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How prominent are patient-reported outcomes in clinical trials of dermatological treatments?

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Summary

Background Assessment of symptoms or disease improvement by study participants is an important aspect of assessing new dermatological therapies in clinical trials, especially for chronic skin diseases that lack objective severity markers.

Objectives We sought to determine the frequency and prominence of reporting of participants' subjective efficacy outcomes in dermatological clinical trials. Our secondary objective was to determine whether participant and physician outcomes agree in terms of direction and magnitude.

Methods Systematic review of 125 randomized controlled trials identified from the *Archives of Dermatology*, *British Journal of Dermatology*, *Clinical & Experimental Dermatology*, *Journal of Dermatological Treatment* and *Journal of the American Academy of Dermatology* published between 1994 and 2001 (25 from each). Studies were retrieved in hard copy from the Cochrane Skin Group specialized register of trials and data were abstracted and summarized.

Results Participant efficacy outcomes were mentioned in some form in only 32 of 125 trials (25·6%, 95% exact confidence interval 18·2–34·2%). Of these 32 studies, participant outcomes were mentioned only in the methods section in two studies, in the methods and results section without further data in nine studies and with further data in 21. Data were presented in figure format only in 12 of these studies and in tables and figures in nine. Participant efficacy outcomes were mentioned in the abstract section in just over half (53%) of the 32 trials that included participant efficacy outcomes. There was not enough information to assess agreement in direction and magnitude of participant vs. assessor outcomes. Overall, only 17 papers (13·6%) clearly declared their main outcome measures beforehand in the introduction or methods section.

Conclusions Asking study participants for their views of treatment efficacy seems like a good idea in dermatological clinical trials, yet only about a quarter of the trials examined in this review did so. Even when such information was recorded, it was often poorly and incompletely reported and given low prominence within the trial report. Our study findings call for a more comprehensive uptake for including participant efficacy outcomes alongside other assessor outcomes in clinical trials and, when included, to report those outcomes in full.

The last 40 years of dermatological research have witnessed an enormous expansion in the number of 'objective' compound scales used to assess disease severity in clinical studies.[1] In order to minimize potential observer bias, it is clearly desirable to use objective measures of disease response if a suitable marker of disease activity can be found. However, for most skin diseases, no satisfactory marker of disease activity is available. Instead, many compound scales have emerged that incorporate different aspects of the disease such as disease extent and specific signs such as erythema, which are then combined in various ways into an overall score.[2,3] Although such scales may appear objective because they are recorded by an observer rather than the participant, and even though they may sound very precise because they are expressed in a numerical form, few have been validated properly, and many have not been validated at all.[1] Clinical interpretation of a

change in score of 2·5 points in a scale such as the Psoriasis Area and Severity Index, for instance, can also be problematic, unless the reader is very familiar with the properties, range and clinical correlates of the scale, which is not always the case for a practising clinician working in a busy clinic.[4] Jacobe *et al.*[5] have drawn attention to the importance of outcome measures in dermatological research, and how such measures have received little attention. While it is important for investigators to continue to find and use the best validated scales for examining the effects of treatments for skin diseases in clinical trials in order to permit some degree of standardization and international comparison, it is also important to include some aspects of the participant's views of the treatments being tested. The participant (because not all people taking part in dermatology clinical trials are patients, the term 'participant' will be used throughout) is, after all, the only person who can ultimately judge whether the effects of a new treatment for a condition such as psoriasis have produced a satisfactory improvement from their perspective, as opposed to the physician's point of view. Participants' assessments of efficacy of treatments are especially important in dermatology as many symptoms such as pruritus and sleep disturbance are difficult for physicians to assess objectively. Some aspects such as the *value* placed on various degrees of clinical improvement can *only* be assessed by study participants. The validity, reliability and responsiveness of some participant-reported outcomes (Dermatology Life Quality Index, Psoriasis Symptom Assessment and two itch measures) have already been demonstrated by Shikiar *et al.*[6]

Despite the manifest importance of participants' assessments, a previous systematic review of atopic eczema treatments suggested that participant-based outcome measures were rarely used or reported in dermatology clinical trials.[7] We therefore sought to survey a representative sample of published randomized controlled clinical trials (RCTs) from the dermatological literature to see (i) to what extent participants' assessments were included and (ii) how prominently and where they featured in the article when included. The focus of our study was on participant efficacy measures related to disease symptoms or overall improvement rather than quality of life scales which have been reviewed elsewhere.[8] As a secondary aim, we also wished to explore the extent to which subjective participant assessments of efficacy agree with the objective outcome measures of treatment efficacy in terms of direction, magnitude and precision, i.e. do clinicians and participants agree on the efficacy of treatments?[9]

