points, given that all other predictors remained unchanged. Similarly, women had a PDI score 2.64 point higher (more impaired) than men. For every year a person grew older, however, the PDI score improved by 0.05 point, and for every month after the start of the therapy the PDI score improved by (1/12) x 14.39. We also found interaction between age and SAPASI, meaning that for each point increase in the interaction term (product) of the SAPASI score and age (SAPASI x age) the PDI score improved a further 0.02 point.

For visual conceptualisation, the estimated means of the PDI and the SF-36 domain SF are depicted in figures 1 and 2 as function of the SAPASI score for the different subgroups and mean values of other predictors.

Figure 1 – Impact of the SAPASI on the Psoriasis Disability Index (PDI)

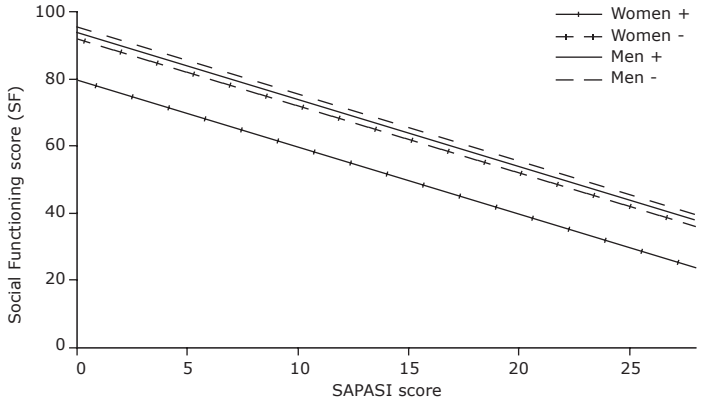


The impact of the SAPASI on the PDI at inclusion in the study, using the multilevel model of the PDI:

Mean PDI = 23.676 + (2.333 x SAPASI) + 2.643 (only for women) + (-0.053 x Age) + (-14.393 x Time from start therapy) + (-0.02 x Age x SAPASI)

Used values for 'age' and 'time from start therapy' were mean values at baseline. Mean age at baseline = 43.11 years. At baseline, the mean time from start therapy = -0.076 years.

Figure 2 – Impact of the SAPASI on Social Functioning (SF)



The impact of the SAPASI on social activities and contact with family/friends/neighbours (= SF, the SF-36 Social Functioning domain), using the multilevel model of the SF:

Mean SF = 95.667 – (1.983 x SAPASI) – 3.624 (only for women) – 0.708 (only when children living at home) – 12.083 (only for women with children living at home)

Women + : Women with children living at home

Men + : Men with children living at home

Women - : Women without children living at home

Men - : Men without children living at home

Table 2 – Regression coefficients[1] for the linear multilevel models

Predictors	PDI	EQ-5D (x100)[2]	SF-6D (x100)[2]	SF-36 domain scores	
				PF[3]	
Intercept[4]	23.676 (2.610)	89.843 (2.328)	82.499 (1.667)	93.034 (5.606)	
SAPASI (0 to 28 points)	2.333 (0.396)	-1.428 (0.162)	-0.976 (0.192)	-0.769 (0.149)	
Gender					
Male (0)	0 (ref)	0 (ref)	0 (ref)	0 (ref)	
Female (1)	2.643 (1.348)	-10.339 (2.249)	-7.939 (1.494)	-13.128 (2.408)	
Employment status					
Unemployed (0)		0 (ref)	0 (ref)	0 (ref)	
Employed (1)		8.341 (2.320)	6.471 (1.785)	9.526 (2.806)	
Age (19 to 80 years)	-0.053 (0.053)				
Time since start therapy (-0.33 to 0.72 year)	-14.393 (3.858)				
Children living at home					
No (0)					
Yes (1)					
Level of education					
No/low (0)					
Middle/High (1)					
Employment status x SAPASI[5]					
Unemployed (0) x SAPASI			0 (ref)		
Employed (1) x SAPASI			-0.488 (0.230)		
Age[5] **x SAPASI**[5]	-0.022 (0.008)				
Gender x Time since start therapy[5]					
Male (0) x time since start therapy					
Female (1) x time since start therapy					
Gender x Children at home					
Male (0) without children at home (0)					
Male (0) with children at home (1)					
Female (1) without children at home (0)					
Female (1) with children at home (1)					

1 Using linear multilevel models, the SAPASI score and other important predictors were regressed on various HRQoL outcomes, i.e. the PDI, EQ-5D[2], SF-6D[2] and SF-36 domains[3]. Values presented are fixed effects (standard errors) of the final models and include the significant predictors. Each regression coefficient represents the change in mean HRQoL for 1 point increase in the corresponding predictor, given that all other predictors remain unchanged. An empty cell indicates that the variable was of no predictive value for the HRQoL-item of interest.

2 EQ-5D and SF-6D utility scores times 100

	RP[3]	BP[3]	GH[3]	VT[3]	SF[3]	RE[3]	MH[3]
	81.341 (4.087)	75.458 (3.118)	56.208 (5.637)	62.275 (6.090)	95.667 (1.652)	96.976 (2.562)	81.337 (1.378)
	-2.073 (0.313)	-1.424 (0.262)	-0.876 (0.146)	-2.678 (0.516)	-1.983 (0.196)	-2.946 (0.359)	-1.091 (0.130)
	0 (ref) -17.231 (3.995)	0 (ref) -11.213 (2.901)	0 (ref) -11.240 (2.872)	0 (ref) -10.796 (2.459)	0 (ref) -3.624 (2.768)	0 (ref) -14.586 (4.000)	0 (ref) -8.647 (2.269)
	0 (ref) 14.628 (4.108)	0 (ref) 12.826 (2.647)	0 (ref) 6.087 (3.029)	0 (ref) 5.856 (2.862)			
				0.104 (0.103)			
		10.699 (7.345)					
					0 (ref) -0.708 (2.284)		
			0 (ref) 12.515 (5.634)				
				0.033 (0.011)			
		0 (ref) 21.458 (10.322)					
					0 (ref) 0 (ref) 0 (ref) -12.083 (4.036)		

3 Abbreviations of the SF-36 domain scores: PF= Physical Functioning; RP= Role limitations Physical; BP= Bodily Pain; GH= General Health perception; VT= Vitality; SF= Social Functioning; RE= Role limitations Emotional; MH= Mental Health

4 Intercept: y-intercept, point of origin, the coordinate of the point at which the curve intersects the y-axis

5 Continuous predictor as part of an interaction term. Range is similar to the range presented for the single predictors.

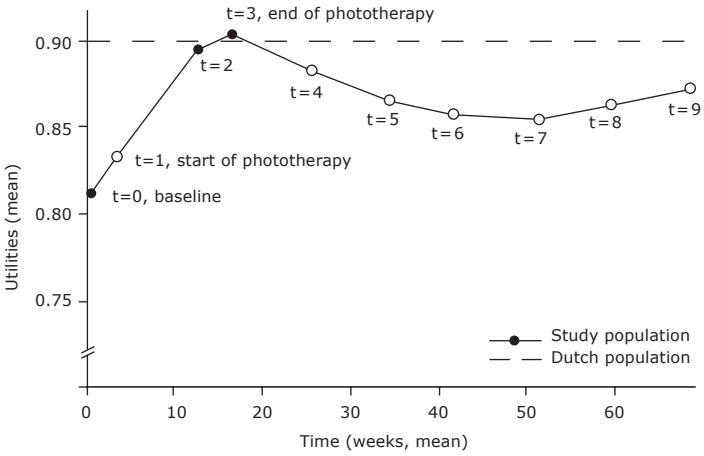
Impact in terms of QALYs

As described in the methods section, we used the regression model for the EQ-5D utilities (presented in table 2), to estimate mean EQ-5D values for the missing measurements at t=1 and t=4 to t=9. Mean EQ-5D utilities for the study population (observed and predicted) are schematically represented in figure 3. The Area Under the Curve (AUC) reflects the quality adjusted time expressed in QALYs.
To allow for comparison with a relevant standard we additionally plotted the Dutch population mean utility score against time. For comparison, the Dutch population mean value of the EQ-5D was 0.90.[39] Mean age of this reference population was 43.4 years and 51% were men, which is fairly comparable to our study population. The difference between both plotted AUCs reflects the impact of psoriasis on QALYs when compared to the average Dutch population. During the entire study (68.7 weeks = 1.317 year), the average Dutch population would have experienced 1.185 QALY (= AUC = 1.317 year x 0.9 utility score). The study population on the other hand experienced 1.142 QALY (AUC). The impact of psoriasis in our population compared to the average Dutch population therefore was a loss of 0.043 QALY (1.185-1.142, area between both curves) during 1.317 year. Assuming that our study population would be a random sample of all psoriasis patients in the Netherlands, psoriasis would hence cause an annual loss of approximately 16.000 QALYs (16 million inhabitants, prevalence psoriasis approximately 3%).

6.5 Discussion

All HRQoL measures showed worse outcome with increasing SAPASI scores, indicating that quality of life is inversely related to psoriasis severity. As a result, during the study period the study population suffered a loss of 0.043 QALY compared with the average Dutch population, which on a national level would account for a considerable annual QALY loss of 16.000 QALYs. These results appear consistent with common sense, yet for the first time do allow more accurate predictions of the impact of self assessed psoriasis severity on HRQoL and on QALYs. Also comparison of the impact of psoriasis with the impact of other chronic diseases on society is now more straightforward.

Figure 3 – EQ-5D utilities against time



Mean EQ-5D utilities for the study population (solid line) and the average Dutch population (dashed line) against time for the duration of the study (68.7 weeks). The mean EQ-5D utility for the average Dutch population was based on a study of Lamers.[39] Mean EQ-5D utilities for the study population at t=1 and t=4 to t=9 were predicted using the multilevel model of the EQ-5Dx100: *EQ-5Dx100 = 89.843 – (1.428 x SAPASI) – 10.339 (only for women) + 8.341 (only when employed)*

● observed mean values of the EQ-5D in study population

○ predicted mean values of the EQ-5D in study population, extrapolated using the linear multilevel model

Key findings

Both the SAPASI score and HRQoL improved significantly over treatment. Baseline HRQoL values in our study were lower than those of the common Dutch population,[24;39] reflecting a decreased HRQoL due to psoriasis. Moreover, the mean baseline EQ-5D utility of our participants (0.81) was comparable to that of patients with other chronic conditions such as cancer, arthritis, stroke, kidney disease, heart diseases and depression.[40]

The results of the repeated measures analyses (multilevel modelling) implicate that HRQoL for patients with psoriasis is primarily predicted by (1) the psoriasis severity, (2) the gender and the (3) employment status of the patient.

For instance, the results show without exception that HRQoL becomes more impaired when the SAPASI score increases. This is not surprising, since psoriasis is a chronic disease that can have a profound impact on the patient's life;

emotional, social, as well as physical.[5;11] It is also in line with many previously published studies.[6] What is new, however, is that now there is an accurate estimate of the actual size of the impact self assessed psoriasis severity on HRQoL. In addition, the absolute size of the impact varies with the specific HRQoL measure used. For instance, the impact on the various HRQoL measures ranges from 0.77 point worsening per point increase of the SAPASI score for the PF domain to 2.9 point worsening per point increase of the SAPASI score for the RE domain, adjusted for other determinants.

Also without exception, HRQoL was always lower for women than for men, even up to a 17.2 point difference for the RP domain of the SF-36. The distinction between men and women is in accordance with previous findings,[2;9;41] and can be explained by the cosmetic and disfiguring consequences of psoriasis (which are likely to have more impact on women than on men).[42] In addition to SAPASI and gender, employment status too appeared to be an important predictor of HRQoL. Being employed was related to a 5.9 to 14.6 point increase in RP, VT, BP, GH, PF, EQ-5D (x100) and SF-6D (x100). It however reduced the SF-6D utility score (x100) for employed individuals with a SAPASI score exceeding 13.26 (13.26 = 6.471 increase in SF-6D when employed / 0.488 reduction in SF-6D per point increase in SAPASI when employed). We did not note similar results being reported in the other studies on HRQoL in psoriasis.

Other interesting findings in this patient population were that with increasing age, the PDI and the VT domain improved. Also, with increasing duration of the 'time since start of therapy', the PDI and BP improved, the latter especially for women. Possibly this phenomenon is caused by increased coping during (the wait for) active treatment. We also found that having children living at home lowered the SF, especially for women (12.1 points). This may be due to the fact that the care of the children is often partly at the expense of social activities, and traditionally this applies to mothers rather than fathers. Finally, a moderate or high level of education resulted in a higher perception of the general health (GH). Wahl et al.[16] found a similar positive effect of education on HRQoL.

Along with the recurrent nature of psoriasis, HRQoL varies. This is reflected in the fluctuating utility scores overtime (figure 3), which ultimately indicated an average loss of 0.033 QALYs per person per year (0.043 QALY/1.317 year) when compared with the average Dutch population. As such, the impact of psoriasis in terms of QALYs lost in our population is comparable with the impact of other chronic diseases, e.g. ulcerative colitis, Crohn's disease, cancer, renal failure,

stroke and heart disease.[40] The total estimated loss in QALYs due to psoriasis on a national level (16.000 QALYs annually) may be used by policymakers to compare the impact of various chronic diseases on society, and to prioritise reimbursement policies.

Comparison with other studies

Our findings are consistent with those of other studies indicating a decreased HRQoL with increased psoriasis severity.[6] Our results are also similar to studies indicating that women and/or younger individuals report a higher impact of psoriasis on HRQoL.[2;9;16;41;43]

However, only five previous studies actually tried to accurately quantify the size of the impact of psoriasis on HRQoL, four of which used cross-sectional data.[9;10;14-16] For instance, Rapp et al. published a paper regressing the SAPASI scores on the eight SF-36 domains.[15] They found younger age, female gender and higher SAPASI scores to be related with impaired HRQoL. We have no explanation for their finding that female gender would only affect PF and RE domains, and that increasing age in their study was beneficial for other domains than it was in our study. Also, the impact of the SAPASI scores on individual HRQoL domains as reported in their study appeared less compared to our findings. The latter may however be explained by the fact that -besides the SAPASI score- they also included 18 variables on different aspects of psoriasis, thereby possibly introducing collinearity (i.e. correlation between the predicting variables). Collinearity is not an issue when the only goal is to make a model that predicts HRQoL from a variety of data (predicting model), but becomes a problem when also trying to explain the magnitude of the impact of the SAPASI in an explanatory setting.

In accordance with the study of Rapp, also Wahl et al.[16] found that younger age and self reported psoriasis symptoms influence the HRQoL (Quality of life scale, QOLS) negatively. By contrast, two other studies concluded that decreased (SA)PASI scores were nòt significantly associated with an improvement in the HRQoL (SF-36, EQ-5D, PDI, Psoriasis Life Stress Instrument = PLSI). For one study[10] this is probably due to a lack of power, they analysed data from only 35 participants. In the other study[14] the use of the PASI score might be the source of the lack of association, because it does not incorporate the patient's perspective, and therefore is not a very powerful determinant of HRQoL.

The only study using longitudinal data to quantify the impact of psoriasis on HRQoL is the study from Unaeze.[9] Regrettably, they only had longitudinal data

concerning HRQoL, and not on psoriasis severity. Therefore, though they had longitudinal data available, they did not perform longitudinal analyses. They pooled subsequent observations on HRQoL assuming independence between subsequent measurements, but this approach may yield overly optimistic model fit and should be avoided. They furthermore analysed the impact of the affected percentage body surface area (%BSA) on HRQoL as measured by the Impact of Psoriasis questionnaire (IPSO). They found that younger age, self reported poor general health, younger age at onset of the psoriasis, and use of prescription drugs were significantly associated with an impaired IPSO score, while the %BSA was not. Also in this study, this might be caused by the fact that the %BSA does not include the patient's perspective of psoriasis severity.

Strengths and limitations

A first strength of the present study is the use of the SAPASI as a variable predicting HRQoL. As is discussed elsewhere, subjective experience of psoriasis is considered a more powerful determinant of HRQoL than the so-called objective professional's measure of severity.[12;13] In our opinion, the SAPASI score includes some degree of subjectivity because it is patient assessed. Thus in theory, it would have better predicting features than a PASI score or a %BSA. Initial modelling confirmed that indeed the SAPASI was a better predictor of HRQoL than the PASI, which is the reason why we continued modelling with the SAPASI instead of the PASI. Based on our experience in this study, we propose that in order to predict HRQoL the use of the SAPASI score is preferable to the PASI score, the %BSA[9] and to non-standardised self reported symptoms.[16]

Another benefit of our study is that, in contrast to some previous studies, we regressed psoriasis severity on several well known and commonly used HRQoL measures. The use of the SF-36, the EQ-5D and the PDI therefore makes interpretation, comparison and future use of our results fairly straightforward.

