Alopecia areata investigational assessment guidelines—Part II

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Alopecia areata is an immunologically mediated disease characterized by extreme variability not only in the time of initial onset of hair loss but in the duration, extent and pattern of hair loss during any given episode of active loss. These variables, as well as the unpredictable nature of spontaneous regrowth and lack of a uniform response to various therapies, has made clinical trials in alopecia areata difficult to plan and implement. In fact, there are currently no drugs FDA-approved specifically for the indication of alopecia areata.

To help facilitate well-controlled clinical trials for alopecia areata, this National Alopecia Areata Foundation (NAAF) sponsored subgroup of investigators/clinicians experienced in clinical trials and/or in the clinical care of patients with alopecia areata has outlined some general principles and potential endpoints for clinical studies in alopecia areata. These guidelines build on the Alopecia Areata Investigational Assessment Guidelines published in 1999[1] which established baseline clinical staging and background information important to gather on any alopecia areata patient involved in clinical research.

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Recommended criteria for assessing a therapeutic response

A. General: The following information should be collected at baseline (in addition to that baseline information outlined in A-D (Part V) in the Alopecia Areata Investigational Assessment Guidelines[1] (see Table I). Stratification is suggested for some characteristics that may have prognostic implications (ex: duration hair loss, percentage hair loss, pattern of hair loss). The stratification into subgroups is meant to prevent inappropriate clustering of patients in clinical therapeutic trials but should not substitute for the collection, and later analysis, of the unqualified data.

1. Duration of current episode of scalp hair loss (beginning with when last had normal complement of scalp hair excluding hair loss from etiologies other than alopecia areata (such as androgenetic alopecia/pattern hair loss). May be stratified by subgroups of duration of current episode including:
   a. < 3 months
   b. 3-12 months
   c. 12-24 months
   d. >2-5 years
   e. >5 years
2. Percent scalp hair loss. This takes into account the percent of the scalp surface with no hair. The hair loss in patients with diffuse alopecia areata without discrete patches of alopecia cannot be captured by this method. Fig 1 is recommended as a visual aid. The diagrams of Fig 1 and the percentage scalp surface area

Table I. Alopecia areata database*

A. Essential background data
- Patient's initials _____
- Date of intake _____
- Age _____
- Date of birth _____
- Age at onset of first episode of alopecia areata _____
- First episode of alopecia areata (month/year of onset) _____

- Current episode alopecia areata
  - Age of onset _____
  - Month/year of onset _____
  - Duration of current episode (months) _____
  - Extent of hair loss _____(S_0-S_5, B_0-B_2)

- Sex
  - Male _____
  - Female _____

- Racial group
  - American Indian or Alaskan native _____
  - Asian or Pacific Islander _____
  - Black, not of Hispanic origin _____
  - Hispanic _____
  - White, not of Hispanic origin _____

B. Predominant hair color
- Black _____
- Brown _____
- Red _____
- Blonde _____
- Gray _____
- White _____

Prior history of alopecia areata

Number of prior episodes of alopecia areata _____

History of alopecia totalis or alopecia totalis/alopecia universalis at any time
1. >2 years duration _____
2. ≤2 years duration _____

C. Pertinent immediate past history

History of infections within 6 months before onset of hair loss
- a. Initial episode of alopecia areata
  - Site of infection _____
  - Type of infection _____
- b. Current episode of alopecia areata
  - Site of infection _____
  - Type of infection _____

History of vaccination within 6 months before onset of hair loss
- a. Initial episode of alopecia areata
  - Type of vaccination _____
- b. Current episode of alopecia areata
  - Type of vaccination _____

Patient's or parent's perception of trigger for hair loss

Initial episode _____

Current episode _____

D. Patient and family medical history

Patient and family medical history	Patient	Mother	Father	Son	Daughter	Brother	Sister	Maternal grandmother	Maternal grandfather	Paternal grandmother	Paternal grandfather	Maternal aunt	Maternal uncle	Paternal aunt	Paternal uncle
Atopic dermatitis															
Allergic rhinitis															
Asthma															
Thyroid disease															
Hashimoto's thyroiditis															
Graves' disease															
Vitiligo															
Diabetes															
Insulin-dependent diabetes															
Non-insulin-dependent diabetes															
Unknown type															
Lupus erythematosus															
Pernicious anemia															
Rheumatoid arthritis															
Ulcerative colitis															
Celiac disease															
Psoriasis															
Other autoimmune disease															
Type															
Down syndrome															
Immunodeficiency															
Type															
Other															

*From Olsen EA, Hordinsky M, McDonald-Hull S, Price V, Roberts J, Shapiro J, et al. J Am Acad Dermatol 1999;40:242-6.