Materials and methods

Sample selection

Based on a preliminary search of 25 papers we estimated that approximately 50% of papers would include a subjective participant-derived outcome measure. We calculated that we needed to retrieve around 125 papers in order to estimate the 95% confidence interval around the 50% estimate to within ± 10 absolute percentage points. A stratified sample of 125 RCTs and clinical controlled trials that did not specifically mention randomization (CCTs) were selected from five leading dermatology journals known through the Cochrane Skin Group to have a high yield of trials (*Archives of Dermatology*, *British Journal of Dermatology*, *Clinical & Experimental Dermatology*, *Journal of Dermatological Treatment* and *Journal of the American Academy of Dermatology*). Starting from the most recent, the first five papers were selected from each year of these journals from those RCTs and CCTs contained in the Cochrane Skin Group's specialist library, Centre of Evidence-Based Dermatology, Nottingham. These trials had previously been identified and catalogued on to a database by the Cochrane Skin Group's hand searching and validation exercise.[10] The 5-year period between 1995 and 1999 was initially chosen for convenience, as complete records for all identified trials during these years were already available at the Cochrane Skin Group editorial base. Where a year's worth of journal contained fewer than five RCTs and CCTs, the number was made up by selecting the remainder from the next available year, thereby extending the search period from 1994 to 2001. One investigator (A.P.T.) abstracted the information about the study design and results, and checked all equivocal results in discussion with another member of the team (H.C.W.).

Main outcome measures

Our main outcome measure was the number of trials that included some form of participant efficacy outcome measure. We defined a participant efficacy outcome measure as any measure that relied directly on a response from the study participants, and included specific symptoms such as degree of itching, sleep loss, and self-nominated global improvements. We did not include other measures such as cosmetic acceptability as primary efficacy measures for participants, although we acknowledge that they can be important. When a participant outcome was recorded, we then recorded whether such an outcome was mentioned only in the methods section (without any further results given), whether it was mentioned in both methods and within tabular form in the results section, whether any figures of the participant outcome data were presented, and finally whether such participant outcome data were mentioned in the abstract. Where studies investigated the efficacy of more than one treatment vs. placebo, the investigator (A.P.T.) analysed the first treatment mentioned in the title or methods vs. placebo.

Comparison of assessor-based outcomes with participant-based outcomes

In order to compare the participant outcomes with other assessor-based outcomes, we also recorded the number and type of other outcome measures reported in the study, as well as whether the main outcome measures were declared beforehand.

Because some papers had many outcomes, it was decided to use the first similar objective and subjective outcome measure mentioned in the methods section for the purpose of our comparisons. Percentage improvements of these outcomes from baseline were calculated for treatments (or placebo) where possible. It was noted if the difference between the improvements of treatments was statistically significant and, if so, its precision (confidence interval and associated P-value). Where information was not sufficient to complete this, details were noted and presented in tabular form.

Directional agreement was regarded as positive when percentage improvements of both subjective and objective outcome were in the same direction providing there was an accompanying P-value showing that they were statistically significant. A statement that 'results were statistically significant', participants 'agreed with investigators' or that they preferred a particular form of treatment without any supporting data was not sufficient to qualify as directional agreement. Trials in which assessors and participants both found improvements but without statistical significance were not recorded as agreement.

Results

Journal yield

In total, 125 trials from the period 1994–2001 were retrieved in full paper form as per the planned sample size. In most cases, five papers were obtained from each year of each journal, as shown in Table 1. The papers covered a range of conditions: psoriasis (n = 32); eczema (n = 8); dermatophytes (n = 8); acne (n = 7); warts (n = 6); onychomycosis (n = 5); seborrhoeic dermatitis (n = 5); and others (n = 54). Overall, only 17 papers (13·6%) clearly declared their main outcome measures beforehand in the introduction or methods section.

Table 1 Number of papers selected from each journal by year

	Journal				
Year	*Arch*	*BJD*	*CED*	*JDT*	*JAAD*
1994	3	4	2	0	0
1995	5	6	2	5	5
1996	5	5	5	5	5
1997	5	5	5	5	5
1998	5	5	3	5	5
1999	2	0	5	5	5
2000	0	0	2	0	0
2001	0	1	0	0	0
Total (n = 125)	25	26	24	25	25

Arch, *Archives of Dermatology*; *BJD*, *British Journal of Dermatology*; *CED*, *Clinical & Experimental Dermatology*; *JDT*, *Journal of Dermatological Treatment*; *JAAD*, *Journal of the American Academy of Dermatology*.