As described in the introduction and methods sections, QALYs are commonly used in economic evaluations. In economic evaluations one is especially interested in the effectiveness of a study population when compared to a national reference population and other patient categories. As such, the calculation of QALYs experienced by our study population, facilitate comparison of the impact of psoriasis with the impact of other diseases.

A fourth strength is that we performed a prospective study and analysed our longitudinal data using a repeated measures analysis (linear multilevel models).

Using this type of statistical analysis the data from the 3 consecutive measurements were optimally used, taking into account the correlation between measurements within persons. This way we were able to reduce variance in the regression coefficients without enlarging the study group.
A possible limitation of our study is that some HRQoL variables were not normally distributed. For these measures, we initially considered logistic regression methods instead of linear regression models. The logistic models, however, revealed the same determinants as were found in the linear multilevel models. Therefore, for comprehensibility, we chose to present only the results of the linear models.

Conclusion and recommendations:

We corroborated that HRQoL worsened with increasing SAPASI scores—that is, HRQoL was inversely related to self assessed psoriasis severity. We showed that in terms of loss QALYs, psoriasis has a considerable impact on society. This impact in terms of loss of QALYs can now be easily compared with the impact of other chronic diseases on society. We furthermore demonstrated that in patients suffering from psoriasis, female gender and being unemployed were also important predictors of a decreased HRQoL. With the models we presented we are able to accurately estimate the size of the impact of self assessed psoriasis severity on HRQoL.
Also we can use these models to predict HRQoL in our study-population when the explanatory variables (such as SAPASI score, gender, and age) are known.
When the results of our study are confirmed in another population, the models presented here might be used to predict HRQoL in other populations as well.

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EQ-5D versus SF-6D in psoriasis

EQ-5D versus SF-6D in psoriasis; comparing scores and sensitivity to change

Mayke BG Koek
Vigfús Sigurdsson
Wendy J Post
Carla AFM Bruijnzeel-Koomen
Erik Buskens

Submitted

7.1 Abstract

Background Mean values of the EQ-5D and the SF-6D utility scores are used to calculate incremental cost-utility ratios in economic evaluations. Literature suggests that both utility scores display different sensitivity to change, and hence cost-effectiveness may depend on the choice of utility measure.

Objective To describe the characteristics and assess the comparability and usefulness of the EQ-5D and SF-6D for calculating incremental cost-utility ratios in economic evaluations in psoriasis studies.

Methods Data from a randomised trial on phototherapy for psoriasis were used. The EQ-5D and SF-6D were completed at three time points until the end of treatment. Psoriasis severity was assessed simultaneously, but also bimonthly during a 12 month follow-up. The distribution and characteristics of the EQ-5D and SF-6D were compared, and agreement was assessed (Bland Altman approach). The course of both utility instruments during follow-up was predicted using previously published multilevel models.

Results The EQ-5D showed a considerable ceiling effect (40%) and had a broader scoring range and higher mean values than the SF-6D (0.81 versus 0.74 at baseline, difference 0.07, 95% CI 0.05 to 0.09). Agreement between both instruments was poor, but correlation between baseline scores was 0.68. Mean improvement in utility scores during treatment was similar; 0.08 for both instruments (difference -0.003, 95% CI -0.03 to 0.02). The observed difference between both mean scores remained stable, which was adequately reflected in the estimated utility scores during follow-up.

Conclusions Agreement between both utility instruments was poor, but the mean scores displayed a similar sensitivity to change in psoriasis severity. In economic evaluations in populations with a burden of disease comparable to ours, the use of either the EQ-5D or the SF-6D may result in similar cost-utility ratios.

7.2 Introduction

Cost-effectiveness analyses are becoming increasingly important in determining the benefits and relevance of treatments in health care. Such an analysis balances the gained effects against the risen costs of a treatment when compared with an alternative, and hence is often the basis for policy decisions. In cost-effectiveness analyses the effects are generally measured in terms of Quality Adjusted Life Years (QALYs), which may be estimated by multiplying time by health utilities. Health utilities can be assessed using several preference based utility measures. One of the most frequently used utility measures is the EuroQol 5D (EQ-5D), which consist of 5 questions thus capturing 5 dimensions.[1;2] Another, relatively new, utility measure is the SF-6D (Short Form-6D), which is derived from the SF-36 (36-item Short-Form General Health Survey).[3;4] It uses a subset of 11 questions yielding 6 dimensions.[5] The SF-6D was developed with the intention to create a utility measure with a better descriptive ability and a higher sensitivity to change than the EQ-5D.[6-8] However, further investigation of the SF-6D was recommended to verify or refute these assumed advantages.[5]

Literature suggests that the EQ-5D and SF-6D utilities may display different sensitivity to change in different circumstances.[5;8-11] The EQ-5D may not be suitable to distinguish between health states close to perfect health due to a gap in the EQ-5D values at the higher end of the utility scale (between 0.883 and 1).[10;12] The five EQ-5D dimensions are limited to three response categories only, resulting in a so-called ceiling effect for the EQ-5D utility score)—that is, individual patients may already have a maximal utility score at baseline, making improvement of the utility score due to treatment impossible.[9] By contrast, the SF-6D has more response categories and a richer descriptive system than the EQ-5D, supposedly leading to better discriminative abilities especially in health states close to perfect health.[5;8;10;11] The SF-6D does not seem to have a ceiling effect,[9] but has a limited range of scores at the lower end of the utility scale, resulting in higher utility scores than the EQ-5D for more severe health states.[10;11] In brief, there is evidence to suggest that the EQ-5D has on average higher utility scores than the SF-6D for health states close to perfect health, but has on average lower utility scores than the SF-6D for more severe health states.[11;13]

When evaluating the effects of an intervention, the differences between various utility instruments such as EQ-5D and SF-6D ultimately might lead to a considerable variation in estimated effects in terms of health utilities and hence

in calculated QALYs. As a result, the primary outcome in economic evaluations of incremental costs per QALY gained may vary with the used utility instrument.[14;15] Consequently, the use of non-equivalent health utilities could potentially affect policy decisions and should therefore be thoroughly investigated.
To the best of our knowledge, the SF-6D has not been used previously in psoriasis research. Also, the EQ-5D has not been applied often. As such, for psoriasis research it is unknown whether the EQ-5D and SF-6D are comparable and useful or not, and whether both instruments equally pick up relevant changes in clinical outcome. Therefore the aim of this study was to describe the characteristics of the EQ-5D and SF-6D utility scores in psoriasis research, and to investigate the agreement between both instruments in terms of absolute values, change scores and sensitivity to change. We also aimed to predict the course of utility scores during the follow-up using previously published multilevel models in order to visualise the course of utility scores over a longer period of time. We discuss the validity of using these multilevel models to obtain long term QALY estimates in cost-effectiveness studies. We addressed these questions using data from a randomised clinical trial.

7.3 Methods

Patients and design

We obtained data from 196 patients with psoriasis who participated in a pragmatic single blind randomised clinical trial comparing home ultraviolet B (UVB) phototherapy with the current outpatient UVB treatment.[16;17] The first consecutive 105 participants were also followed during one year after the end of therapy.
We grouped all data regardless of the randomisation, because there were no differences between both treatment groups.[17] The protocol of this trial has been described in detail in a previous publication (open access on http://www.biomedcentral.com/content/pdf/1471-2288-6-39.pdf).[16] The institutional review board of the University Medical Center Utrecht approved the study (02/090-O), and all participants provided written informed consent prior to inclusion in the study.

Instruments and planning

EQ-5D and SF-6D health utilities were measured using the EQ-5D[1] and the SF-36[3;4] questionnaires. The EQ-5D instrument comprises five questions that were developed to assess the impact of a disease on 5 health domains: pain, mood, mobility, self care, and daily activities. Each domain has 3 levels, resulting in 243 (3^5) possible health states. We applied the MVH A1 algorithm[18] to generate one overall value judgement, a so-called utility score. This algorithm produces an EQ-5D utility score ranging from -0.594 (the pits) to 1 (optimal health).[1;2]

The SF-36 is a generic Quality of Life questionnaire, from which a subset of 11 questions is used to derive the SF-6D utility score.[5;12] The SF-6D comprises 6 domains: pain, mental health, physical functioning, social functioning, role limitations and vitality. The domains have 6, 5, 6, 5, 4, and 5 levels respectively, resulting in 18.000 possible health states. The SF-6D utility score ranges between 0.291 (worst possible health state) and 1 (optimal health).[5]

The instrument applied to measure psoriasis severity was the Self Administered Psoriasis Area and Severity Index (SAPASI),[19-21] ranging from 0 (= no psoriasis) to 72 (= most severe psoriasis). SAPASI measurements were planned at inclusion (t=0), start of therapy (t=1), 23 irradiations (t=2), end of UVB treatment (t=3) and bimonthly during one year after the end of the UVB treatment (t=4 to t=9). When UVB treatment took more than 46 irradiations, the 46th irradiation was defined to be the end of the UVB treatment.[16] The SF-6D and EQ-5D utility scores were applied at time points 0, 2 and 3 only.

Statistical analysis

Comparison of both utility measures was performed analogous to a similar study among patients with coronary heart disease by van Stel.[8] Because both measures are primarily used in cost-effectiveness studies, and in such studies the focus is on mean values rather than on individual or median values, we too focused on comparison of mean values and mean improvements of the utility scores. For completeness of describing the data, however, we also present the median values and the results of nonparametric tests. First we examined and compared the absolute values of the EQ-5D and SF-6D in order to describe their distribution and characteristics, and to assess their agreement. After that we compared both instruments for their change during treatment. Finally, we estimated missing utility scores in order to depict the course of both scores over a longer period of time.

Absolute values

To describe and compare the absolute values of the EQ-5D and SF-6D we computed mean utilities. We compared mean utilities using their differences and 95% confidence intervals (95% CIs). Median values were computed for descriptive purposes only, and were compared using the Wilcoxon test. Using bar-charts we visualised the distribution of the scores. The ceiling effects (percentage maximal scores at baseline) of the EQ-5D and SF-6D were computed using the number of patients having a score indicating perfect health. Alternatively, the floor effects were calculated using the number of patients having the worst score possible. Agreement between EQ-5D and SF-6D values was assessed using the Bland Altman approach.[22;23] In a Bland Altman plot for each participant the difference between both measures was plotted against the mean of both measures. Bland Altman limits of agreement (difference between both measures +/- 1.96 standard deviation of the difference) were calculated.[22] Using Spearman correlation we investigated the construct validity (convergent validity and discriminant validity) between both instruments and their domains.[24]

Change scores

We compared the change scores (change from baseline to end-of-treatment) using a paired t test and a Wilcoxon test. We assessed agreement of the change scores again using the Bland Altman approach: for each participant the difference between both instruments in change score was plotted against the mean change score of both instruments.[22;23]

Course during study

The scores of the EQ-5D and SF-6D that were missing for all participants (scores at t=1 and t=4 to t=9) were estimated using multilevel models resulting from repeated measures analyses described in an associated paper.[25] Using these multilevel models, the utility scores were predicted from the participants SAPASI score, gender and employment status. We subsequently graphically depicted the observed and predicted mean values against time, together with the mean SAPASI values for all 10 time points. In this way, the changes of both measures during the entire study could be considered.

7.4 Results

196 patients participated in the study. Their mean age was 43.1 year (standard error of the mean (SEM)=1.0) and 67% were men (n=132). At baseline we had complete data for both the EQ-5D and the SF-6D. At the end of the treatment (t=3), however, eleven patients (5.6%) were lost to follow up. At t=2 (23 irradiations) data were unavailable for 32 and 33 participants respectively. For 30 participants this was in accordance with the trial protocol—that is, the questionnaire at t=2 had to be completed when reaching 23 irradiations but for 30 patients treatment had already been stopped *before* the 23rd irradiation (due to either success or failure). There were no significant differences at baseline between patients with or without a missing utility score at t=2 and/or t=3. Missing scores for those two measurements were not imputed.

Absolute values

Mean baseline EQ-5D and SF-6D utility scores were 0.81 (range -0.02 to 1.0) and 0.74 (range 0.44 to 1.0) respectively, showing a statistically significant difference between both measurements (difference 0.07, 95% CI 0.05 to 0.09). At t=2 mean values were 0.89 versus 0.81 (difference 0.08, 95% CI 0.06 to 0.11), and at t=3 they were 0.90 versus 0.83 (difference 0.07, 95% CI 0.05 to 0.09). Median values were 0.80 versus 0.73 (t=0), 1.0 versus 0.8 (t=2), and 1.0 versus 0.84 (t=3) respectively (all p values= 0.000). Figure 1 illustrates that the baseline EQ-5D utility score was already skewed towards perfect health, with increased skewing during the treatment. The SF-6D utility score on the other hand was not skewed, at none of the three measurements (see figure 2).

The ceiling effects (percentage maximal scores at baseline) of the EQ-5D and its domains were much larger than those of the SF-6D (see table 1). In both utility scores there were no floor effects, with minimum values of -0.02 and 0.44 respectively.

We assessed agreement using the Bland Altman approach. The Bland Altman plot of SF-6D and EQ-5D at baseline showed rather poor agreement and wide limits of agreement (figure 3). The deviation between the scores was systematic: persons with a poor health state (mean<0.6) tended to have higher scores on the SF-6D, while healthier persons (mean>=0.6) tended to have higher scores on the EQ-5D. The Bland Altman approach for data of t=2 and t=3 showed essentially similar results (data not shown).

Rank correlations between the EQ-5D and SF-6D utility scores were 0.68 at baseline, 0.55 at t=2 and 0.58 at t=3 (all p-values 0.000). At baseline there were no strong correlations (>0.7) between the domains, see table 2. Twelve correlations were moderate (0.4 to 0.7), of which only four correlations were above 0.5. Correlation for the other two time points yielded essentially similar results (data not shown).

Table 1 – Domain comparison ceiling effects (%)

EQ-5D	Ceiling effect		SF-6D	Ceiling effect
Pain/discomfort	48%		Bodily Pain (BP)	23%
Anxiety/depression	72%		Mental health (MH)	8%
Mobility	84%		Physical Functioning (PF)	47%
Self care	96%		Social Functioning (SF)	37%
Daily activities	72%		Role Limitations (RL)	53%
*	*		Vitality (VT)	5%
Utility EQ-5D	40%		Utility SF-6D	1%

Percentage maximal scores at baseline (ceiling effects) for the EQ-5D and SF-6D and their domains.

* Not applicable

Table 2 – Correlation at baseline between EQ-5D domains and SF-6D domains

	EQ-5D				
SF-6D	Mobility	Self care	Daily activities	Pain/discomfort	Anxiety/depression
Physical Functioning (PF)	**0.502**	**0.328**	**0.435**	0.475	0.308
Role Limitations (RL)	0.232	0.201	**0.472**	0.474	**0.522**
Social Functioning (SF)	0.289	0.188	**0.331**	0.430	0.386
Bodily Pain (BP)	0.449	0.234	0.412	**0.620**	0.316
Mental health (MH)	0.071	0.122	0.169	0.163	**0.499**
Vitality (VT)	0.141	0.224	0.266	0.208	0.517

Correlations (spearman) between corresponding domains are indicated in bold.

All correlations above 0.141 are significant at p<0.05. All correlations above 0.232 are significant at p<=0.001.