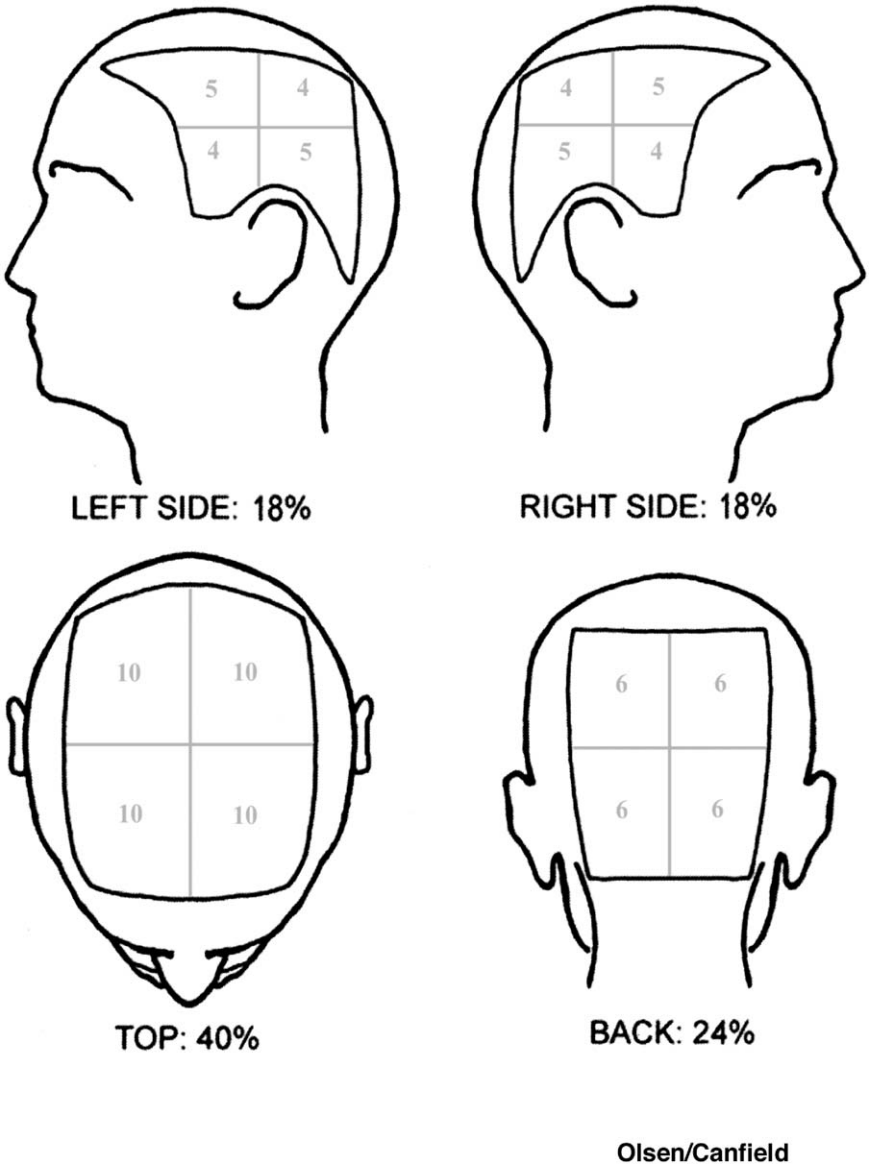


Fig 1. Visual aid (Olsen/Canfield) for estimating percentage scalp hair loss, "x" score and percent regrowth. Using this diagram, one can determine the percent scalp hair loss in a given quadrant and multiply this by the total scalp area delineated by that quadrant and sum the resultant numbers for each quadrant to give the total percent scalp hair loss. This diagram also allows the evaluator to graph the area(s) of alopecia, if desired, in order to facilitate the estimate of percent scalp hair loss and to compare the hair loss on subsequent evaluations. This percent hair loss can later be corroborated by image analysis if desired.

were made by first dividing the scalp up on a representative mannequin and determining by image analysis the percent scalp coverage.