Main outcomes

Overall, only 32 papers (25·6%, 95% exact confidence interval 18·2–34·2%) included some sort of participant-nominated efficacy outcome measure. The breakdown according to journal is shown in Table 2. Two of these studies mentioned the participant outcomes only in the methods section, without giving any form of results thereafter. Of the remaining 30 trials that included some form of reporting of the participant outcome results, results were presented in full in the results section in only nine (30%) trials, although a further 21 studies (70%) included some form of figure or graphical representation of the participant data. Data were presented in figure format only in 12 of these studies and in tables and figures in nine. One of the 21 studies was not analysed further as a large number of participants was withdrawn due to intolerance of the treatment resulting in a change of study design. Participant outcomes were mentioned in the abstract section in 17 of 32 trials (53%) that reported participant outcome results.

Agreement between objective and subjective findings

Of the 29 studies that contained both assessor and participant outcomes shown in Table 3, only five included enough information to support directional agreement.[11–15] It was considered inappropriate to compare the direction of results if investigators and participants were measuring very different outcomes. Most of the remaining studies recording similar types of outcomes did not give sufficient information, for example, just P-values without any supporting data.[16]

Discussion

This study has confirmed our suspicion that the participant's subjective assessment of treatment efficacy is infrequently reported in dermatological clinical trials. Only around a quarter of the trials included in this study reported participant-nominated efficacy outcomes and, when included, they were often poorly reported and afforded low priority in the body of the paper. Although previous surveys of trials of specific skin diseases such as psoriasis, acne and atopic eczema have found that issues such as quality of life are rarely recorded,[7,17,18] we are not aware of other reports that specifically estimate the proportion of trials across dermatological care that mention participant subjective outcomes. Our experience of reviewing trial protocols suggests that participant outcomes are often recorded in many clinical trials, yet the results are often not mentioned in the final journal published report, or are mentioned only briefly. This is perhaps not surprising given that the quality of reporting of trials in dermatological journals in the past has been generally poor.[19,20]

As trial participants are often in the best place to say whether the benefit they received from treatment was worthwhile, and in what way the treatment might have benefited them most, it is hard to understand the reluctance to include and report such measures in dermatology trials. One reason is

Table 2 Summary of main results on studies that included participant outcomes

	Journal					
	Arch	*BJD*	*CED*	*JDT*	*JAAD*	Total (%)
No. including subjective participant outcomes	5 (4%)	5 (4%)	5 (4%)	11 (8·8%)	6 (4·8%)	32 (25·6)[a]
Status of participant outcomes						
Just mentioned in Methods	1	1	0	0	0	2 (1·6)
Methods & Results	0	2	3	3	1	9 (7·2)
Methods, Results or figure given	4	2	2	8	5	21 (16·8)
Any mention in abstract	3	4	0	7	3	17 (13·6)

[a]95% confidence interval 18·2–34·2% (exact method). Percentages shown in parentheses refer to the number in relation to the total number of trials (n = 125). *Arch*, *Archives of Dermatology*; *BJD*, *British Journal of Dermatology*; *CED*, *Clinical & Experimental Dermatology*; *JDT*, *Journal of Dermatological Treatment*; *JAAD*, *Journal of the American Academy of Dermatology*.

perhaps a concern among trialists that their results sound too 'subjective' even though it is precisely a subjective outcome they are trying to measure in many cases. Such a notion is partly supported by the profusion of unvalidated scales that have been developed in dermatology that give an illusion of objectivity and precision.[1,17] Perhaps drug regulatory bodies have also been partly responsible in the past in promoting reductionist outcomes that are difficult to interpret clinically in dermatology trials. Such bodies are in a unique position to reverse this trend in favour of a more balanced approach to including participant outcomes alongside physician-assessed outcomes. There are early signs that things are beginning to improve as patient-reported outcomes are now beginning to feature prominently in some studies of biologics in psoriasis.[21] In some instances, it is possible that trialists have played down the participant outcomes because their results did not look as good as the other objective outcomes. For example, a trial of 2% minoxidil against placebo for androgenetic alopecia in women found a statistically significant increase in nonvellus target area hairs in the minoxidil-treated group vs. the vehicle-treated group after 32 weeks ($P = 0{\cdot}006$), although the 'subjects discerned no difference'.[22] The study, which was otherwise well conducted, should have concluded something along the lines of 'a treatment response seems to be happening, but it is not clinically useful yet'. However, the authors' conclusion was that '2% minoxidil appears to be effective in the treatment of female androgenetic alopecia'. Effective for whom?