Figure 1 – Distribution of EQ-5D values

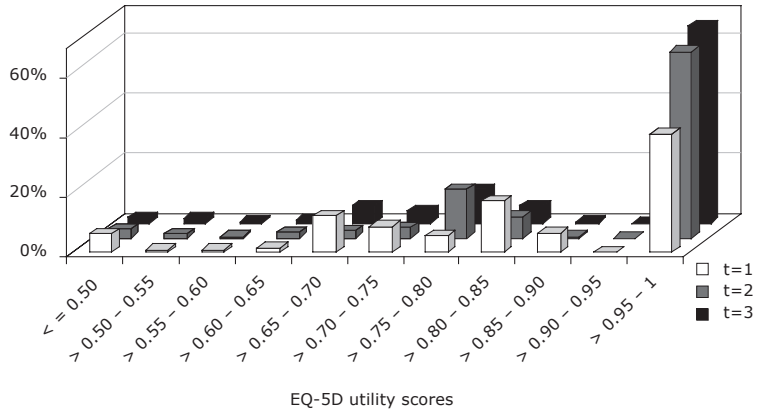
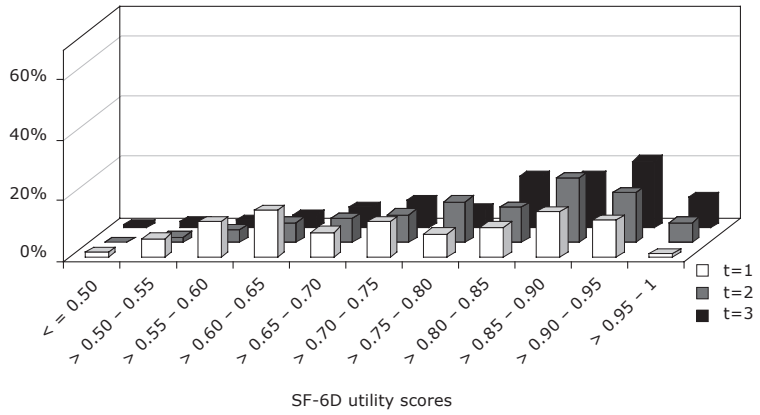


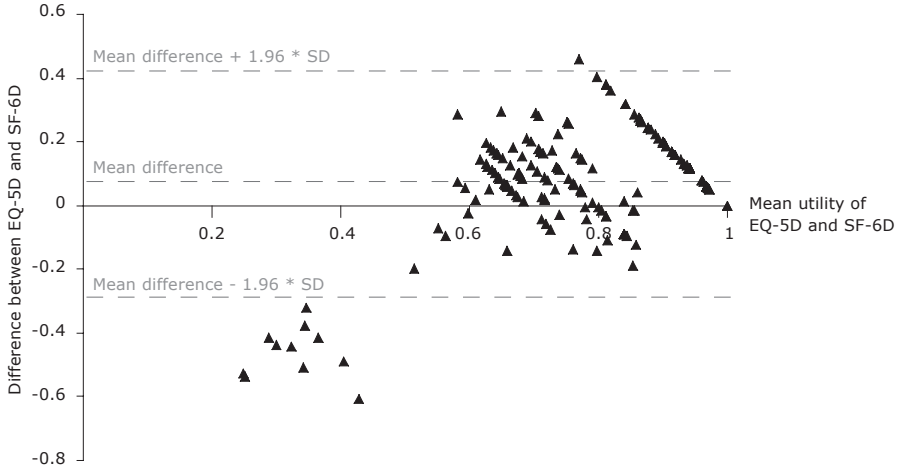
Figure 2 – Distribution of SF-6D values



Change scores

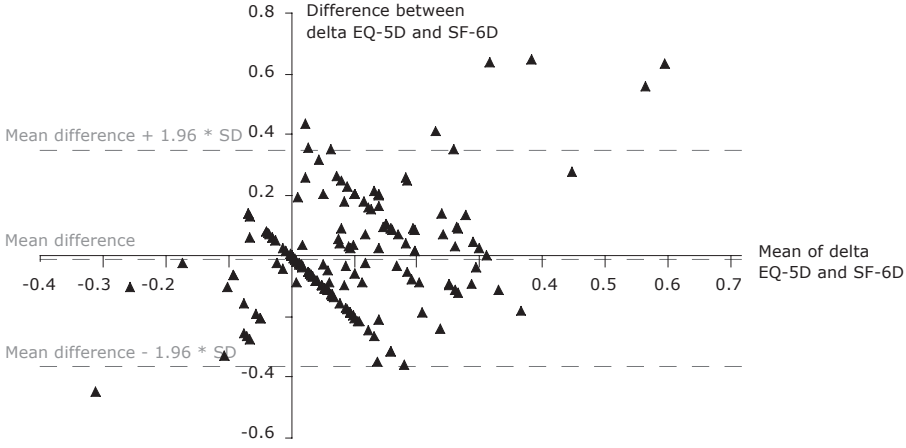
From baseline till the end of treatment the EQ-5D and SF-6D utility scores both showed a mean improvement of 0.08 point (difference -0.003, 95% CI -0.03 to 0.02). Median improvements were 0.00 for the EQ-5D and 0.06 for the SF-6D, Wilcoxon p=0.264. A Bland Altman plot of the change scores revealed a mean difference in change scores of -0.003 with limits of agreement ranging from -0.366 to 0.360, and most of the plotted values lying within those limits of agreement (figure 4).

Figure 3 – Bland Altman plot of EQ-5D and SF-6D



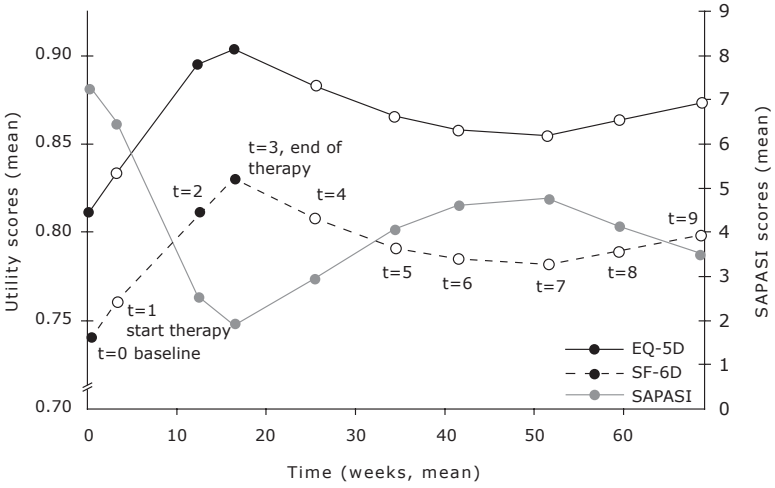
Bland Altman plot of EQ-5D and SF-6D values at baseline. For each individual the difference between EQ-5D and SF-6D, and the mean of both scores were calculated (difference = EQ-5D - SF-6D, mean = (EQ-5D + SF-6D)/2). Limits of agreement = mean difference ± 1.96xSD

Figure 4 – Bland Altman plot of delta EQ-5D and delta SF-6D



Bland Altman plot of EQ-5D and SF-6D change scores. For each individual the difference between change in EQ-5D and change in SF-6D, and the mean of both change scores were calculated (difference in change scores = change in EQ-5D – change in SF-6D, mean change scores = (change in EQ-5D + change in SF-6D)/2). Limits of agreement = mean difference ± 1.96xSD

Figure 5 – SAPASI, SF-6D and EQ-5D against time



Observed (filled) and predicted (blank) values of the SAPASI, SF-6D and EQ-5D are shown. The SAPASI was measured during the entire study, measurements 0-9. The SF-6D and EQ-5D were administered at moments 0, 2 and 3, and predicted for measurements 1 and 4 to 9. Multilevel models used to predict the EQ-5D and SF-6D are presented in an associated paper.[25] The plotted values are based on 196 (t=0), 187 (t=1), 164 (t=2), 185 (t=3), 94 (t=4), 96 (t=5), 94 (t=6), 93 (t=7), 91 (t=8) and 87 (t=9) observations respectively.

Course during study

For visual conceptualisation of the course of the mean utility scores during the study, we decided to plot both the mean utility scores and the psoriasis severity against time (weeks). The EQ-5D and SF-6D had been measured at three time points: t=0, t=2 and t=3. The SAPASI score however was measured during the entire study (10 measurements). With use of previously published linear multilevel models that regressed the SAPASI score, gender and employment status on the utility score[25] we were able to predict mean EQ-5D and SF-6D utility scores for the seven missing measurements (at t=1, and t=4 to t=9). As such we were able to plot the mean EQ-5D and SF-6D scores over time for the entire study period; figure 5 depicts both the observed values and predicted values for both instruments and also shows the course of the SAPASI score. In this figure, the similar sensitivity to change of mean EQ-5D and SF-6D at t=0, t=2 and t=3 is reflected in the estimated values at t=1 and t=4 to t=9. As presented earlier in

this chapter, mean differences between the EQ-5D and SF-6D values at t=0, t=2 and t=3 (observed values) were 0.0701, 0.0827 and 0.0735 respectively. Weighted mean of these three differences was 0.075. This indicates that in our study population the EQ-5D utility score was on average 0.075 point higher than the SF-6D utility score.

7.5 Discussion

In this study we compared the characteristics and performance of the EQ-5D and the SF-6D in a group of patients with psoriasis who were treated with ultraviolet B phototherapy. The reported data describe clear differences between the results of both instruments, but also indicate certain similarities.

With regard to the differences, just like several other studies we found that the mean and median EQ-5D utility scores were higher than the mean and median SF-6D utility scores.[8;9;11;26;27]

A second difference between the EQ-5D and SF-6D was found in the scoring range and distribution of both instruments. The EQ-5D had a wide scoring range (-0.02 to 1.0)—that is, starting much lower than the SF-6D. The EQ-5D, however, also had a considerable ceiling-effect (40%) already at baseline. Conversely, the SF-6D exhibited a much narrower scoring range (0.44 to 1.0) and had almost no ceiling effect. These findings are also consistent with previous studies comparing the SF-6D and EQ-5D.[8-10]

The ceiling effect and the skewed distribution of the EQ-5D were partly caused by the clear gap in EQ-5D values between 0.883 and 1, with no scoring possibilities for health states within this range.[10;12] As a result, the improvement in median EQ-5D score was larger (0.20, from 0.80 to 1.0) than the improvement in median SF-6D score (0.11, from 0.73 to 0.84). This so-called gap, however, also decreased the discriminative ability of the EQ-5D for individuals with health states close to perfect health: many participants had a maximal score at baseline already. Due to this and due to the fewer possible health states of the EQ-5D, the point estimates of the median improvement were 0.00 for the EQ-5D compared to 0.06 for the SF-6D (not significantly different).

Fourthly, agreement between both instruments was poor, as depicted in both Bland Altman plots. In figure 3, individual measurements were scattered conically from the left lower corner to the right upper corner, indicating that healthier

persons tended to have higher scores on the EQ-5D while persons with a poorer health state tended to have higher scores on the SF-6D.[27;28] This observation is similar to that of a paper implying that SF-6D and EQ-5D utility scores 'crossover' at approximately 0.7.[13] Both Bland Altman plots furthermore showed wide limits of agreement, which -as well as the mean difference (0.075) between both instruments- exceeded the so-called 'minimal important difference' of both utility measures.[29-31]

Lastly, alike the results of van Stel,[8] correlations between the separate domains of the EQ-5D and SF-6D showed a scattered pattern with several moderate and no high correlations. Since one would expect high correlations between similar domains (convergent validity), and low correlations with others (discriminant validity),[24] our data do not completely support construct validity of the analogous domains. Nevertheless the mentioned differences, there were also striking similarities between both instruments. For instance, in contrast to the correlation between their domains, the overall SF-6D and EQ-5D utility scores showed a moderate to high correlation (0.68 at baseline). Thus they seem to measure the same construct at least to a certain extent. Furthermore, from the similar improvements of mean utility scores (both improved 0.09 point during treatment, from 0.81 to 0.9 and from 0.74 to 0.83) and from the similar mean improvements in utilities (both 0.08, not significantly different) it is evident that the mean SF-6D and EQ-5D displayed a similar sensitivity to change in psoriasis severity. As such, both mean scores displayed a parallel course inversely related to psoriasis severity, which was also reflected in the mean utility scores predicted using the multilevel models. We conclude that the sensitivity to change of the mean EQ-5D and SF-6D scores was similar, and that the results suggest that a relationship between both measures exists. Apparently the patients in our group had a disease severity and symptoms that can be described by moderate utility scores in a range in which the mean EQ-5D and SF-6D improve equally under treatment.

Thus, unlike the conclusion of other investigators[11;14;15;29] the use of the SF-6D rather than the EQ-5D did in our study-population not result in different mean health gains and would therefore not lead to higher or lower incremental costs per QALY gained in an economic evaluation.

Initially, one might maintain that for very severe or very mild psoriasis or for other diseases still a problem exists. After all, agreement between both measures was poor, and the scoring range of the EQ-5D is much wider than that of the

SF-6D. It is therefore plausible that the use of the EQ-5D for very severe diseases might lead to greater utility gains than the SF-6D.[11;14;15;29] By contrast, for very mild diseases with a health state close to perfect health, the EQ-5D might not have sufficient discriminative ability to detect any health gain, and possibly results in underestimation of the cost-effectiveness of a treatment.[11] Both of these statements are in line with the results of Kontodimopoulos.[13] Their results imply that above a certain threshold (which probably lies between 0.7 and 0.75) the EQ-5D exceeds the SF-6D, while below this threshold the opposite holds true. Based on this, the authors state that the use of both instruments might provide contradictory estimates of QALY gains, and that therefore the two instruments are not interchangeable. Yet, in this conclusion, they forget to incorporate one potentially important part of their results. In fact, the results of their cross-sectional study showed that in both study-populations the mean EQ-5D and SF-6D utilities started to follow parallel courses fairly prompt above the point of crossover, when the EQ-5D reached the approximate value of 0.8. Taking this into account and incorporating the results of our own study, we therefore suggest that despite all differences between both measures, the EQ-5D and SF-6D are probably very well capable to show similar mean utility gains for diseases with a mean baseline EQ-5D utility score of approximately 0.8 or higher. Of course this hypothesis should be confirmed in further studies.

Summarising, the differences between both instruments indicate a poor agreement, meaning that on an individual level the EQ-5D utility score cannot be reliably predicted from the SF-6D and vice versa. We however noted that for our population, both mean utility scores display a parallel course and have a similar sensitivity to change. The use of multilevel models for estimating and depicting utility scores during follow-up seems a sensible method in the situation where there are missing values during follow-up.

Conclusion and recommendations.

Despite different absolute values, different distributions and the lack of agreement between both instruments, the sensitivity to change of the mean EQ-5D and mean SF-6D was similar. In fact, both mean utility scores displayed a parallel course. Thus in populations with a burden of disease comparable to ours or a baseline EQ-5D utility of 0.8 or higher, the use of either instrument may yield equal incremental costs-QALY ratios. Further investigation is however warranted to confirm this hypothesis.

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Costs and cost-effectiveness of home UVB phototherapy

Cost-effectiveness of home UVB phototherapy for psoriasis: economic evaluation of a randomised clinical trial (PLUTO study)

Mayke BG Koek
Vigfús Sigurdsson
Huib van Weelden
Paul HA Steegmans
Carla AFM Bruijnzeel-Koomen
Erik Buskens

Submitted

8.1 Abstract

Objective To assess the costs and cost-effectiveness of home narrowband UVB (TL-01) phototherapy for psoriasis compared with outpatient UVB phototherapy.
Methods 196 patients with psoriasis were included in a pragmatic multicentre single blind randomised trial comparing home UVB phototherapy with outpatient UVB therapy. Both therapies were conducted in a setting reflecting routine practice in the Netherlands. Patients were followed from inclusion through the end of UVB therapy (horizon 1, mean 17.6 weeks). The first 105 consecutive patients were also followed for one year after the end of UVB therapy (horizon 2, mean 68.4 weeks). For both horizons, a cost-utility analysis, cost-effectiveness analysis and cost minimisation analysis were performed. Main outcome measures were the total costs to society, quality adjusted life years (QALYs, derived from the EQ-5D), and the number of days with a relevant treatment effect (a 50% or more improvement of the baseline Self Administered Psoriasis Area and Severity Index, SAPASI-50)
Results The mean total costs for horizon 1 (end of UVB therapy) were € 800 (home) and € 752 (outpatient), showing an incremental cost per patient of € 48 (95% CI € -77 to € 174). Mean total costs for horizon 2 were € 1272 and € 1148 (difference € 124, 95% CI € -155 to € 403). There were no safety issues and the patients experienced equal health benefits: a gain of 0.296 versus 0.291 QALY during horizon 1 (difference 0.0052, 95% CI -0.0244 to 0.0348), and 1.153 versus 1.126 QALY during horizon 2 (0.0267, 95% CI -0.024 to 0.078). Incremental costs per QALY for home UVB treatment did not exceed € 9276, an amount well below the normally accepted standard of € 20.000 per QALY. The mean number of days with a relevant treatment effect (SAPASI-50) was 42.4 versus 55.3 until the end of UVB treatment (difference -12.9, 95% CI -23.4 to -2.4) and 216.5 versus 210.4 for horizon 2 (6.1, 95% CI -41.1 to 53.2). Incremental costs per QALY for home UVB therapy were € 9276 and € 4646 for the two horizons; the incremental costs per day with a relevant treatment effect were € -4 and € 20 respectively. We noted that the number of days with a relevant treatment effect for home UVB treatment may easily been improved by reducing the waiting time for home UVB treatment.
Conclusions Costs and effectiveness of home UVB phototherapy for psoriasis do not differ from those of UVB treatment in an outpatient setting. Therefore, home UVB treatment should be regarded as a cost-effective intervention, and should be routinely reimbursed.
Trial registration Controlled-trials, ISRCTN83025173. Clinicaltrials, NCT00150930.