3. The type of hair remaining on the scalp may be further characterized.
   a. The percent of hair that is terminal hair
      i. percent pigmented hair
      ii. percent nonpigmented hair
   b. The percent of hair that is vellus/indeterminant
4. A global alopecia areata severity score based on the combination of extent and density of scalp hair loss. The score is determined by visually determining the amount of terminal hair loss in each of the four views of the scalp and adding these together with a maximum score of 100%. Fig 2 illustrates how the views of an actual patient's scalp may be correlated with the Fig 1 diagrams. Please note that the

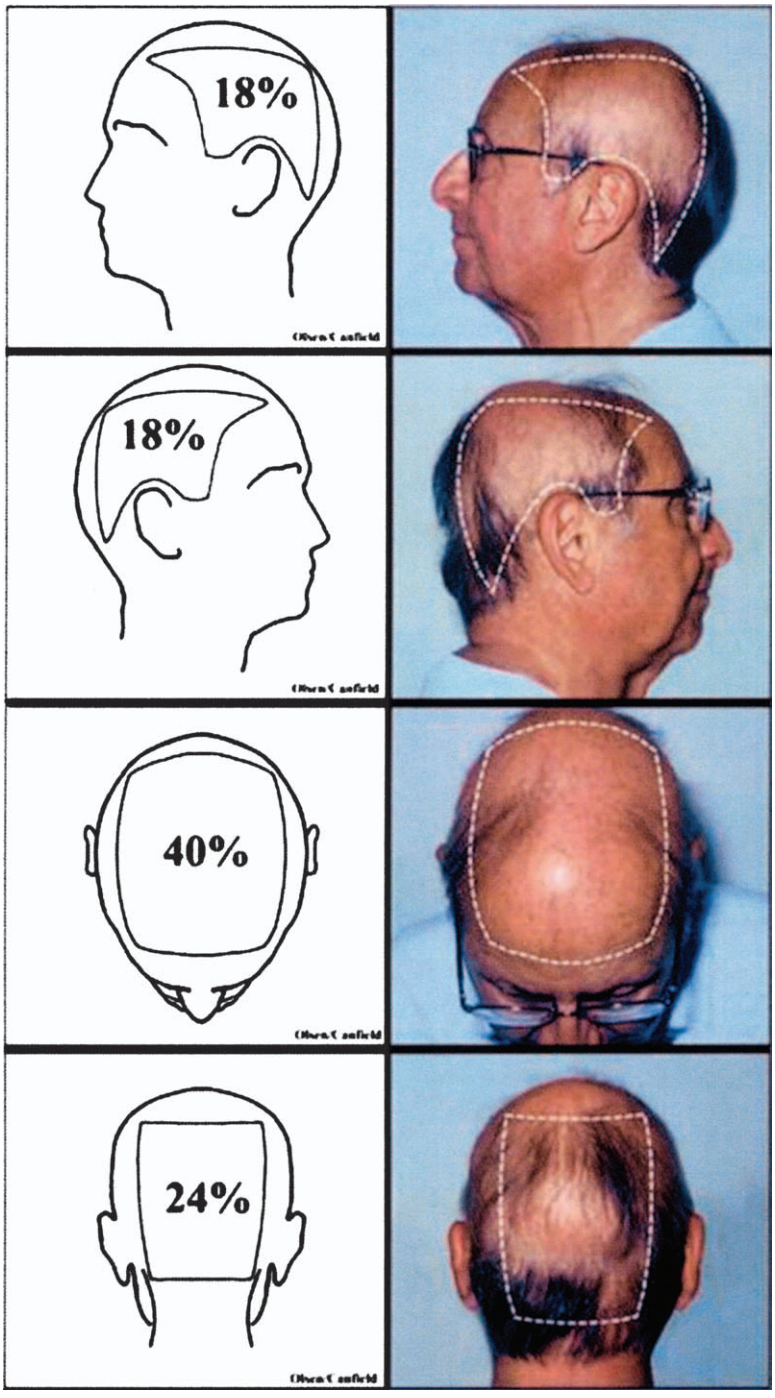


Fig 2. *Right*, Photographs taken of the four views can also be done to help corroborate the percent hair loss by the patient or other evaluators/photograph reviewers, the latter potentially as has been done for hair growth promoters in pattern hair loss/androgenetic alopecia. However, except in very extensive scalp hair loss, photographs may be a less accurate means of assessing percentage scalp hair loss than direct scalp observation.
Left, SALT score. The percentage of hair loss in any one of the four views (areas) of the scalp = the percentage hair loss × percent surface area of the scalp in that area. The SALT score then equals the sum of the scalp hair loss in each area.
(a) Top (left side view) = 95% × .18 = 17.1
(b) Second(right side view) = 90% × .18 = 16.2
(c) Third (top of scalp) = 95% × .40 = 38 (realizing that most of hair loss is probably male pattern hair loss)
(d) Bottom (back of scalp) = 55% × .24 = 13.2
a+b+c+d = 17.1 + 38 + 16.2 + 13.2 = 84.5% hair loss or SALT 84.5

superimposition onto the scalp, either on paper or visually at the bedside, of an arbitrary figure derived from a model head cannot be exact. This global severity score may be called the "Severity of Alopecia Tool" or SALT score. Fig 2 can be used to illustrate how the SALT score may be determined in a given patient. The SALT score may be determined at the bedside by the investigator and the patient or by review of representative photographs by investigator, subject or expert panel.