Another possible reason for an avoidance of participant subjective outcomes is that such outcomes carry more variability and less responsiveness to change than other physician-assessed scales in dermatology, thereby increasing the sample size (and expense) needed to obtain a statistically significant result. Although plausible, we know of no published evidence in the field of dermatology to support such a notion. Our study was too small to comment on a comparison of variability of participant- vs. physician-recorded outcomes, and a further detailed study exploring such an aspect is warranted. In addition, more research is needed on assessing the reliability of patient-reported outcomes by conducting repeatability testing in the same respondents. Further research is also needed to determine the optimum number of points (e.g. 1–5 or 1–7) and best adjectival descriptors (such as moderate or good or excellent improvement) to use in such scales in order to inform a more standardized approach to using patient-reported outcomes in published studies.

Our study was too small to carry out a conclusive comparison of the direction and magnitude of participant vs. physician outcomes. Such a comparison was a secondary outcome of our study, and a much larger study of around 2000 trials would probably be needed to conduct such a study, given the unexpectedly low proportion of participant subjective outcomes when compared with our pilot study, and the incomplete reporting of outcome data. Our study was also not large enough to provide a meaningful breakdown and analysis of participant outcomes into specific symptoms, and further larger studies are needed. We concentrated on efficacy outcomes such as improvement in symptoms or global disease improvement rather than secondary issues such as tolerability/acceptability outcomes, although we acknowledge the latter factors might be important issues for patients – especially for choice of topical therapies. Given that the results of this study are based on 125 trial reports from 1994 to 2001, it is possible that they are no longer valid in 2008. However, a recent update of the NHS systematic review of RCTs for atopic eczema (H.C.W., unpublished observations) suggests that little has changed in the last 5 years. It is also possible that other journals not included in our survey are better at insisting on clearer and more complete reporting of participant subjective outcomes, but we are not aware of any at this stage. Some degree of observer bias was also possible given that our 'hunch' was that subjective outcomes were not recorded universally. We mitigated against such a possibility by using a standardized data abstraction form and by ensuring that at least two members of the team discussed equivocal results. The overall finding of around a quarter of trials reporting some form of subjective

Table 3 Summary of the 29 papers that included both assessor- and participant-reported outcomes. The five trials with agreement of assessor- and participant-reported outcomes are indicated in bold

First author and year	Main objective outcome	% improvement	P-value	Main patient outcome	% improvement	P-value	Comment
Archives of Dermatology							
DeVillez (1994)[11]	**Hair count**	**105·0**	**0·0004**	**Hair growth**	**50·0**	**0·002**	Directional agreement although magnitude of improvement less from a participant perspective
Guillaume (1995)[24]	Complete remission	84·6	< 0·0001	Sleepiness			Only the number of participants suffering side-effect was noted
Drake (1995)[12]	**Pruritus**	**33·3**	**0·01**	**Pruritus**	**37·0**	**0·001**	Similar in magnitude and direction
Stiller (1996)[25]	Global severity	85·4	< 0·05	Facial appearance			Participants recorded statistically significant improvement from baseline but improvement also noted with vehicle
British Journal of Dermatology							
Molin (1997)[26]	PASI	17·9	0·17	Overall response			Not enough data given to confirm participant outcomes
Chu (1997)[16]	Acne grade		0·03	Global improvement		< 0·001	Only a statement with P-values; no further detail
Ruzicka (1998)[27]	PASI	9·3	< 0·001	Global improvement			Not enough data to calculate improvement in participant outcomes
van de Kerkh of (1998)[13]	**Global response**	**63·0**	**0·005**	**Global improvement**	**40·0**	**0·005**	Similar in magnitude and direction
Clinical & Experimental Dermatology							
Oliwiecki (1994)[28]	Erythema	No significant difference		Erythema	No significant difference		No data included
Simons (1997)[29]	Severity index	38·2	Not statistically significant	Pruritus			No participant results given
Glade (1998)[30]	Global severity	No details given		Global severity	No significant change		No participant data given
Green (1998)[31]	Fine wrinkles on face	No significant change		Overall skin ageing	No significant change		No data given
Watson (2000)[32]	Urticaria	No significant change		Pruritus	No significant change		Comparison of two treatments. Both had significant effects for both objective and subjective outcome measures but no significant difference between the two treatments
Journal of Dermatological Treatment							
Pigatto (1996)[33]	Severity grade	No data		Cosmetic appearance	No data		Statement that treatment improved condition and that patients agreed
Ortonne (1996)[34]	Ulcer appearance	138·1	< 0·05	Overall improvement	No statistical significance		No data for participant outcomes – only a statement on significance
Reidhav (1996)[35]	Severity score			Pruritus			No statistically significant results and so no data given. Paper then concentrated on treatments' ease of use