8.2 Introduction

Psoriasis is a chronic recurrent skin disorder that can be treated symptomatically in several ways. A highly effective treatment for psoriasis is ultraviolet B (UVB) phototherapy,[1-4] which is indicated when topical treatment becomes insufficient. UVB phototherapy is generally offered in an outpatient clinic, requiring patients to travel to the outpatient department during working hours two to three times a week. This makes it a relatively time-consuming treatment for both the patient and the hospital personnel, imposing a substantial burden on patients and apparently society. Another drawback may be the limited availability of outpatient phototherapy units in sparsely populated areas. As a result, patients living far from an outpatient phototherapy unit may more often receive new potent but expensive biological treatments, just because the infrastructure to deliver a well established and cheaper UVB treatment is lacking.[5]

To overcome the drawbacks of UVB treatment in the outpatient clinic, home UVB phototherapy was introduced in the late 1970s.[6-9] Nevertheless, few dermatologists have actually embraced home UVB phototherapy. The safety, effectiveness and costs of home UVB treatment have been subject of debate, due to the lack of (randomised) clinical research on this treatment.[8-16] Recently, however, we published the results of a randomised trial, providing evidence that home UVB treatment for psoriasis is equally safe and equally effective as the conventional outpatient UVB treatment.[17] Furthermore we demonstrated that home UVB therapy is associated with a lower burden of treatment and is better appreciated by patients than UVB treatment in an outpatient setting.[17]

Now that we delivered evidence that home UVB treatment is equally safe and effective compared to the current outpatient UVB treatment, the costs of both treatments become an increasingly important factor in the choice of treatment and reimbursement. A factual cost-effectiveness analysis on the subject, balancing the costs and the effects of either treatment is however still lacking. We consider it essential to determine the costs of home UVB treatment and to establish whether home UVB treatment for psoriasis is a cost-effective treatment when compared with the standard outpatient UVB treatment. Especially for policy-makers and health care insurers, who are generally still reluctant to reimburse home UVB treatment as opposed to reimbursing the use of biologicals, the results of such a cost-effectiveness analysis will be of importance. Therefore we carried out an economic evaluation alongside a randomised clinical trial to investigate the costs,

cost-effectiveness and cost-utility of home UVB phototherapy compared with conventional outpatient UVB phototherapy in a setting reflecting routine daily practice in the Netherlands. We used the societal perspective, and the focus was on narrowband UVB treatment for psoriasis (TL-01 lamps). The Dutch acronym for the trial is PLUTO.[18] The clinical results of the trial have been published previously.[17] Notably, the accompanying editorial already drew attention to the relevance of an elaborate economic evaluation.[5]

8.3 Methods

Full details of the study design and interventions of this trial have been described in detail in our associated paper presenting the clinical results of this trial,[17] and in a previous publication outlining the study protocol (open access on http://www.biomedcentral.com/content/pdf/1471-2288-6-39.pdf).[18] In brief, the trial was a pragmatic, multicentre, single blind, randomised clinical trial enrolling 196 patients with psoriasis who were considered 'clinically' eligible for narrowband (TL-01) UVB phototherapy.[17;18] In accordance with the pragmatic design, patient selection and administration of the interventions in our trial reflected routine practice.

Clinical study

Consenting persons of 18 years of age or older with plaque or guttate psoriasis were randomly assigned to home TL-01 UVB phototherapy or conventional outpatient TL-01 UVB treatment. Patients randomised to outpatient UVB phototherapy received treatment in their local hospital setting. Patients were treated two or three times per week, in accordance with current practice for their local hospital. The hospital personnel routinely evaluated the treatments and prepared the equipment for each subsequent irradiation. Patients randomised to receive home UVB phototherapy were temporarily provided with a TL-01 home phototherapy unit (Waldmann 100, Waldmann, Villingen-Schwenningen, Germany) in their homes. The unit was rented out by home care organisations (independent suppliers of medical equipment, inclusive of support from specialist nurses), who also delivered the units at the patients' homes. After instruction, the patients received a treatment schedule. The patients evaluated the treatments and set the treatment times by themselves, and could contact the nursing staff of the home

care organisations for supervision. Irradiation took place three to four times per week (every other day), sometimes starting with daily irradiations. At the end of the treatment period, the home care organisations collected the units. The cost for their services, delivery and pick up of the phototherapy unit was included in the rental price.

Summarising, in both treatment arms the irradiation schedules were the schedules normally used by the hospitals and home care organisations. Neither equipment nor schedules were modified for the trial. To avoid interfering with routine practice, we allowed adjuvant use of topical therapy to continue throughout the UVB treatment. Also, all treatment changes initiated after inclusion and randomisation were permitted and were no reason for exclusion. Blinding participants for treatment obviously was impossible, and because of the pragmatic design it was undesirable to blind the dermatologist. The extent and severity of the psoriasis was, however, assessed by an independent research nurse blinded to treatment arm.[17;18]

Clinical effectiveness of both treatments was assessed using the proportion of patients achieving a relevant treatment effect—that is, a 50% or greater reduction of the baseline Psoriasis Area and Severity Index (PASI, range 0-72)[19] or Self Administered PASI (SAPASI, range 0-72),[20-22] the so-called PASI-50 and SAPASI-50. Other measures were the percentage reduction in median (SA)PASI scores, and the (SA)PASI-75 (successful treatment effect) and (SA)PASI-90. Safety of both treatments was assessed by monitoring the occurrence of acute side effects and measuring the total cumulative dose of UVB. We also collected data on concomitant use of medication, demographics, burden of treatment, patient satisfaction, preferences and Health Related Quality of Life (HRQoL). Figure 1 schematically represents the planned measurements. The first four measurements were planned according to individual clinical landmarks—that is, coinciding with inclusion in the study (t=0), actual start of UVB treatment (t=1), around the 23rd irradiation (t=2), and at the end of UVB therapy (t=3). All data were analysed according to the intention to treat principle.[17;18]

Economic evaluation

We performed a within trial economic evaluation, conducting it from the societal perspective. We used two time horizons; the first time horizon (horizon 1) took from inclusion in the study (t=0) until the end of the UVB therapy (t=3), see figure 1. During this period, we followed all 196 participants, mean duration was 17.6 weeks. Horizon 2 lasted from inclusion (t=0) until 12 months after the end of

Figure 1 – Schematic representation of planned measurements

	Horizon 2 (n=196)									
	Horizon 1 (n=196)				Follow-up (n=105)					
	Baseline (inclusion, n=196)	Start of therapy	23 irradiations	End of therapy	2-month FU	4-month FU	6-month FU	8-month FU	10-month FU	12-month FU
Visit to research nurse	Visit 1		Visit 2	Visit 3						
t=	0	1	2	3	4	5	6	7	8	9
Introductory questionnaire	x									
SAPASI	x	x	x	x	x	x	x	x	x	x
PASI	x		x	x						
EQ-5D	x		x	x						
SF-6D	x		x	x						
Diary[b]		x	continuous	x						
Health and Labour	x		x	x						
Follow-up questionnaire					x	x	x	x	x	x

Time horizon 1 runs from t=0 to t=3. Time horizon 2 runs from t=0 to t=9.

a End of therapy: When UVB treatments exceeded 46 irradiations, we defined 46 irradiations as the end of the therapy (cut off point).

b Continuous measurements from t=1 to t=3.

the UVB therapy (t=9), also see figure 1. From the end of UVB treatment onwards, we followed a consecutive sample of (the first) 105 participants bimonthly for one year (t=0 to t=9). Therefore, the analyses for horizon 2 is based on data of 105 participants, mean duration of horizon 2 was 68.4 weeks.

For both time horizons, we compared differences in costs to society with the differences in health effects—that is, the gain of quality adjusted life years (cost-utility analysis) and the difference in the number of days that participants experienced a 50% or greater improvement of their baseline SAPASI score (cost-effectiveness analysis). Since a priori our assumptions with regard to

effectiveness and safety were such that relevant clinical differences in either direction could not be definitively excluded, we planned a full economic evaluation. We however also performed a cost-minimisation analysis.

Resource use and unit costs

Costs to society included direct and indirect costs, both medical and non-medical. Medical costs consisted of cost of the UVB treatments, costs of consultations (dermatologist plus general practitioner (GP)) and cost of medication. Non-medical costs included expenses for travelling and parking, productivity losses due to absenteeism from work and presenteeism (reduced productivity while at work), and costs of absenteeism during unpaid work. During the trial we used several methods to collect data on use of healthcare resources.

Using a diary we recorded frequency and duration of the irradiations as well as frequency of visits paid to the dermatologist or general practitioner (GP) until the end of the UVB treatment (t=3). During the follow-up (t=4 to t=9), frequency of visits to the dermatologist and GP were recorded using a bimonthly questionnaire. Occurrence and duration (in months) of a second UVB treatment during the follow-up was monitored using the bimonthly questionnaire as well. At baseline we applied a questionnaire to collect details on travel distances, travel time, means of travelling to the dermatology outpatient department (visit to the dermatologist, phototherapy) and to the GP, and parking costs. Concomitant use of medication for psoriasis (topical and systemic medication) was retrieved retrospectively from the patients' pharmacists.

Absenteeism and presenteeism from paid work, and absenteeism from unpaid work were registered until the end of treatment (t=3) using the 'health and labour questionnaire'.[23] Estimates of costs due to absenteeism and presenteeism during the follow-up (t=4 to t=9) were based on assessments made during the treatment period (t=0 to t=3).

We assessed costs of both treatment strategies following the guideline for economic evaluations of the Dutch Health Care Insurance Board (CVZ).[24] All costs were assessed in Euros (€) and were based on the 2003 price level or were adjusted accordingly using national indices.[25] The information necessary to accurately calculate the treatment costs for home UVB treatment were not made available. Therefore the treatment costs of home UVB phototherapy were based on the invoice tariffs of the two home care organisations. All other resource costs were assessed from the societal perspective and were calculated per patient by

multiplying the volume of resource use by the unit costs. Costs of UVB treatment in the outpatient department included the costs of personnel, equipment, maintenance, depreciation, accommodation and overhead. Consultation costs of dermatologist and GP were based on the CVZ guideline,[24] costs of other personnel was based on the wage classifications of the hospitals. We determined costs of outpatient UVB treatment and costs of consultations of a dermatologist separately for university hospitals and general hospitals. Subsequently we computed weighted mean prices per irradiation and per consultation (using the ratio of the number of irradiations and the ratio of the number of consultations in both type of hospitals). Cost of concomitant medication was determined using the prices in the medication guide 2003 of the CVZ[26] and increased with the 2003 pharmacist's fee of € 6.30.[27] Travel costs were calculated using travel distances and a price of € 0.16 per km. Parking costs were € 2.50 per visit to the outpatient department.[24] Based on data from one of the questionnaires, the average parking costs for visits to the GP were estimated to be € 0.25 per visit. To compute costs due to absenteeism and presenteeism during working hours we applied mean hourly productivity costs varying with age and gender, ranging from € 20.07 (women, 15-24 years) to € 47.82 (men, >=55 years) per hour.[24] According to current guidelines for economic evaluations, we planned to calculate costs of lost productivity using an elasticity of 0.8, meaning that absence of 10 hours at work causes only 8 hours of productivity losses. Our data (see later) and previous studies, however, led us to conclude that short-term absence is often compensated for during normal working hours.[28;29] Therefore we computed the costs of presenteeism using an elasticity of 0.8, but considered the costs due to short term absenteeism from paid and unpaid work negligible.

Health outcomes

We measured health benefit in terms of Quality Adjusted Life Years (QALYs) using EQ-5D utilities[30] which were measured at three moments during the study (t=0, t=2 and t=3), see figure 1. At actual start of the treatment (t=1) and during the one year follow-up (t=4 to t=9) the utility scores were predicted using a linear multilevel model.[31] This multilevel model estimates the utility score from the SAPASI, gender and employment status. As an alternative utility measure we used the Short Form-36 to calculate SF-6D utilities.[32;33] We measured the SF-6D utilities simultaneously with the EQ-5D utilities, and predicted them similarly at t=1 and t=4 to t=9 using a multilevel model for the SF-6D.[31]

As a measure of clinical effectiveness we used the number of days that participants experienced an improvement of the baseline SAPASI score of 50% or greater (a relevant treatment effect). This measure was calculated using linear interpolation from the SAPASI scores and the various dates of measurement. Similarly, we assessed the number of days with an improvement of the baseline SAPASI score of 75% or greater (successful treatment effect).

Statistical analysis

During horizon 1 for 23 participants at least one component of the total costs was missing, and was imputed with the mean value for the treatment arm. During the 12 month follow-up after the end of treatment (t=4 to t=9), all estimates of costs of absenteeism and presenteeism were based on assessments made during the treatment period. The costs of UVB treatment during the follow-up were derived from (1) the number of irradiations exceeding 46, and (2) the length (months) of newly started UVB therapy.

We calculated QALYs by plotting utilities against time, using the area under the curve approach. Missing measurements in the curve were imputed using a three-step-method. Firstly, when utility scores were missing but SAPASI scores were known, the missing utility scores were estimated using previously published linear multilevel models.[31] Secondly, occasional missing values within the curve were imputed using linear interpolation. Finally when utility data from part of the curve were still missing, they were imputed with the group mean for that time period. Note that due to the study design (see figure 1) no utility scores were measured during the one year follow-up after the end of treatment (t=4 to t=9). Consequently, for this part of the study all utility scores were either estimated using the previously mentioned linear multilevel models,[31] or imputed by the mean value of the rest of the treatment group. Missing data necessary to calculate the number of days with a 50% or greater improvement versus a 75% or greater improvement, were imputed with the mean value of the treatment arm.

Initially, we analysed cost and effects separately. We calculated mean costs, mean QALYs, and mean number of days with a relevant treatment effect with their standard deviations for both treatment groups for both time horizons. Mean differences between both treatment arms are presented with their 95% confidence intervals (95% CIs).

After that, we combined incremental costs with (1) QALYs gained (cost-utility) and with (2) the difference in the number of days with a 50% or greater improvement

of the baseline SAPASI (cost-effectiveness) in four incremental cost-effectiveness ratios (ICERs), two ICERs for both time horizons. We estimated uncertainty around the ICERs using bootstrapping, generating 1000 replications of each ICER (replicated ICERs). For the ICERs representing additional costs per QALY we used the replications to estimate cost acceptability curves[34] to indicate the level of uncertainty around the point estimates of cost per QALY. For visual conceptualisation, we depicted the replicated ICERs in a so-called cost effectiveness plane. Thus the simultaneous dispersion of costs and effects could be evaluated, and an inference regarding the likelihood of one treatment being more cost-effective than the other was possible. It was not necessary to discount costs and outcomes, as psoriasis is a chronic recurrent disease and the beneficial effect of UVB therapy will generally not last beyond one year.

Finally we examined the robustness of our results using sensitivity analyses. First we investigated the effects of calculating QALYs from the SF-6D instead of the EQ-5D. Secondly, we examined the effects of re-estimating the costs of absenteeism as being maximal costs instead of being negligible. We calculated the maximal costs of absenteeism from paid work using the participants full-time equivalent (FTE) multiplied by the time needed to visit the GP, the dermatologist or the hospital for UVB treatment. The maximal costs of absenteeism during unpaid work were valued at € 10 per hour (going rate for informal labour in the Netherlands in 2003) instead of being negligible. As a third part of the sensitivity analysis, we determined costs of treatment as if costs of UVB treatment in the hospital had been based on invoices tariffs (similar to the costs of home UVB treatment), rather than based on the costs for society.

All analyses were performed on an intention to treat basis using SPSS 15.0 and Microsoft Excel.

8.4 Results

A total of 196 patients were randomised into two treatment arms of each 98 participants. Mean ages at baseline were 41.2 and 45.0 years (home versus outpatient treatment), and two thirds of each group (67%, n=66) was male. Mean SAPASI scores at baseline were 7.2 and 7.3 respectively. The majority of the participants was employed, 74.5% (73) versus 70.4% (69), their mean full-time equivalents (FTEs) were 0.86 versus 0.87. Mean travel distances to

the hospital and GP were 8.2 and 2.2 km for the group assigned to home UVB treatment, versus 11.5 and 2.2 km for the outpatient UVB treatment group.
All 196 participants were followed until the end of the UVB treatment (horizon 1). Mean duration of horizon 1 was 17.6 weeks (17.9 versus 17.4). The first consecutive 105 patients (54 home versus 51 outpatient) continued the trial until one year after the end of UVB treatment, their data were analysed for horizon 2 (t=0 to t=9). Mean duration of horizon 2 was 68.4 weeks (68.7 versus 68.1).