5. Further subgrouping of percent scalp hair loss into the following SALT subclasses:
   S_0 = no hair loss
   *S_1 = < 25% hair loss
   *S_2 = 25-49% hair loss
   *S_3 = 50-74% hair loss
   *S_4 = 75-99% hair loss
   a = 75-95% hair loss
   b = 96-99% hair loss
   S_5 = 100% hair loss

*This represents a revision of the S_1-S_4 categories from the original Alopecia Areata Investigational Guidelines.

6. Pattern of scalp hair loss
   a. Patchy
   b. Ophiasis
   c. Totalis (100% scalp hair loss)
7. Body hair loss
   B_0 = No body hair loss
   B_1 = Some body hair loss
   B_2 = 100% body (excluding scalp) hair loss. The latter determination must involve a complete physical examination and include facial, axillary, truncal, genital, and extremity hair evaluation.
8. Nail involvement
   N_0 = No nail involvement
   N_1 = Some nail involvement
   a. Twenty-nail dystrophy/trachyonychia (must be all 20 nails)†
9. Standardized photographs should be taken of the 4 views of the head (see Fig 2).
10. Quality of Life questionnaire (to be determined)

B. Exclusions to subject participation:
1. Any subject who is currently experiencing significant spontaneous regrowth of terminal hair
2. Any subject treated with a topical, intralesional or systemic agent likely to cause regrowth in alopecia areata within the past month

† This does not include stippling of 20 nails.

C. Length of study. An investigational period allowing at least 6 months' observation of the subjects' scalp hair growth is recommended. The active treatment period should be for a duration likely to see a treatment effect but, in general, no less than 3 months.

D. Potential end points
All of these end points have potential usefulness but not all are practical, feasible or validated for large clinical trials. All of these end points are not meant to be used in each clinical trial.