Table 3 (*Continued*)

First author and year	Main objective outcome	% improvement	P-value	Main patient outcome	% improvement	P-value	Comment
Patel (1997)[36]	Pruritus	3·9	Not statistically significant	Pruritus	−9·6	Not statistically significant	Difficult to assess agreement as neither outcome was significant
Katz (1998)[37]	Severity score	10·3	0·01	Overall improvement	Treatment preferred but no data given	0·03	Not clear if analysis of the participant outcomes compared two treatment groups with each other or with baseline
Shuttleworth (1998)[38]	Severity score	13·0	No significant differences between groups	Overall opinion	−12·2	No significant differences between groups	Two studies included in paper. The first was the one analysed. Changes from baseline were statistically significant although this was not the case when comparing the treatments
Shuttleworth (1998)[39]	Severity score	240·0		Severity score	−4·3		No statistically significant difference between the treatment and placebo but the improvement with the treatment was statistically significant from baseline
van 't Veen (1998)[40]	Severity score	14·0		Severity score	−1·0		By the end of the study (4 weeks) statistically significant differences between the two active treatment groups were no longer seen
Davies (1999)[14]	**Area of affected scalp**	**66·7**	**< 0·01**	**Dandruff severity score**	**125·0**	**< 0·001**	Two studies analysed. The first study was active treatment vs. placebo. Good agreement in terms of direction and magnitude of benefit
Christensen (1999)[41]	ESI score	−41·7		Pruritus	−28·0	Not statistically significant	Results merged severity scores from other areas of the body which were statistically significant different. No analysis carried out on separate areas
Farkas (1999)[42]	mPASI	11·9		Overall benefit	Not statistically significant		mPASI score improvements were statistically significant between the two groups at 6 weeks ($P < 0·05$) but no data given for 8 weeks (end of treatment). Statement that assessment of efficacy by patients showed 'no statistically significant difference' but no data given
Journal of the American Academy of Dermatology							
Miller (1997)[43]							Study looking at nonsurgical treatment of BCCs. Investigators and participants scored pain, erythema etc. but no data presented!

Table 3 (*Continued*)

First author and year	Main objective outcome	% improvement	P-value	Main patient outcome	% improvement	P-value	Comment
Oranje (1997)[44]	PASI	40·2	0·14	Overall response	3·6	0·19	PASI score difference between groups was not statistically significant. Participants rated efficacy on a five-point scale. We took the top two categories as success (marked improvement and cleared). These differences were not statistically significant either
Mayser (1998)[45]	PASI	49·3	0·048 but not clear if at end or during treatment	Overall improvement			'No noticeable differences between groups' present concerning participant outcomes. Some data included but not clear if from PASI or visual analogue scale
Lok (1999)[15]	**No of treatments until clean ulcer**	**Median of 11·5 vs. > 15**	**0·019**	**Pain**	**Mean scores of 2·3 vs. 5**	**0·003**	Agreement in direction and magnitude
Leyden (1999)[46]	Hair count	580·0	Unclear what P-value relates to	Hair growth		< 0·05	Statement that patient assessments were significant but no tables of data – just diagrams

PASI, Psoriasis Area and Severity Index; mPASI, modified Psoriasis Area and Severity Index; BCC, basal cell carcinoma. Blank cells indicate not enough or no data.

outcome was also much lower than the 50% we anticipated from our pilot study. The sample size was large enough to estimate our main outcome with good precision, and several journals were included to give a representative sample of dermatological papers. Our protocol dictated that little importance was given to statements of trends or significance without evidence in the form of actual data, although such data might have been available from authors if requested.

Few are likely to disagree that recording the participant's own views of clinical efficacy, tolerability and acceptability is an important aspect of any dermatological trials where 'hard outcomes' such as death are rare. Yet for some reason, investigators appear to be afraid of asking study participants what they think about treatments and, when asked, their views are rarely recorded or afforded any prominence within published trials reports. Some recent systematic reviews produced by the Cochrane Skin Group are placing more emphasis on participant-centred outcomes by declaring them as main outcome measures in the review protocols,[23] a trend that we hope trialists, manufacturers and regulators will embrace. Patient representative groups sitting on grant-giving bodies and ethics committees are also in a good position to request participant-centred outcomes where appropriate, and journal editors are in a strong position to ensure that such outcomes are reported fully when recorded. It is important to emphasize that we do not suggest that well-validated physician scales should be dropped from dermatological clinical trials in favour of subjective outcomes recorded by study participants, rather that the two aspects should be recorded alongside each other and be reported with equal attention.

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