Clinical study

The results of the clinical study[17] indicated that home UVB phototherapy and outpatient phototherapy are equally safe and equally effective. For instance at the end of the UVB treatment, 82% of the patients treated at home versus 79% of the patients treated in the hospital had reached the SAPASI-50 and 70% versus 73% had reached the PASI-50 (95% CIs of the differences -8.6 to 14.2 and -15.7 to 11.1). For the SAPASI-75 these figures were 69.1 versus 59.2 (9.8, 95% CI -4.0 to 23.6), while for the PASI-75 they were 40.7 versus 41.7 (-1.0, 95% CI -15.6 to 13.6). Results of the other measures of effectiveness yielded similar conclusions. Safety as assessed by measuring the total cumulative doses of UVB was similar (51.5 versus 46.1 J/cm^2, difference 5.4, 95% CI -5.2 to 16.0) across both groups, and the occurrence of short term side effects also did not differ.[17] The burden of treatment reported was, however, significantly lower for patients treated at home ($p<=0.001$). Also, patients treated at home evaluated their therapy significantly more positive than patients treated in the outpatient department ($p=0.001$). Waiting time (time between inclusion in trial and actual start of UVB treatment) for home UVB treatment was sometimes considerable, but 73% (63/86) of the patients treated at home thought the waiting time was acceptable or not a problem. For the group treated in the outpatient department, this proportion was 79% (46/58).[17]

Resources and costs

Table 1 summarises the various resources with their unit costs, and table 2 the mean use of resources during the trial for both time horizons.
Until the end of the UVB treatment (t=3), four patients who were initially randomised to receive UVB treatment in the outpatient department, switched in order to receive the UVB treatment at home. Similarly, one patient who was initially randomised to receive home UVB treatment, switched to receive

Table 1 – Resources and their unit costs (€)

Resource	Unit cost (€)*	Source
Home UVB treatment †	By individual patient	Home care organisations
Outpatient UVB treatment (per irradiation) ‡	9.13	Calculated from our data (see methods section)
Consultation dermatologist (per 10 minutes) ‡	57.50	Guideline for Economic evaluations[24]
Consultation GP	20.20	Guideline for Economic evaluations[24]
Medication	By individual drug	Medication Guide 2003[26]
Travelling costs (per km)	0.16	Guideline for Economic evaluations[24]
Parking costs for visits to hospital (per visit	2.50	Guideline for Economic evaluations[24]
Parking costs for visits to GP (per visit)	0.25	Calculated from questionnaire data
Absenteeism paid work (per hour)	0	NA
Presenteeism paid work (per hour) ¶	By individual patient	Guideline for Economic evaluations[24]
Absenteeism from unpaid work (per hour)	0	NA
For scenario analyses:		
Outpatient UVB treatment including cost of consultations of dermatologist (per year) §	1011.67	National Health Tariffs Authority[41]
Consultations dermatologist (per year) **	190.74	Online list tariffs[42]
Absenteeism/presenteeism paid work (per hour) ¶	By individual patient	Guideline for Economic evaluations[24]
Absenteeism from unpaid work (per hour)	10.00	Going rate for informal labour in The Netherlands in 2003

* Based on 2003 price level

† Based on invoice tariffs, see appendix

‡ Weighted mean price of university hospitals and general hospitals

§ Weighted mean price (2006) for the participating hospitals, adjusted to the 2003 price level

¶ Depending on gender and age

** Mean tariff (2008) adjusted to the 2003 price level

NA = Not Applicaple

outpatient UVB treatment. Three other patients randomised in the home UVB group started with outpatient UVB treatment during the wait for home UVB treatment, and later on continued their UVB treatment at home. During the follow-up period (t=4 to t=9), 14 patients randomised in the group treated at home versus 11 patients randomised to the group treated in the outpatient department started a new UVB treatment. The new UVB treatment took place

Table 2 – Use of resources during the trial

Resources	Horizon 1* (n=196, 17.6 weeks)		Horizon 2* (n=105, 68.4 weeks)	
	home	outpatient	home	outpatient
UVB irradiations at home	33.96 (11.70)	1.73 (8.54)	37.35 (19.62)	4.33 (13.75)
UVB irradiations in outpatient department	0.48 (2.61)	26.89 (12.03)	5.04 (12.21)	30.90 (18.96)
Consultations dermatologist	1.19 (0.99)	1.60 (1.16)	4.12 (3.20)	3.93 (2.39)
Consultations GP	0.25 (0.80)	0.13 (0.43)	0.72 (1.59)	1.00 (4.08)
Medication †	-	-	-	-
Presenteeism at work (hours)	2.09 (8.16)	4.80 (17.83)	2.67 (7.19)	3.39 (8.68)

Values are presented as mean numbers (sd)

* 196 patients were followed until the end of treatment (t=0 to t=3, horizon 1), 105 patients were followed until the end of the study (t=0 to t=9, horizon 2).

† By individual drug

at home for 8 of them (5 versus 3), and in the outpatient department for 17 participants (9 versus 8).

Mean hours of absenteeism from paid work as registered using the health and labour questionnaire were largely influenced by gross absence due to sickness by a few individuals. Therefore we considered the results from the health and labour questionnaire not reliable to estimate costs from absenteeism due to UVB treatment. Our data, however, indicated that patients in fact have flexible arrangements with their employers, and therefore can minimise the costs of absenteeism due to their treatment. In a pilot study among 36 patients treated with phototherapy we were able to confirm this hypothesis, and also in literature it is found that short-term absence is often compensated for during normal working hours.[28;29] Therefore we considered (the costs due to) short term absenteeism from paid and unpaid work negligible.

The mean overall costs of the intervention were calculated from the direct and indirect medical and non medical costs (see table 3), and mounted up to € 801 for home UVB treatment and € 752 for outpatient UVB treatment at the end of the UVB treatment (horizon 1) (difference € 48, 95% CI € -78 to € 174). One year after the end of the UVB treatment (horizon 2) these costs had risen to € 1272 and € 1148 respectively (€ 124, 95% CI € -155 to € 403).

Health benefits

During the entire study (horizon 2), patients treated at home experienced 1.1528 QALYs whereas patient treated in the outpatient department experienced 1.1261 QALYs (difference 0.0267, 95% CI -0.024 to 0.078). For horizon 1 these figures were 0.2960 and 0.2908 respectively (difference 0.0052, 95% CI -0.0244 to 0.0348). The mean number of days that patients experienced a 50% improvement (relevant treatment effect) was 216.5 versus 210.4 for horizon 2 (difference 6.1, 95% CI -41.1 to 53.2) and 42.4 versus 55.3 for horizon 1 (difference -12.9, 95% CI -23.4 to -2.4). For comparison: the number of days with a 75% or greater improvement (successful treatment effect) were 127.6 versus 111.1 (16.5, 95% CI -27.3 to 60.2) and 23.0 versus 24.6 (-1.6, 95% CI -9.2 to 6.0) respectively.

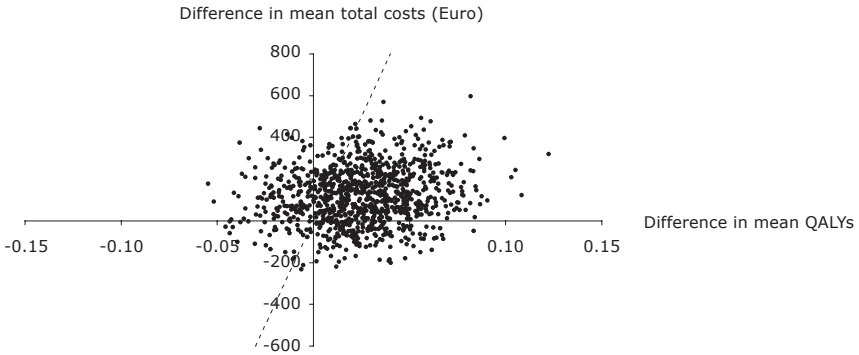
Cost-utility and cost-effectiveness

Incremental mean cost of home UVB treatment to society was € 124 per patient for the entire study period (horizon 2, 68 weeks) and € 48 per patient for horizon 1 of the study (see Table 3). The incremental cost effectiveness ratio (ICER) that relates differences in total costs to differences in QALYs, was (€ 124.05/0.0267 QALY=) € 4646 per QALY for horizon 2. This ICER indicates that € 4646 was needed to gain one QALY. For horizon 1 the ICER was € 9276 per QALY (€ 48.24/0.0052 QALY). Figure 2 represents the 1000 replicated ICERs for cost per QALY during the entire study (horizon 2) generated with the bootstrapping technique, together with the cost effectiveness threshold line of € 20.000 per QALY. Cost acceptability (proportion of replicated ICERs on the right side of the line) was 76.3%. Figure 3 shows the cost acceptability curve for this scenario, illustrating the level of uncertainty around the point estimates of cost per QALY. To illustrate, if policymakers are prepared to pay € 20.000 for each QALY gained, than they can be 76.3% sure that home UVB treatment is cost-effective. But if they are willing to pay € 10.000 or € 30.000 per QALY, they can be 66.7% or 79.2% sure that home UVB treatment is cost-effective. For horizon 1 the cost acceptability of € 20.000/QALY was 56.9%.

The ICER that relates incremental costs of home UVB treatment to differences in the number of days with a relevant treatment effect (50% improvement) was € 20.50 per day with a relevant treatment effect for horizon 2, indicating that per patient € 20.50 was needed to add one day with a relevant treatment effect. For horizon 1 of the trial the ICER was € -3.73 per day, signifying a dominated strategy—that is, outpatient UVB treatment yielding a better patient outcome

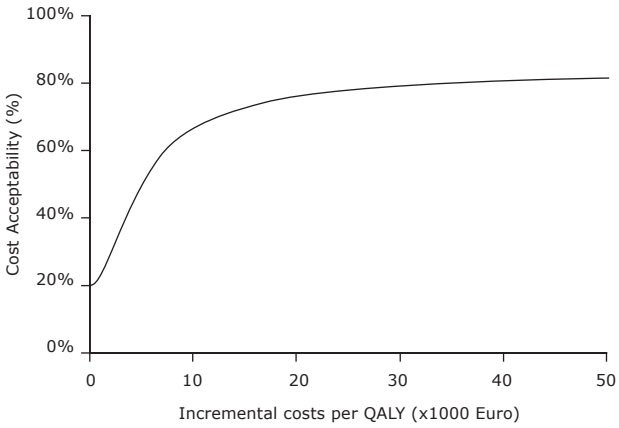
while saving costs. Figure 4 represents the 1000 replicated ICERs for cost per number of days with a 50% or greater improvement for horizon 2.

Figure 2 – Cost effectiveness plane: costs against QALYs



Cost effectiveness plane for incremental costs (home minus outpatient) and incremental QALYs (home-outpatient) for horizon 2 (entire study period, 68 weeks), with a cost effectiveness threshold line of €20.000/QALY.

Figure 3 – Cost acceptability of home UVB phototherapy (horizon 2)



Cost acceptability curve for incremental costs of home UVB phototherapy per QALY (home minus outpatient) for horizon 2 (entire study period, 68 weeks).

Table 3 – Mean costs (€) of UVB treatment for both treatment arms

	Horizon 1* (n=196, 17.6 weeks)		
	At home	**Outpatient**	**Difference (95% CI)**
Direct medical costs (€)			
UVB treatment	577	275	301 (257 to 346)
Consultations Dermatologist	69	92	-23 (-41 to -6)
Consultations GP	5.0	2.6	2.4 (-1.2 to 6.1)
Medication	77	95	-18 (-53 to 17)
SUBTOTAL	**727**	**464**	**263 (199 to 326)**
Direct non-medical costs (€)			
Travel costs treatment	2.9	144	-141 (-168 to -115)
Travel costs visits to dermatologist	5.3	8.6	-3.3 (-5.4 to -1.1)
Travel costs visits to GP	0.24	0.12	0.12 (-0.09 to 0.32)
SUBTOTAL	**8.5**	**153**	**-144 (-171 to -117)**
Indirect non-medical costs (€)			
Absenteeism from paid work	0	0	NA
Presenteeism	65	135	-70 (-180 to 40)
Absenteeism from unpaid work	0	0	NA
SUBTOTAL	**65**	**135**	**-70 (-180 to 40)**
TOTAL COSTS (€)	**801**	**752**	**48 (-78 to 174)**

Table 4 – Sensitivity analysis: revised mean total costs (€)

	Horizon 1* (n=196, 17.6 weeks)		
	Home	**Outpatient**	**Difference (95% CI)**
A Outpatient UVB costs based on invoice tariffs †	838	1362	-524 (-657 to -392)
B Maximum costs of absenteeism ‡	1112	1816	-704 (-1053 to -356)
C A+B	1149	2426	-1277 (-1637 to -917)

	Horizon 2* (n=105, 68.4 weeks)		
	At home	**Outpatient**	**Difference (95% CI)**
	672	358	314 (204 to 424)
	237	226	11 (-52 to 74)
	15	20	-6 (-29 to 18)
	228	261	-33 (-168 to 103)
	1151	**864**	**287 (50 to 523)**
	20	160	-140 (-204 to -75)
	21	20	0.36 (-9 to 9)
	0.55	0.41	0.14 (-0.38 to 0.66)
	42	**181**	**-139 (-211 to -68)**
	0	0	NA
	80	103	-23 (-123 to 76)
	0	0	NA
	80	**103**	**-23 (-123 to 76)**
	1272	**1148**	**124 (-155 to 403)**

* 196 patients were followed until the end of treatment (t=0 to t=3, horizon 1), 105 patients were followed until the end of the study (t=0 to t=9, horizon 2).

	Horizon 2* (n=105, 68.4 weeks)		
	Home	**Outpatient**	**Difference (95% CI)**
	1336	1805	-469 (-768 to -169)
	1857	2209	-351 (-973 to 270)
	1921	2865	-944 (-1608 to -280)

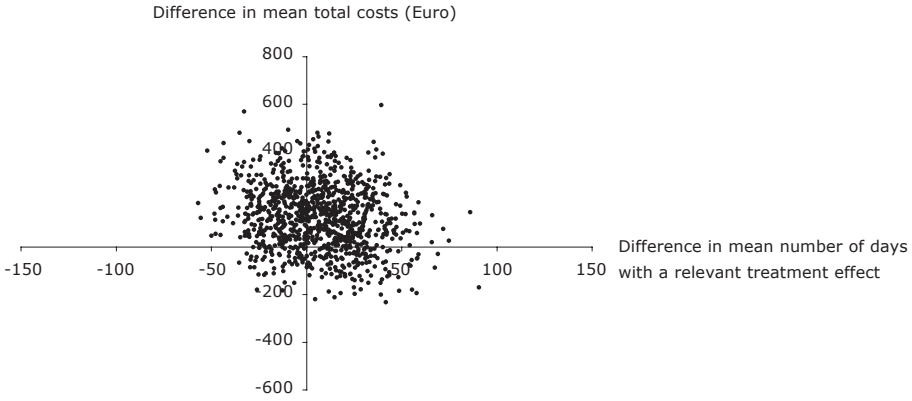
Mean total costs (€) as calculated based on revised assumptions.

* 196 patients were followed until the end of treatment (t=0 to t=3, horizon 1), 105 patients were followed until the end of the study (t=0 to t=9, horizon 2).

† Costs of outpatient UVB treatment based on invoice tariffs rather than based on the real costs for society.

‡ costs of absenteeism at paid work calculated from participants employment status, Full-time Equivalent (FTE), and age andgender[24]; costs of absenteeism at unpaid work valued at € 10 per hour.

Figure 4 – Cost effectiveness plane: costs against number of days with a relevant treatment effect



Cost effectiveness plane for incremental costs (home minus outpatient) and incremental number of days with a relevant treatment effect (>=50% improvement of the baseline SAPASI, home minus outpatient) for horizon 2 (entire study period, 68 weeks).

Sensitivity analyses

The sensitivity analysis addressed three areas of subjectivity, two concerning a revised calculation of costs, and one concerning calculation of QALYs.
Firstly, if utilities had been assessed using the SF-6D instead of the EQ-5D, the calculation of QALY-gain and ICERs would have yielded identical results. The ICERs would have totalled € 7802 per QALY for horizon 2 and € 7908 per QALY for horizon 1, with a cost acceptability of 67.9% and 62.1% respectively.
Secondly, if costs had been calculated based on the revised assumptions, the total costs for society would increase for both treatment arms. Table 4 gives the results of the newly calculated costs per group with the differences and 95% CIs.
The increase in costs for the group randomised to receive home UVB treatment, however, would be much smaller than the increase in costs for the group of patients randomised to outpatient UVB treatment. As a result, for all three cost-scenarios the mean costs for the home UVB treatment arm were lower than the costs for the outpatient UVB treatment group. Combined with the gain in QALYs for the group treated at home, the alternative calculation of costs would produce dominated strategies.