1. Change in absolute percent scalp hair loss from baseline (baseline percent scalp hair loss minus percent scalp hair loss at follow-up). Example: 75% hair loss at baseline, 50% hair loss at follow-up = 25% change from baseline hair loss.
2. Percent scalp hair regrowth based on only extent of absolute hair loss. Example: 75% hair loss at baseline, 50% hair loss at follow-up, the percent regrowth = $\frac{75\% - 50\%}{75}$ = 33% regrowth.
3. The type of hair remaining on the scalp may be further characterized.
   a. The percent of hair that is terminal hair
      i. % pigmented hair
      ii. % nonpigmented hair
   b. The percent of hair that is vellus/indeterminant: ___%
   c. The percent change from baseline may then be calculated
4. Change in SALT score from baseline. Same principle as described in D.1 but incorporates density as well as extent into scoring system. Example: SALT 75 − SALT 50 = SALT 25

**5. Percent scalp hair regrowth based on SALT score. Same principle as described in D.2. Example: (SALT 75 − SALT 50)/SALT 75 = 33% regrowth or $SALT_{33}$ where the subscript equals the percent change in SALT score.

6. Global assessment: overall improvement. This takes into account extent and density of regrowth by the SALT scoring system. First note percent regrowth, then further categorize by:
   A_0 = no change or further loss
   A_1 = 1-24% regrowth
   A_2 = 25-49% regrowth
   A_3 = 50-74% regrowth
   A_4 = 75-99% regrowth
   A_5 = 100% regrowth
7. Global photograph assessment by blinded expert panel and SALT score determined. Standardized photographs as in Fig 2 would need to be taken at critical follow-up time points.

8. Body hair (for subjects treated with either topical scalp and/or systemic treatment)
   New loss ___(yes) ___ (no)
   New growth ___(yes) ___ (no)
9. Nontreated scalp areas (for subjects treated with topical or intralesional therapy only)
   New loss ___(yes) ___ (no)
   New growth ___(yes) ___ (no)
10. Nail involvement
    Improved ___
    No change ___
    Worse ___
11. Patient assessment
    a. Global assessment (SALT equivalent)
       A_0 = no change or further loss
       A_1 = < 25% regrowth
       A_2 = 25%-49% regrowth
       A_3 = 50%-74% regrowth
       A_4 = 75%-99% regrowth
       A_5 = 100% regrowth
    b.

Total scalp hair loss — No change — Total scalp hair regrowth

The principal investigator must specify for the patient what is the comparative time point for each follow-up evaluation ie scalp hair loss compared to baseline or compared to end of treatment

    c. Quality of Life questionnaire (to be determined)

Table II. Sequential determination of categories of scalp hair loss and SALT score in patients with alopecia areata

	Evaluators						
	#1	#2	#3	#4	#5	#6	#7
Patient #1							
Initial read	S_2	S_2	S_2	S_3	S_3	S_3	S_3
Second read	55%	40%	NC	53%	65%	60%	60%
Patient #2							
Initial read	S_3	S_4a	S_4a	S_4a	S_4b	S_4a	S_4b
Second read	78%	96%	ND	87%	97%	95%	97%
Patient #3							
Initial read	S_2	S_3	S_3	S_3	S_3	S_3	S_3
Second read	56%	64%	ND	51%	60%	80%	70%
Patient #4							
Initial read	S_1	S_1	ND	S_1	S_3	S_1	S_3
Second read	3%	15%	ND	5%	50%	5%	40%
Patient #5							
Initial read	ND	S_2	S_2	S_2	S_2	S_2	S_2
Second read	26%	31%	NC	30%	35%	25%	30%
Patient #6							
Initial read	S_1	S_1	S_2	S_1	S_3	S_2	S_2
Second read	5%	25%	NC	12%	50%	15%	30%

NC, Not complete; *ND*, not done.
*Evaluators included: Maria Hordinsky, Elise Olsen, Vera Price, Janet Roberts, Jerry Shapiro, Len Sperling, Maria Turner.