8.5 Discussion

Home UVB treatment seemed to be slightly more effective but also slightly more expensive than UVB treatment in the outpatient department. Yet for both time horizons, differences between both treatment groups were mostly small and not significant. The incremental cost effectiveness ratios (ICERs) remained well below the generally accepted standard of € 20.000 per QALY. As such, home UVB treatment should be regarded a cost-effective intervention.

Key findings

For both time horizons, the total costs for home UVB phototherapy were slightly higher than the total costs for outpatient UVB treatment. But the differences were not significant and were small (€ 48/17.6 weeks and € 124/68.4 weeks), especially when the lower burden of treatment and higher patient satisfaction of home UVB treatment are considered.[17]

Similar to the fact that the costs between both treatments did not differ, also the health effects as measured in QALYs did not differ significantly between both treatment groups. When both measures were combined, the ICERs for both time horizons remained far below € 20.000 per QALY, yielding home UVB treatment a cost-effective intervention. Calculating QALYs and ICERs using the SF-6D instead of the EQ-5D did not change these conclusions (see sensitivity analysis).

The use of more clinical measures of effectiveness (the number of days with a relevant/successful treatment effect) did, however, add some interesting detail to our results. Our data show that for horizon 1, the patients treated in the outpatient department experienced significantly more days with a relevant treatment effect (50% improvement). The difference was 13 days in favour of patients treated in the outpatient setting. This effect was not observed for the number of days with a successful treatment effect (75% improvement). For horizon 2, for both measures the effect seemed to be reversed (not significantly), indicating that patients treated at home might have a better outcome. Since patients treated at home on average experienced a waiting time of 5.8 weeks (compared to 2.2 weeks in an outpatient setting),[17] we conclude that the longer waiting time for home UVB treatment affects time with relevant reduction of symptoms adversely. On the other hand, we demonstrated that the majority (76%) of the participants thought the waiting time was not a problem or was acceptable[17]. Also the majority of both groups (92% and 60% respectively) would prefer home UVB therapy in

case of a future episode of UVB treatment, and most important: home UVB treatment was better appreciated by the patients.[17] Therefore, seen from a patient's perspective, the difference in number of days with a 50% improvement for horizon 1 -although significant- does hardly alter the valuation of treatment. Besides, all other measures of effectiveness show no significant differences between both groups. Taking a closer look at the calculation of costs, it should be noted that the home care institutions were reluctant to submit commercially sensitive information on pricing. For that reason, we were not able to calculate the treatment-costs for home UVB treatment from a societal perspective, but had to use invoice prices to approximate these costs. By doing so, we probably overestimated the costs of home UVB treatment for society. This contrasts with the treatment costs of phototherapy in an outpatient setting, which were calculated from a societal perspective. It is therefore plausible to assume that the previously mentioned non-significant difference in costs of both strategies will in fact become smaller, or that in the end home UVB treatment will be found to be even cheaper than outpatient based UVB phototherapy. In order to examine the effect of using invoice prices for treatment on the overall costs, we performed a scenario analysis in which we studied the effect of using UVB invoice prices for both treatment modalities. We discovered that mean invoice prices for outpatient UVB treatment are way higher than the costs estimated for society, and also higher than mean invoice prices for home UVB treatment. As a result, this scenario caused so-called dominated strategies for both time horizons—that is, home UVB treatment being more effective ànd cheaper than outpatient UVB phototherapy.
Another point to consider is that the results discussed above were calculated assuming that the costs of absence at work were negligible. By doing so, we might have underestimated the total costs of UVB treatment, especially those of outpatient UVB treatment. The results of the sensitivity analysis clearly show that by incorporating costs of absenteeism, the costs of outpatient UVB therapy would increase more than the costs of home UVB treatment. As a result, home UVB treatment would become the cheaper option (significantly cheaper for horizon 1), i.e. again resulting in a situation of dominance for home therapy.

Comparison with other studies

To our knowledge, this is the first clinical trial on cost-effectiveness of home UVB treatment compared to outpatient UVB treatment for psoriasis. No previous economic evaluations comparing home UVB treatment with the standard outpatient

UVB treatment have been published, but there are some papers that touch the subject. For instance, Yelverton et al[35] also reported that home UVB treatment was cost-effective. They however compared home UVB treatment to systemic treatments and PUVA. Also, they did not perform a cost-effectiveness analysis but estimated the costs of a 30 year treatment period. Since psoriasis is a chronic disease that pre-eminently is treated by a rotation of several different therapies, calculation of the costs of a 30 year treatment period with just one therapy does not make much sense. Their results do however hint towards home UVB treatment being cost-effective also for short-term treatments. Also a study of Cameron[13] and several other papers[36-39] suggest that home UVB treatment is likely to be more cost-effective than office-based phototherapy. A study of de Rie et al. published in 2001,[40] confirms the accuracy of the range of the cost-prices that we calculated for outpatient UVB phototherapy.

Strengths and weaknesses

This economic evaluation benefited from being part of a pragmatic randomised clinical trial. Due to the parallel group design the two interventions were compared throughout the same season, while selection bias was prevented by randomly assigning participants to both treatment groups. In addition, the pragmatic design ensured that the two treatments were applied and compared as they are used in daily practice, hence guaranteeing a good generalisability of the results. Measurement planning throughout the study took place according to individual clinical landmarks (see figure 1) and did not use fixed time-points starting from baseline. This way of planning measurements was an advantage for the clinical study, because it ensured that both groups could be compared at clinically comparable moments. For the cost-effectiveness study the applied planning of measurements had a drawback. Namely, due to individual differences in number and frequency of irradiations, the length of the time horizons varied per patient. As a result, the mean total study duration was slightly different for both groups: after imputation of missing values, the entire study (horizon 2) lasted on average 68.7 weeks for patients treated at home and 68.1 weeks for patients treated in the outpatient department. Similarly, for horizon 1 these figures were 17.9 weeks and 17.4 weeks. This half week difference in mean study duration might have given a small overestimation of both the incremental costs and incremental effects of home UVB treatment. For the cost-effectiveness and cost-utility analyses, however, this is likely to have no influence because the overestimation of both values will disappear when they are combined in an ICER.

A second point of consideration concerning the planning of measurements is that during follow-up, we deliberately did not apply certain questionnaires (see figure 1). This was decided in order to reduce the total number and length of the questionnaires per measurement and thereby maintaining adequate response rates. We chose not to apply questionnaires to measure health utilities (EQ-5D, SF-6D), as well as the Health and Labour Questionnaire, theoretically making the calculation of QALYs and costs less accurate. We are however of the opinion that we have estimated QALYs accurately using the multilevel linear models described previously.[31] Also, the uncertainty for the estimated costs during the follow-up mainly concerns the productivity costs (due to absenteeism and presenteeism). Our data, however, indicated that most patients compensate for their short-term absence during normal working hours, and a pilot study among 36 patients confirmed that most patients can minimise costs of productivity losses owing to flexible arrangements with their employers. As such, we consider productivity losses to be of minor significance in determining the total costs for both treatment arms.

Despite the mentioned limitations, we feel that the results of our study are unambiguous. Even more, we think that the results of this study are relevant not only for patients with psoriasis, but for all patients that may benefit from UVB treatment. After all, the results demonstrate that UVB treatment can just as well be given at home instead of in the outpatient department. We therefore feel that the results can very well be generalised to other patient groups considered for phototherapy, such as eczema and vitiligo.

Implications for practice and policy makers

The waiting time for home UVB treatment affects its effectiveness adversely, although this is not directly reflected in patients' satisfaction with the treatment. For the home care organisations, it is however important to conclude that the wait for home UVB treatment (mean 5.8 weeks)[17] does affect the effectiveness of the treatment negatively, and that by reducing the waiting time for their services, they will also improve effectiveness. By doing so, they will probably also increase patient satisfaction with home UVB treatment even further.

Despite the above-mentioned adverse effect on effectiveness, the overall effectiveness of home UVB corresponds with effectiveness of office based UVB treatment, while -from a societal perspective- home UVB treatment is similarly priced as UVB treatment in the outpatient department. This result is what we anticipated, but had not been confirmed previously. Our results indicate that home UVB

phototherapy is cost-effective. Indicated by our data, reimbursement of home UVB phototherapy may provide significant savings for society and patients, but -looking at invoice prices- also for insurance companies. Even more, for patients living in sparsely populated areas home UVB treatment may be a highly efficacious and cheap alternative to the expensive biological treatments. Nevertheless, reimbursement of home UVB treatment is not routine practice, and in some countries reimbursement is even often denied.[10;35;37] As such, routine reimbursement of home UVB treatment should be reconsidered.

Conclusion

The results of this economic evaluation demonstrate that effectiveness and costs of home UVB phototherapy for patients with mild to severe psoriasis do not differ from the normal UVB treatment in the outpatient department. As such, this study makes a valuable and important contribution to the evidence-base for the use of home UVB phototherapy for patients with psoriasis. It has produced solid estimates for costs, effects and cost-effectiveness of home UVB treatment compared to UVB phototherapy in an outpatient setting. Besides, we have previously demonstrated that home UVB treatment is -seen from a clinical perspective- equally effective and safe, and is also better appreciated by the patients than office based UVB treatment. Concluding, home UVB phototherapy should be regarded to be an effective, safe and cost-effective intervention, and should therefore be routinely reimbursed by insurance companies.

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Competing interests: none declared
Ethical approval: The institutional review board of the University Medical Center Utrecht approved the study (02/090-O).

Appendix

Tariffs for home UVB treatment based on the 2003 price level:

Home care organisation A:		**Home care organisation B:**	
Minimum fee: 8 weeks	€ 421.20	Minimum fee: 12 weeks	€ 631
Every additional week	€ 42.12	Every additional week	€ 34
13 weeks	€ 589.68		
26 weeks	€ 982.80		
52 weeks	€ 1432.08		

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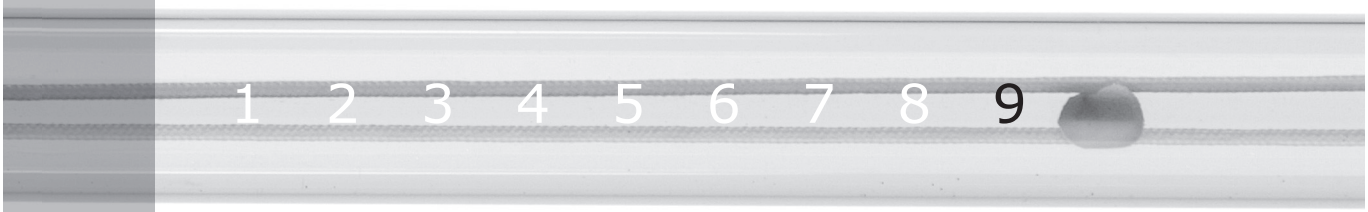
General discussion



The main objective of this thesis is to settle the long lasting discussion concerning the advisability of home UVB phototherapy for psoriasis. As such, this thesis presents the results of a randomised clinical trial investigating effectiveness, safety, burden of treatment and patient satisfaction of home UVB phototherapy for psoriasis. Furthermore, the results of an economic evaluation are presented and the impact of psoriasis on quality of life is described.
In this chapter the main conclusions of this thesis are summarised, and discussed with emphasis on methodology and generalisability. At the end of this chapter, implications for daily practice and policymakers are given.

9.1 Background and perspective

Starting point of this thesis was a letter from the national Health Care Inspectorate (IGZ) to the Dutch Society of Dermatologists (NVDV), advising to develop professional standards concerning the application of UVB phototherapy at home. This advice resulted from growing concerns among dermatologists, when in 1998 a healthcare insurance company decided to cover the costs of home UVB phototherapy. The concerns expressed by the dermatologists were specified in our exploratory study. We noted that many dermatologists think that home UVB treatment yields suboptimal results and carries higher risks. We also detected that many dermatologists have no confidence in the capability and compliance of their patients. In our review of related literature and guidelines, however, we found no evidence to support or refute these concerns. In fact, literature and guidelines on the subject were surprisingly scarce, revealing a clear lack of evidence concerning the advisability of home UVB treatment. Only two studies that compared two groups of patients were found, but neither was a randomised study. Moreover, personal views and non evidence based opinions appear widespread. In general guidelines suggest being cautious, but nevertheless we found that home UVB phototherapy is prescribed by a considerable proportion of the (particularly Dutch) dermatologists. On the basis of the expressed concerns and the lack of evidence concerning home UVB treatment, we concluded that home UVB treatment remained a contentious and debated treatment. We subsequently concluded that only randomised research into the benefits and shortcomings of home UVB treatment could settle the discussion.

9.2 Main findings of the clinical study

The trial presented in this thesis is the first randomised study ever concerning home UVB phototherapy. We performed a pragmatic* non-inferiority multicentre single blind randomised controlled trial of 196 patients with psoriasis, while focussing on TL-01 (narrowband) UVB light.

Effectiveness and safety

The results of our trial univocally demonstrate that home UVB treatment is at least equally effective when compared to outpatient UVB treatment. Primary outcome, a 50% or greater improvement of the baseline psoriasis severity (a relevant treatment effect, SAPASI-50), was reached by approximately 80% of the patients of both groups. Secondary outcomes SAPASI-75 and SAPASI-90 seemed to be more frequently reached by persons treated at home, rendering home UVB phototherapy not inferior to outpatient UVB treatment. The results of the PASI-50, PASI-75 and PASI-90 were slightly less positive but did not alter the conclusion of non-inferiority. From the fact that the occurrence of acute side effects and total cumulative dose did not differ between both groups, we also concluded that both treatments are at least equally safe. Due to the rental system in the Netherlands, there was no risk of unsupervised continuation or restart of irradiations. On the basis of this study, however, we cannot make any statements on the risk of non-prescribed irradiations in other countries. Several ways to prevent non-prescribed use of home UVB do however exist.[1]

In the study we observed differences in treatment frequencies and irradiation schedules between both treatment groups. These differences, however, reflect daily practice and are therefore part of the comparison. The study also revealed that patients randomised to home UVB treatment on average experienced a considerable waiting time before the home UVB irradiation unit to become available. Hence home UVB treatment started later than UVB treatment in the outpatient setting. When asked, however, the vast majority of the patients considered the waiting time for home UVB treatment to be acceptable or not a problem. And due to the higher frequency of irradiations at home resulting in shorter treatment durations, the period from prescription of UVB until the end of the UVB treatment was not different between both groups. We observed differences between both groups in the proportion of patients using additional medication; differences during waiting time, and differences in the opposite direction during UVB treatment. In total, however,

* A pragmatic design is a well recognised methodology for tackling questions on effectiveness in daily practice as opposed to efficacy in a 'controlled' setting, see also chapter 4.

the proportion of patients using topical medication from inclusion in the study until the end of the treatment was similar.

Quality of life, burden of treatment and patient satisfaction

For both treatment groups, quality of life was similar and increased equally during the UVB treatment, indicating that it was primarily influenced by treatment effect and not by treatment arm. Multilevel analyses confirmed that quality of life was inversely related to the SAPASI score. But also female gender and being unemployed appeared to be important predictors of an impaired quality of life. Patient assessed psoriasis severity (SAPASI) was a better predictor of quality of life than the so-called objective PASI score. This finding was in line with our expectation that the SAPASI score better reflects the patient's experience.
In contrast to the similar quality of life across both groups, the burden of treatment differed significantly. Patients treated at home experienced a lower burden of treatment than patients treated in an outpatient setting. Especially the additional loss of time seemed to markedly increase the burden of treatment for those treated in an outpatient setting. Even more importantly, patients treated at home evaluated their treatment significantly more positive than patients treated in a hospital setting, and were also on average more satisfied with the final treatment result. Besides, the majority of both groups would prefer home UVB treatment over outpatient UVB treatment in the future. On the other hand, patients treated at home were less satisfied with the nursing care and supervision than the patients treated in an outpatient setting. The far majority of the patients of both groups, however, were still satisfied or very satisfied with the service provided.