DISCUSSION

The literature is replete with small studies on alopecia areata that are not able to be directly compared due to either endpoints that are non-quantitative, poorly defined or which were unnecessarily linked to the sites of hair loss and the sites of regrowth.[2-14] For example, the term "cosmetically acceptable" has been a commonly utilized term that unduly weighs improvement in the top relative to the sides of the scalp since growth here can camouflage remaining hair loss on the sides of the scalp.[7-14]

These guidelines serve to offer several different means of assessing hair loss and growth in alopecia areata: not all are meant to be used in any individual trial. Recognizing that there are two main changes in the hair that occur in alopecia areata ie a decrease in the extent of scalp hair coverage and a decrease in terminal hair density in remaining areas of hair growth, both these characteristics of the hair loss should be part of any primary endpoint for alopecia areata. In these guidelines, both extent and density have either been graded together visually in the SALT (Severity ALopecia Tool) score.

Absolute changes in the SALT score compared to baseline or the percent change from baseline (a more representative figure) can be used to track response to treatment. For recording purposes, the percent change from baseline can be noted as a subscript of the SALT score, ie 50% improvement = $SALT_{50}$. A $SALT_{50}$ would be an acceptable endpoint for trials involving extensive alopecia areata and systemic agents. A $SALT_{50}$ may be too low for trials of topical agents in limited alopecia areata. An acceptable percentage change in SALT should take into account the duration of the study, the time course for maximum efficacy of the individual treatment, the inherent responsiveness to treatment and the potential for spontaneous regrowth (which in turn are dependent on the subject's age, duration of the current episode of alopecia areata, extent and pattern of hair loss) of the subjects in the clinical trial.

The SALT score has been previously tested and has been used by several of the authors. At a NAAF-sponsored workshop in Washington, DC in 1997, seven clinical investigators experienced in hair growth (M. Hordinsky, E. A. Olsen, V. Price, J.

Roberts, J. Shapiro, L. Sperling, M. Turner) evaluated 6 patients with alopecia areata of varying ages and with varying degrees of scalp hair loss using the diagram shown as Fig 1. Evaluators were first asked to estimate the percent scalp hair loss according to the Alopecia Areata Investigational Assessment Guidelines categories of hair loss (S_0-S_5) and then to determine the absolute percent scalp hair loss, what we now propose as the SALT score (Table II). One can see from the results that determining the SALT score first would have increased the accuracy of the S_0-S_5 classification. The recommended sequence is thus the determination of the SALT score at baseline, then the S_0-S_5 score. Determining the SALT score first is critical to determining the percent regrowth; looking only for changes in the S_0-S_5 score will underestimate the regrowth response, especially in patients who have lesser degrees of hair loss at baseline. There are nuances regarding using the SALT score and a teaching session with all potential investigators or users is necessary before this is actually put into use in any given clinical trial: this assures that the data collected by various principal investigators can be collated.

The SALT score relies on the determination of terminal hair loss or growth only. Terminal hair is what patients should have covering their scalps except for those men, and some women, who have vellus or intermediate hairs in discernible areas of androgenetic alopecia/pattern hair loss. While it is certainly reasonable, and may be important prognostically, to note the presence of non-terminal hair growth in patients with alopecia areata where terminal growth is not present or nondominant (see Sections A3 and D3), it is extremely difficult to quantify this clinically. Also, since not all vellus/intermediate hairs eventually become terminal hairs and may have a greater proclivity to fall out once a hair growth promoter is removed, terminal hair is clearly the most important type of hair to track. Vellus or indeterminate hair growth may, however, both give an idea of potential utility of a new therapeutic agent and promise of responsiveness of a patient to treatment.

Hair pigmentation is a characteristic of the hair regrowth in alopecia areata which should be noted but, at this point, is not included in any scoring system. Ultimately, whether terminal hair initially regrows unpigmented or pigmented may have prognostic implications but only large scale studies that track this as an independent variable will be able to sort this out.

Standardized global photographs should be taken at baseline to help determine changes in extent, density and patterns of hair growth or loss. These photographs are best done to mimic the schematic drawings shown in Fig 1. They may be then utilized for expert panel review, and determination of SALT score (analogous to that done with global photographs in pattern hair loss) either by expert panel review or by image analysis. Photographs will be most reliable when either the hair loss is extensive and regrowth is clearly apparent or the patients' hair is sufficiently short at baseline and all follow-up time points so all areas of loss are clearly seen. Combing of remaining hair to expose all areas of hair loss for photographic documentation is critical for the success of this method.