9.3 Main findings of the economic evaluation

Costs and cost-effectiveness

The economic evaluation performed alongside the clinical trial demonstrated that home UVB treatment is a cost-effective treatment. Most data on costs and health effects in terms of quality adjusted life years (QALYs) were recorded until the end

of the UVB treatment (mean 17.6 weeks). Using multilevel models we estimated the number of QALYs gained until one year after the end of the UVB treatment (mean 68.4 weeks). Point estimates of costs and effects suggested that home UVB treatment is more expensive, but also better in terms of QALYs. Mean differences between both groups were however small, and not statistically significant. For instance, mean difference in total costs until the end of the UVB treatment was only € 48; total costs were € 801 (home) and € 752 (outpatient) respectively. For both time horizons the incremental cost-effectiveness ratios (ICERs), combining incremental costs with QALYs gained, remained far below the informal standard of €20.000 per QALY, rendering home UVB phototherapy a cost-effective intervention. We also evaluated cost-effectiveness from a more clinical perspective, using the number of days that patients experienced a relevant treatment effect (SAPASI-50). Due to the longer waiting time for home UVB treatment, patients treated at home initially experienced fewer days with a relevant treatment effect. At one year after the end of the therapy, however, home UVB treatment seemed to be more beneficial, at a cost of € 20 per additional day with a relevant treatment effect. Note however, that the costs of home UVB treatment are likely to have been overestimated.

Calculation of costs

The direct medical costs of outpatient UVB phototherapy were calculated from a societal perspective. The direct medical costs of phototherapy at home, however, had to be calculated using commercial invoice prices because accurate information on real treatment costs was not available. As such, societal costs of home UVB treatment have probably been overestimated in this study. As a consequence, it might very well be that home UVB treatment in fact is less costly than outpatient UVB treatment.

The indirect costs were calculated assuming that production losses due to short term absences from work were negligible. This seemed appropriate, because our data indicated that short term absence was often compensated for during normal working hours. This was confirmed in a pilot study, showing that patients either have flexible arrangements with their employers or plan visits to the outpatient clinic in their own spare time. We intend to present the results of this pilot study in the near future; the results are, however, in line with previous reports concerning short term absence.[2;3] We are aware of the fact that our assumption that patients easily compensate for their absence due to UVB treatment, may not hold true in situations where the average travel time to an outpatient clinic is significantly

longer. As such, in less densely populated areas with patients living further away from an outpatient clinic, productivity losses for treatment in an outpatient department are likely to increase, causing home UVB treatment to become even more cost-effective.

9.4 Methodological considerations

Design and power

The study was designed as a pragmatic non-inferiority randomised trial. The pragmatic design was chosen to optimally compare home UVB treatment for psoriasis with the current standard outpatient UVB phototherapy, including potential differences in management. This type of comparison is very useful to facilitate policy decisions, but the exact health benefit for each aspect of the treatment cannot be determined separately.[4] That is, we may not be able to differentiate between treatment effect due to UVB, due to medication, or due to other causes. Also, because of heterogeneity of the study population, the results may tell the clinician little about how to manage individual patients.[5] One could therefore argue that a more explanatory approach should be chosen, more strictly controlling application of both treatments and minimising differences. But by doing so we would have compared two non-existent treatments, thus impeding generalisation of the results. Another reason to prefer a pragmatic approach is that the results provided by pragmatic trials are, in contrast to those of explanatory trials, pre-eminently suited to use in cost-effectiveness analyses, which was also an important aim of the study.

Another point of consideration concerns the non-inferiority design; to be precise it concerns the choice of a non-inferiority margin (Δ) of 15%. We chose this margin because we considered a decline in relevant response (SAPASI-50) from 85% to 70% acceptable. This view may be subject to debate. A smaller margin of 10% instead of 15% would however not have drastically changed our conclusions, but would have required more than twice as many participants in the trial. Similarly, based on the results of a previous review we expected the proportion of patients achieving at least a 50% improvement of their baseline psoriasis (SAPASI-50) to be approximately 85%. In our study this proportion was 80%, thereby reducing the power and requiring more participants (113 per arm) in order to exclude a difference of 15% from the confidence interval.

Statistical analysis

The combination of a pragmatic and a non-inferiority design presented us with partially conflicting recommendations concerning the statistical analysis, i.e. the preferred intention to treat analysis in pragmatic studies as opposed to the fact that intention to treat analysis in non-inferiority trials may bias the findings towards the preferred outcome. Therefore, for non-inferiority trials, it is advised to additionally present the results of per protocol analysis. We, however, only presented the results of the intention to treat analysis and did not present the results of the per protocol analysis. We think that the crossovers and dropouts, which may dilute differences in outcome between both groups, do reflect clinical reality. And after all, it was daily practice we were interested in. Besides, the direction of bias in per protocol analysis is indeed more unpredictable, but per protocol analysis may lose its value when rates and reasons for dropouts differ between both groups.[6] To a certain extent this may be the case in our study. Although we did not present the results of the per protocol analysis, we did perform this type of analysis. In line with our expectations, the results yielded conclusions similar to those of the intention to treat analysis.

Another detail of the analysis to reflect upon is the decision to calculate 2-sided 95% confidence intervals (95% CIs), while interpreting non-inferiority (i.e. 1-sided). As such we in fact determined non-inferiority using 1-sided 97.5% CIs, which is a conservative approach. In case we had calculated 1-sided 95% CIs, none of the confidence intervals for the measures of effectiveness would have included the predefined non-inferiority margin.

9.5 Generalisability

The generalisability of the outcome of randomised trials may depend on several issues, such as patient selection, disease severity at baseline, the health care system or the design of the study.[7] As explained before, the use of a pragmatic design facilitates optimal generalisation of the findings of the study, because -when applied adequately- it reflects variations between patients and treatments that occur in daily practice. Since patient selection reflected clinical practice, we are confident that patients included in our trial represent patients with psoriasis treated with UVB outside the trial. In addition, because both interventions were performed similarly to routine practice, we consider the results of our study applicable to

a wide arrange of patients with psoriasis who are considered clinically eligible for narrowband UVB treatment. Nevertheless, we will discuss the factors possibly affecting generalisability.

Patient selection

For dermatologists with a critical opinion on home UVB treatment, it may be tempting to rigidly assess applicability of the results of our study. As such, it is always easy to find a reason why a patient might differ from the participants of a study. A more reasonable approach would however be to ask whether that particular patient is that much different from those in the study, that the results of the study are not informative anymore—that is, can no longer aid in deciding on a treatment.[8]

In our study, not all patients with psoriasis who were prescribed narrowband UVB treatment during the study period were referred to us for inclusion in the trial. It was impossible to keep a record of all reasons for non referral. A reason may be that at some point during the trial there was a considerable wait for home UVB treatment. As a result, some patients or their doctors may have preferred a more prompt start of UVB treatment in the outpatient department, and hence were not willing to undergo randomisation. It is possible that these non-randomised patients may have had a more severe psoriasis than those included in the trial. The average baseline psoriasis severity of the study population, however, was similar to that of a non-selected group of patients in our hospital at a later period, and even higher than that of another study using the same principle of clinical eligibility.[9] This suggests that selection of only milder cases did not occur in our study. Moreover, we did perform a subgroup analysis on the patients with a more moderate to severe psoriasis and noted that these patients showed a similar responsiveness to home UVB treatment as did the average trial participant. For that reason, we are confident that our findings can be directly generalised to patients with psoriasis ranging from mild to severe, who are clinically eligible for narrowband UVB treatment.

A second reason for patients not wanting to participate in the trial might perhaps be that some patients did not consider outpatient UVB treatment to be a burden, and for this reason preferred a quick start of treatment in the outpatient department over risking a considerable wait. In case this type of selection happened, patients who do regard treatment in the outpatient department to be a burden should be overrepresented in our population. This would not have caused

different results in terms of effectiveness, but could possibly have resulted in a more pessimistic view on burden of treatment in the outpatient department. Such bias, however, would in our opinion be minimal as the results concerning burden of treatment adequately reflect our anticipations.

Health care system

Specific differences between health care systems may affect generalisability[7] on an international level. For instance the availability of home UVB phototherapy services in other countries may not be similar to that in the Netherlands. Also, differences in population density may affect the distances patients have to travel to an outpatient clinic. These travel-differences will however not affect the clinical results of the study, but merely the calculated costs and cost-effectiveness. Evidently, when travel distances are great, travel costs and productivity losses for those treated in a hospital setting will increase rendering home UVB treatment even more cost-effective. Conversely, when patients have to buy a home UVB treatment device (as may be the case in some countries) instead of being able to rent it, the costs of a single treatment period with UVB at home will rise and affect cost-effectiveness. However, considering that home UVB equipment may endure many operational years (perhaps a lifetime), it has been suggested that long term cost-effectiveness of home UVB equipment must be dramatic in comparison to other options.[10] International differences in reimbursement policies and the need to privately purchase home UVB equipment in some countries, may however result in home UVB treatment only being available for a selected group of patients who are financially well-off.

9.6 Positioning of (home) UVB phototherapy among other treatments

Since evidence regarding the effectiveness and safety of home UVB treatment thus far was lacking, up to this day guidelines recommend to be cautious with this treatment.[11] Concerning UVB treatment in an outpatient setting, however, guidelines and consensus agree that outpatient (narrowband) UVB phototherapy is the primary treatment option after failure of topical therapies, because it is highly effective, cost-effective, and safe.[12-16] In clinical practice, however, there are more issues to

be considered when choosing a therapy. For instance: the feasibility of the treatment, the burden of treatment and the patient's preferences. To assess feasibility of outpatient UVB phototherapy, an important question is whether a patient can be expected to attend to an outpatient clinic two or three times per week during working hours. For patients living far from an outpatient clinic, it may be impossible. Hence in sparsely populated areas, outpatient UVB phototherapy may not be available for many patients,[17] despite it being the treatment of choice. In a small country as the Netherlands, where most patients live locally to an outpatient clinic, outpatient UVB treatment is available to almost every patient. But even for the Netherlands, a previously performed study demonstrated that most patients prefer oral therapies to outpatient phototherapy.[18] Especially the discomforts associated with outpatient phototherapy, such as the burden of travelling and interference with all kinds of activities, were found to be an issue for most of the patients.

So what to do when according to the guidelines the treatment of choice is UVB phototherapy, but the patient concerned is living too far from the outpatient clinic? Or when the patient is having difficulties or is not willing to attend that frequently during working hours? Should we switch to alternative treatments—that is, traditional systemic drugs or biological agents? In our opinion, the answer is negative. Firstly and principally because the results of our clinical study clearly indicate that the discomforts and feasibility problems encountered in outpatient UVB phototherapy can very well be solved by performing the treatment at home. On the basis of similar effectiveness and safety, and taking into account the similar lamps (TL-01) used, home and outpatient UVB treatment should therefore in our opinion not be regarded as two different treatments, but as one treatment being offered at two locations: at home and in an outpatient clinic.

Another reason not to switch to alternative treatments is that, although most traditional systemic treatments may be regarded similarly effective to UVB phototherapy,[12;19;20] they are still considered to produce more side effects.[19] Also, the new potent biological agents (biologicals) that have been added to the treatment options are costly. As such they raise the costs of managing psoriasis considerably, and are in general less cost-effective than other treatment options. A final reason is that the results of a previous study indicate that adherence rates of home UVB phototherapy are higher than those of oral medication.[21]

Summarising, we believe that the effectiveness and safety of home UVB phototherapy are such that this treatment should be regarded a valuable and

satisfactory alternative to outpatient UVB treatment. Even more, when also taking into account the patient preferences, burden of treatment and cost-effectiveness, we argue that home UVB treatment should be the primary treatment option for patients who are clinically eligible for UVB phototherapy—that is, home UVB treatment should be favoured above UVB treatment in an outpatient setting.

9.7 Implications for daily practice

In the past decades, care for all types of chronically ill patients has increasingly shifted from the hospital to the patients home, due to the development of various home care technologies.[22;23] The development of a home UVB phototherapy service to treat skin disease fits in this trend, but unfortunately has not yet received many credits. The results of our study univocally demonstrate that implementation of home UVB phototherapy should be encouraged and facilitated.
Patients, health care professionals and policy makers should be informed that home UVB treatment is at least equally effective and safe as outpatient UVB treatment. Subsequently, the positioning of home UVB treatment among other treatment options should be reconsidered and agreed upon. Home UVB treatment should become the primary treatment option for patients who are clinically eligible for UVB, and guidelines should be adapted to reflect this view. Furthermore, home UVB treatment should be routinely reimbursed, and provision should be improved. In order to allow patients to show their preferences, they too have to be informed about the possibility to receive UVB treatment at home. This might be achieved by informing patients' associations. When treatment with UVB is indicated, however, it is also the responsibility of the health care professionals (dermatologists) to adequately and objectively inform the patients of the possibility to receive UVB treatment at home.[8] Concerning the provision of home UVB phototherapy we agree with Anstey,[17] that it would appear to be inappropriate for patients to receive systemic medication or biological agents only because the infrastructure to deliver a highly efficacious and cheaper treatment with narrowband UVB at home is lacking. As such, in countries where home UVB treatment is not common practice it should be investigated how home UVB treatment may be implemented. At the same time, in the Netherlands, the service provided with home UVB treatment and its cost-effectiveness could even be further improved by making minor adjustments.

Reimbursement of home UVB phototherapy

Now that we have provided evidence that home UVB treatment is an effective and also cost-effective intervention, we argue that home UVB treatment should -just like outpatient UVB treatment- be routinely covered, while co-payments should be refrained from. Policy makers and health care insurance companies should recognise our findings and adapt reimbursement policies.

It has already been suggested by others that treatment at home with UVB is a cost-effective treatment.[10;24] In the present study, we provided evidence of cost-effectiveness. We additionally detected that in our country, costs from the payors perspective (invoice prices) are generally higher for outpatient treatment than for home UVB treatment.[25] Despite these findings, requests for reimbursement are often denied, or co-payments are required. These co-payments and the inconvenience of UVB treatment in an outpatient setting push the patients into treatment with oral medication, which in general is either more expensive or less safe.[10] Policy makers and health care insurance companies should become aware that not the patients, but the pharmaceutical companies benefit from such policies. Even more, the decision to reimburse expensive treatments may have a considerable impact on the total budget available for health care on a national level. That is, large scale reimbursement of an expensive treatment will either result in financial constraints in other areas of health care (i.e. other diseases or treatments), or will raise the financial burden of health care costs for society.

In line with the above, one may reason that coverage of outpatient UVB treatment should be preferred above reimbursing home UVB treatment, because outpatient UVB treatment seemed to be slightly cheaper than home UVB treatment. The differences in costs observed in the study were however very small and had broad confidence intervals. Moreover, the costs of home UVB treatment were based on tariffs and were probably overestimated.

Improving home UVB phototherapy services

Although home UVB treatment turned out to be effective, cost-effective, safe, and preferred by the patients, we also detected some imperfections in the 'Dutch system' which might be improved. For instance, the average waiting time for home UVB treatment was considerably longer than that of treatment in an outpatient clinic. This was partly due to capacity problems at the home care organisations during winter times, and partially due to the fact that coverage of home UVB treatment had to be requested and approved before the treatment

could be initiated. Although our study revealed that most patients still felt that the waiting time for home UVB treatment was acceptable, we think the home care organisations should be encouraged to reduce the average wait. When home UVB treatment gets to be routinely reimbursed, the delay caused by requesting reimbursement will be solved. The delay caused by capacity problems can however only be solved by the home care organisations themselves, for instance by enlarging the fleet of home UVB equipment. When the average wait for home UVB treatment is reduced, the treatment may become even more cost-effective. Another point to consider is that patients treated at home were slightly less satisfied with the nursing care and supervision than patients treated in an outpatient setting. The vast majority of the patients treated at home were, however, still satisfied or very satisfied with it. The home care organisations may, however, want to improve patient satisfaction with the nursing care and supervision. Perhaps the development of an e-health service (providing additional health care using the internet) could help increase patient satisfaction with the service and supervision.

9.8 Future research and recommendations

As mentioned above, patients treated at home were slightly less satisfied with the nursing care and supervision than those treated in the outpatient department. The exact cause of the decrease in satisfaction with the service, however, is unknown. It may be due to less frequent contacts, or maybe the quality of the care and supervision was lower. It might be a subject for further investigation. Because of differences in health care systems, it is also recommended to investigate whether a lease system for home UVB equipment would also be profitable in other countries. It might very well be that for some countries, purchasing the equipment while providing a full reimbursement may be a more attractive option, especially when considering that home UVB equipment may last for many years. We note that despite the findings of our study, some dermatologists may still be worried about suboptimal dosage or long term use of the equipment without supervision. The latter, however, can be prevented by new technologies like an electronic control system such as the one that has been developed in the USA.[1] It provides a set number of treatments, requiring patients to contact a dermatologist for a new code to get additional treatments. Contact with patients and supervision of the treatment may be improved by developing a service using the internet (e-health). Patient

satisfaction with e-health services may subsequently be investigated and compared with the conventional supervision and care provided for home UVB treatment.

9.9 Final conclusion

In contrast to prevailing opinions, we observed that patients are perfectly capable of performing UVB treatment at home themselves. Furthermore, home UVB treatment is at least equally effective and safe as UVB treatment in the outpatient department when applied in a setting that precludes non-prescribed irradiations. The burden of treatment, however, is lower, and patients are more satisfied with the final treatment result. Economic evaluation revealed that home UVB treatment is cost-effective. Reduction of the average waiting time for home UVB phototherapy will even further increase cost-effectiveness. We regard home UVB phototherapy a valuable and satisfactory alternative to standard outpatient UVB treatment. Taking into account that patients prefer treatment at home, we claim that home UVB treatment should be the primary treatment option for patients who are clinically eligible for UVB phototherapy. As such, UVB treatment at home should be routinely reimbursed.

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Summary & Samenvatting

Summary

Psoriasis is a chronic recurrent skin disorder, that is mostly treated topically with creams and ointments. When this fails, narrowband ultraviolet B (UVB) light becomes the primary treatment option. Treatment with UVB light, however, has considerable consequences for the patient since it is nearly always carried out in an outpatient clinic. It is considered time-consuming, because patients have to attend the outpatient clinic during working hours two to three times a week for several months. In many developed countries, dermatology clinics typically cover a large geographical area making treatment with UVB light only available for those patients living locally to an outpatient clinic. Therefore, to treat patients living far from their local hospital, home UVB treatment was introduced in the late 1970s. Ever since, however, the effectiveness and safety of this therapy have been debated and few dermatologists have embraced treatment with UVB light at the patient's home.

Chapter 2 describes the results of a review of the literature, a search for professional guidelines and a survey among dermatologists. The study showed that in fact very little research on home UVB treatment has been conducted. But despite the scarcity of literature on the subject, personal and non-evidence based opinions were widespread. And in contrast to the official opinion suggesting to be cautious, home UVB phototherapy was found to be described by a considerable proportion of the (particularly Dutch) dermatologists. We concluded that only a randomised study can settle the ongoing discussion concerning the advisability of home UVB phototherapy for psoriasis.

Accordingly, we designed a randomised clinical trial comparing home UVB treatment with the current outpatient UVB treatment. In *chapter 3* the protocol of this study is presented. Patients who were about to be treated with UVB and who were willing to participate were randomised to receive either home or outpatient UVB treatment. Both treatments were performed in a setting reflecting daily practice, a so-called 'pragmatic' design. *Chapter 4* elaborates on the methodological particulars of the study design.

In *chapter 5* we describe the clinical results of this randomised trial. It became clear that home and outpatient UVB treatment can be considered equally effective and equally safe. Quality of life was also comparable across both groups of participants, since it was primarily influenced by treatment effect and not by treatment group. The burden of treatment, however, was significantly lower for

patients treated at home. There was -on average- a considerable waiting time before home UVB treatment could be started. The far majority of the patients, however, considered the waiting time to be acceptable or not a problem. In fact, patients treated at home valued their treatment significantly more positive than patients treated in a hospital setting, and were on average more satisfied with the final treatment result. Also, the majority of both groups would prefer home UVB treatment over outpatient UVB treatment in the future.

In *chapter 6* the impact of psoriasis on quality of life is further specified. The study results confirm that an improvement of patient assessed psoriasis severity is related to an improved quality of life, but at the same time reveal that the impact of psoriasis severity varies for the several quality of life instruments and domains. Besides the effect of psoriasis severity, also the male gender, older age and being employed turned out to be important predictors of a better quality of life. The impact of psoriasis on quality adjusted life years (QALYs, a generic measure of quality of life that is commonly used in economic evaluations) appeared to be considerable and comparable to the impact of other diseases such as ulcerative colitis, renal failure and heart disease.

In *chapter 7* we compared the EQ-5D and the SF-6D for their agreement and usefulness in psoriasis studies. The EQ-5D and SF-6D are two questionnaires that -with use of specific algorithms- both can be used to calculate QALYs. The use of different instruments might lead to a considerable variation in calculated mean QALYs (and consequently in incremental costs per QALY gained), and may therefore potentially affect policy decisions. We detected that agreement between both measures was poor, indicating that on an individual level the EQ-5D could not be reliably predicted from the SF-6D and vice versa. On a group level, however, the mean scores of both instruments displayed a similar sensitivity to change and hence a similar course during the study. We concluded that in our population, the use of either instrument may yield equal incremental costs-QALY ratios.

In *chapter 8*, the results of the economic evaluation are given. The point estimates of the costs and effects suggest that home UVB treatment is more expensive but also better in terms of QALYs. Differences between both groups were however very small and not significant, yielding home UVB phototherapy a cost-effective intervention. We also evaluated cost-effectiveness from a more clinical perspective, using the number of days that patients had experienced a so-called 'relevant treatment effect'. Due to the longer waiting time for home UVB treatment, patients treated at home initially experienced fewer days with a relevant treatment

effect. At one year after the end of the treatment, however, home UVB treatment seemed to be more beneficial. Overall, we concluded that home UVB treatment is a cost-effective treatment, and that cost-effectiveness could even been improved by reducing the waiting time for home UVB treatment.

In *chapter 9*, the general discussion, the main findings of this thesis are summarised and discussed with emphasis on methodology and generalisability. The content of this book clearly demonstrates that home UVB treatment is an effective, safe and cost-effective treatment, and that it is preferred by most patients. We therefore claim that the use of home UVB treatment should be encouraged and facilitated. Positioning of home UVB treatment should be reconsidered and agreed upon, and guidelines should be adapted to reflect this view. Furthermore, home UVB treatment should be routinely reimbursed and provision should be improved. As such, in countries where home UVB treatment is not common practice, it should be investigated how home UVB treatment may be implemented. In The Netherlands, the home care organisations should be encouraged to reduce the average wait.

Samenvatting

Psoriasis is een chronische huidziekte met een wisselend beloop: periodes van verbetering en verslechtering wisselen elkaar af. In eerste instantie wordt psoriasis behandeld met crèmes en zalven. Wanneer dit echter onvoldoende effect heeft is behandeling met smalband ultraviolet B (UVB) licht de eerstvolgende therapie van keuze. Behandeling met UVB licht heeft echter aanzienlijke consequenties voor de patiënt, omdat het bijna altijd in het ziekenhuis (poliklinisch) plaats vindt. De behandeling wordt vaak als tijdrovend beschouwd omdat patiënten er maandenlang twee- tot driemaal per week tijdens kantooruren voor naar het ziekenhuis moeten reizen. In veel landen bedienen ziekenhuizen en buitenpoli's een groot gebied, waardoor lichtbehandeling met UVB feitelijk alleen toegankelijk is voor degenen die in de buurt van een polikliniek wonen. Om ook degenen die ver van het ziekenhuis wonen te kunnen behandelen, is daarom eind jaren '70 UVB thuisbelichting ingevoerd. Sindsdien zijn de effectiviteit en veiligheid van deze behandeling echter vaak onderwerp van discussie geweest, waardoor slechts weinig dermatologen UVB thuisbelichting voorschrijven.

Hoofdstuk 2 geeft een overzicht van de literatuur over UVB thuisbelichting, en beschrijft de resultaten van een zoektocht naar professionele richtlijnen over UVB thuisbelichting en een enquête onder dermatologen. Hieruit blijkt dat er heel weinig onderzoek naar UVB thuisbelichting is gedaan. Ondanks de schaarse literatuur blijken er echter wel veel meningen te heersen, die voornamelijk persoonlijk en niet wetenschappelijk onderbouwd zijn. Door het gebrek aan bewijs adviseren de professionele richtlijnen om terughoudend te zijn met het voorschrijven van UVB thuisbelichting. Toch blijkt er een redelijk aantal (Nederlandse) dermatologen te zijn die deze behandeling wel geregeld voorschrijft. Wij kwamen tot de conclusie dat alleen een gerandomiseerd onderzoek de discussie over de aanbevelens-waardigheid van UVB thuisbelichting kan beëindigen.

Daarom hebben we een gerandomiseerde klinische studie opgezet die UVB thuis-belichting vergelijkt met de gangbare poliklinische UVB lichtbehandeling. Het onderzoeksprotocol hiervan wordt beschreven in *hoofdstuk 3*. Patiënten die aan het onderzoek wilden meedoen werden door middel van loting (randomisatie) ingedeeld in ofwel de groep die thuis zou worden behandeld, ofwel de groep die poliklinisch zou worden behandeld. Tijdens het onderzoek werden beide vormen van lichttherapie uitgevoerd zoals ze normaliter (in de dagelijkse praktijk) ook uitgevoerd zouden worden. Dit noemen we een pragmatische onderzoeksopzet.

Hoofdstuk 4 geeft nadere uitleg over de methodologische bijzonderheden van dit onderzoeksontwerp.
In *hoofdstuk 5* worden de klinische resultaten van dit gerandomiseerde onderzoek beschreven. Hieruit blijkt dat UVB thuisbelichting even veilig en even effectief is als poliklinische behandeling met UVB. Ook de kwaliteit van leven verschilde niet tussen beide behandelgroepen, doordat deze voornamelijk beïnvloed werd door het behandelresultaat (verbetering van de psoriasis) en niet zozeer door de plek waar de behandeling plaats vond. Patiënten die thuis behandeld waren, vonden de lichtbehandeling echter wel beduidend minder belastend dan de mensen die poliklinisch waren behandeld. Er bleek gemiddeld genomen een aanzienlijke wachttijd te zijn voor UVB thuisbelichting. De overgrote meerderheid van de patiënten vond deze wachttijd echter acceptabel of geen probleem. Patiënten die thuis waren behandeld beoordeelden hun behandeling zelfs positiever dan de mensen die lichttherapie in het ziekenhuis ontvingen. Ook waren ze meer tevreden met het behandelresultaat. Daarbij komt dat de meerderheid van beide groepen in de toekomst thuisbelichting zou verkiezen boven lichttherapie in het ziekenhuis.
In *hoofdstuk 6* wordt de impact van psoriasis op de kwaliteit van leven nader bestudeerd. De onderzoeksresultaten bevestigen de relatie tussen een verbetering van de psoriasis en een verbeterde kwaliteit van leven, maar ze laten tegelijkertijd zien dat de sterkte van de relatie verschilt per vragenlijst waarmee de kwaliteit van leven is gemeten, en bovendien ook verschilt voor de verschillende aspecten (domeinen) van kwaliteit van leven. Naast een minder ernstige psoriasis, bleken ook het hebben van een hogere leeftijd, het behoren tot de mannelijke sekse en het hebben van werk belangrijke voorspellers van een hogere kwaliteit van leven. De impact van psoriasis op QALYs* (QALY=een algemene maat voor kwaliteit van leven die veel wordt gebruikt in economische evaluaties) bleek aanzienlijk en is vergelijkbaar met de impact van andere chronische ziekten op QALYs (ziekten zoals colitis ulcerosa, nierfalen en hartziekten).
Hoofdstuk 7 beschrijft de vergelijking van de EQ-5D en de SF-6D voor hun overeenstemming (agreement) en bruikbaarheid in onderzoeken naar psoriasis. De EQ-5D en de SF-6D zijn twee vragenlijsten die beide kunnen worden gebruikt om -met behulp van specifieke formules- QALYs te berekenen. Het gebruik van verschillende vragenlijsten c.q. methoden om QALYs te berekenen kan leiden tot variatie in het berekende gemiddelde aantal QALYs (en daarmee in de te berekenen gemiddelde kosten per QALY), en kan daardoor beleidsmatige beslissingen beïnvloeden. In ons onderzoek bleek dat de agreement tussen beide vragenlijsten laag was, zodat op

* een Quality Adjusted Life Year (QALY) is een algemene maat voor de kwaliteit van leven die rekening houdt met zowel een vermindering in de kwaliteit van leven als een eventuele afgenomen levensduur.

individueel niveau de EQ-5D niet betrouwbaar voorspeld kon worden uit de SF-6D en omgekeerd. Echter op groepsniveau bleken de gemiddelde waarden even gevoelig te zijn voor veranderingen in de ernst van de psoriasis, wat weergegeven werd door een parallel verloop van beide gemiddelden tijdens de gehele onderzoeksperiode. Daarom concludeerden wij dat in onze studiegroep het gebruik van de twee vragenlijsten zou resulteren in gelijke kosten per QALY.
In *hoofdstuk 8* worden de resultaten van de economische evaluatie gepresenteerd. De gemiddelde waarden van de kosten en de effecten impliceren dat UVB thuisbelichting duurder is, maar ook beter wanneer uitgedrukt in QALYs. Verschillen tussen beide behandelgroepen waren echter klein en niet significant, waardoor UVB thuisbelichting als een kosteneffectieve behandeling te beschouwen is. We onderzochten de kosteneffectiviteit ook van een meer klinische kant, waarbij we keken naar het aantal dagen dat de deelnemers een zogenaamd 'relevant behandeleffect' hadden ondervonden. Omdat de wachttijden voor UVB thuisbelichting langer waren dan die voor lichtbehandeling in de polikliniek, ervoeren de mensen die thuis waren behandeld aanvankelijk minder dagen met een 'relevant behandeleffect'. Echter aan het einde van het onderzoek, op één jaar na het einde van de UVB behandeling, leek de groep die thuis was behandeld het beter te doen dan de groep die in de polikliniek was behandeld. Alles bij elkaar genomen concludeerden we dat UVB thuisbelichting een kosteneffectieve behandeling is, en dat thuisbelichting zelfs nog kosteneffectiever zou kunnen worden als de wachttijden voor UVB thuisbelichting bekort kunnen worden.
In *hoofdstuk 9*, de algemene discussie, worden de belangrijkste bevindingen van dit proefschrift samengevat en besproken. De nadruk ligt hierbij op de gebruikte methoden en de generaliseerbaarheid van de resultaten. De inhoud van dit boek toont aan dat UVB thuisbelichting een effectieve, veilige en kosteneffectieve behandeling is, en dat de meeste patiënten bovendien de voorkeur geven aan UVB thuisbehandeling. Wij stellen daarom dat het uitvoeren en voorschrijven UVB thuisbelichting aangemoedigd en vergemakkelijkt dient te worden. De plek van UVB thuisbelichting in het therapeutische arsenaal zal heroverwogen en herbepaald moeten worden, waarop professionele richtlijnen vervolgens kunnen worden aangepast. UVB thuisbelichting zou standaard vergoed dienen te worden, en in landen waar UVB thuisbelichting niet tot de bestaande mogelijkheden behoort moet onderzocht worden hoe UVB thuisbelichting verwezenlijkt kan worden.
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Curriculum Vitae

Available from author

Abbreviations

AUC	Area Under the Curve
BoT	Burden of Treatment questionnaire, an instrument to measure the burden of the (UVB) treatment
BP	Bodily Pain, one of the eight domains of the SF-36, also one of the 6 domains of the SF-6D
CEA	Cost Effectiveness Analysis
EQ-5D	EuroQol 5 dimension questionnaire, an instrument to measure health related quality of life in terms of utilities
GH	General Health perceptions, one of the eight domains of the SF-36
HRQoL	Health Related Quality of Life
ICER	Incremental Cost Effectiveness Ratio
MED	Minimal Erythema Dose
MH	Mental Health, one of the eight domains of the SF-36, also one of the 6 domains of the SF-6D
PASI	Psoriasis Area and Severity Index, an instrument to measure psoriasis severity
PDI	Psoriasis Disability Index, an instrument to measure disease specific quality of life
PF	Physical Functioning, one of the eight domains of the SF-36, also one of the 6 domains of the SF-6D
PLUTO	Psoriasis: Landelijk UVB Thuisbelichtings Onderzoek
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RCT	Randomised Clinical Trial
RE	Role limitations Emotional, one of the eight domains of the SF-36
RL	Role Limitations, one of the 6 domains of the SF-6D

RP	Role limitations Physical, one of the eight domains of the SF-36
SAPASI	Self Administered Psoriasis Area and Severity Index, a patient assessed instrument to measure psoriasis severity
sd	standard deviation
SEM	Standard Error of the Mean
SF	Social Functioning, one of the eight domains of the SF-36, also one of the 6 domains of the SF-6D
SF-36	Short Form 36 item questionnaire, an instrument to measure generic (health related) quality of life
SF-6D	Short Form-6D (a 6 dimension questionnaire derived from the SF-36), an instrument to measure health related quality of life in terms of utilities
UV	Ultraviolet
UVB	Ultraviolet B
VT	Vitality, one of the eight domains of the SF-36, also one of the 6 domains of the SF-6D
95% CI	95% Confidence Interval
%BSA	% Body Surface Area

Have you seeeen the light?

Reverend Cleophus James

http://tinyurl.com/haveyouseeeenthelight