How nail involvement and degree of body hair involvement should be factored into the overall response to treatment is unclear. Clearly, only systemic agents, versus those applied only to the scalp, can potentially effect hair growth outside the scalp or nail growth. However, until better understanding of the precise interrelatedness of these processes, nail and body hair, even with systemic agents, are best recorded, but not factored, into overall response.

Finally, it is very important what subjects think of their overall response to treatment. Their assessment of response will vary with extent and location of loss—those with less loss ($< 50\%$) scalp surface area will need to have less improvement in key areas to camouflage the remaining loss whereas those with extensive loss ($\geq 50\%$ scalp surface area) must have much more regrowth to camouflage the loss. This consensus group recommends one of two measures of subject assessment of response—a more objective measure of regrowth, either the SALT or a visual analog scale (Section D, 1.2a and b)—as well as a Quality of Life measurement. Although there are several Quality of Life tools in use for dermatology and some would lend themselves to modification for alopecia use, there has not been one published specifically for alopecia areata. The NAAF is currently developing a new Quality of Life measurement. Any Quality of Life measurement will need validation before recommendations for general use can be made.

In summary, we have recommended specific data to collect at baseline before any clinical trial for alopecia areata and several potential endpoints to track during the study. As a primary endpoint, the SALT score appears ideal for investigators, subjects and expert panel review to use in tandem, thus cross-referencing their assessments. All of these endpoints will require assessors to be educated in their use before initiation of any clinical trial in order to increase reliability of the results. A validated Quality of Life scale will be extremely useful and give additional information on subject appreciation of the utility of any new treatment for alopecia areata.

REFERENCES

1. Olsen E, Hordinsky M, McDonald-Hill S, Price V, Roberts J, Shapiro J, Stenn K. Alopecia areata investigational assessment guidelines. J Am Acad Dermatol 1999;40:242-6.
2. Dillaha CJ, Rothman S. Therapeutic experiments in alopecia areata with orally administered cortisone. JAMA 1952;150:546-50.
3. Kern F, Hoffman WH, Hambrick GW, Blizzard RM. Alopecia areata: Immunologic studies and treatment with prednisone. Arch Dermatol 1973;107:407-12.
4. Galbraith GMP, Thiers BH, Jensen J, Hoehler F. A randomized double-blind study of Inosiplex (isoprinosine) therapy in patients with alopecia totalis. J Am Acad Dermatol 1987;16: 977-83.
5. Krook G. Treatment of alopecia areata with Kromayer's ultraviolet lamp. Acta Derm Venereol (Stockh) 1961;42:178-81.
6. Wiseman MC, Shapiro J, McDonald N, Lui H. Predictive model for imunotherapy of alopecia areata with diphencyprone. Arch Dermatol 2000;137:1063-8.
7. Sharma VK. Pulsed administration of corticosteroids in the treatment of alopecia areata. Int J Dermatol 1996;35:133-6.
8. Gupta AK, et al. Oral cyclosporine for the treatment of alopecia areata: A clinical and immunohistochemical analysis. J Am Acad Dermatol 1990;22:242-50.
9. Weiss VC, et al. Alopecia areata treated with topical minoxidil. Arch Dermatol 1984;120:457-63.
10. Price VH. Topical minoxidil in extensive alopecia areata, including 3-year follow-up. Dermatologica 1987;175(suppl 2): 36-41.
11. Fiedler-Weiss VC, West DP, Buys CM, Runsfeld JA. Topical minoxidil dose-response effect in alopecia areata. Arch Dermatol 1986;122:180-2.
12. Fiedler-Weiss VC. Topical minoxidil solution (1% and 5%) in the treatment of alopecia areata. J Am Acad Dermatol 1987; 16:745-8.
13. Schmoeckel C, Weissman I, Plewig G, Braun-Falco O. Treatment of alopecia areata by anthralin induced dermatitis. Arch Dermaol 1979;115:1254-5.
14. Fiedler-Weiss VC, Buys CM. Evaluation of anthralin in the tretment of alopecia areata. Arch Dermatol 1987;123: 1491-3.