# Guidelines for clinical trials in melasma

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## Summary

There have been very few well-conducted trials in melasma and this makes the process of comparing treatment outcome between trials difficult. The Pigmentary Disorders Academy has examined the issues relating to clinical trials on melasma, and has proposed recommendations on how they should be conducted. This covers all aspects including correct diagnosis of the condition, evaluation of efficacy and safety outcome, and overall clinical trial design. It is anticipated that the establishment of accepted guidelines on the conduct of clinical trials in melasma will greatly assist the dermatological community.

## Introduction

Well-designed, randomized controlled trials give the best evidence for the efficacy of a particular therapeutic intervention. Trials of agents for treatment of melasma have often been performed without controls, randomization, or blinding. Bias can occur in poorly designed trials, which can mislead clinicians into making the wrong decisions and cause unnecessary treatment for patients.[1] The Pigmentary Disorders Academy (PDA) has examined the issues relating to clinical trials, in particular those relating to the melasma, and here makes recommendations on how clinical trials in this area should be conducted. Also reviewed by the PDA are the Consolidated Standards of Reporting Trials (CONSORT) guidelines[2] on the reporting of clinical trials.

## Melasma

Melasma (also known as chloasma or mask of pregnancy) is an acquired, chronic, recurrent, symmetrical hypermelanosis, which is characterized by brown patches of variable darkness on sun exposed areas of the body. Hyperpigmentation typically occurs on the face (lower cheeks, forehead, nose and upper lip).[3] Melasma is more common in women, accounting for 90% of all cases, and appears in all racial types, particularly those with skin types IV and V who live in areas of high ultraviolet (UV) radiation. A recent study in North America[4] showed that melasma can be seen frequently in phototypes II–III suggesting that the disease in these skin types can often be underdiagnosed or mistaken for photodamage. Factors involved in the pathogenesis of the condition include genetic influence, exposure to UV radiation, pregnancy and hormonal therapy (including oral contraceptives and thyroid hormones). Other factors implicated are phototoxic drugs, anticonvulsant medications and the use of certain cosmetics.[3] The actual pathogenicity of melasma is not yet fully understood. A recent study suggests that a high expression of α-melanocyte-stimulating hormone in the lesional keratinocytes of melasma play a key role in the hyperpigmentation of melasma skin.[5] The disease course of melasma follows the pattern of worsening hyperpigmentation during the sunny season and spontaneous improvement during autumn and winter.

Melasma can have a significant psychological impact on a patient. One survey showed that melasma was associated with a significant impact on health-related quality of life (HRQoL).[6] The strongest predictors of decreased HRQoL in women with melasma were increased disease severity, increased fear of negative evaluation and better perception of HRQoL without melasma.

### Differential diagnosis

A differential diagnosis between melasma and a variety of other hyperpigmentary disorders is necessary in patients enrolled in clinical trials. The primary diseases that should be distinguished are shown in Box 1.

## Evaluation of treatment outcome: efficacy

Evaluation of the outcome of a clinical trial in melasma can be divided into subjective and objective evaluation techniques.

### Subjective evaluation techniques

Although inferior to objective evaluation techniques, subjective evaluation – particularly the physician's global assessment

 

**Box 1.** Differential diagnosis of melasma[15]

- Post-inflammatory hyperpigmentation
- Ephilides
- Solar lentigo
- Lentigo simplex
- Naevus of ota
- Acquired bilateral naevus of ota-like macules
- Erythose peribuccale pigmentaire of Brocq
- Erythromelanosis follicularis faciei et colli
- Poikiloderma of civatte
- Riehl's melanosis
- Berloque dermatitis
- Café au lait macules
- Seborrhoeic keratoses
- Actinic lichen planus
- Periorbital hyperpigmentation

(PGA) – is often the primary efficacy endpoint by which a new treatment is evaluated. A crucial aspect of evaluation techniques is agreement on rating systems by all investigators prior to beginning a study. This avoids large differences in outcomes between investigational sites. A list of the various scoring systems that have been employed in pigmentation studies is shown in Box 2. The most commonly used scoring system is the Melasma Area and Severity Index (MASI) score (see below).

### Physician's global assessment

The PGA is the primary efficacy endpoint in clinical trials in melasma (Table 1). It is a clinically relevant subjective measure of the change in severity of pigmentation following treatment compared with baseline.[7] Implicit in the evaluation is very precise cartography of the initial lesions. Dynamic PGA is achieved with photography at baseline and following treatment and this is considered an important tool is assessing therapeutic efficacy.

### Melasma Area and Severity Index

The MASI score is an attempt to quantify the pigmentation area, darkness and homogeneity in patients with melasma.

**Box 2.** Scoring systems for the subjective evaluation of pigmentation

- Physician's global assessment
- Melasma area and severity index
- Melasma severity scale from 0 to 3
- Much worse (−2) to much improved (+2)
- Munsell colour chart
- Hyperpigmentation scale from 1 to 10
- Total improvement vs. partial improvement vs. failure
- Target lesion assessment compared with surrounding skin
- Linear analogue scale
- Patient global evaluation

First used by Kimbrough-Green *et al.*,[8] the MASI score is calculated by first assessing the hyperpigmented area of the face. Four areas are evaluated: forehead (F), right malar region (MR), left malar region (ML), and chin (C), corresponding to 30%, 30%, 30% and 10% of the total face, respectively (Fig. 1).[8] The melasma in each of the four areas is given a numerical value: 1, <10%; 2, 10–29%; 3, 30–49%; 4, 50–69%; 5, 70–89%; and 6, 90–100%. Darkness of pigment compared with normal skin (D) is assessed in each area on a scale of 0 (absent) to 4 (severe); homogeneity (H) is also assessed on a scale of 0 (minimal) to 4 (maximum). To calculate the MASI score, the sum of the severity rating for D and H is multiplied by the numerical value of the area (A) involved; the maximum score is 48 and the minimum 0.

### Melasma Severity Scale

The Melasma Severity Scale is a four grade scoring system that rates the severity of melasma as: 0, melasma lesions almost equivalent to surrounding normal skin or with minimal residual pigmentation; 1, mild, slightly darker than surrounding normal skin; 2, moderate, moderately darker than surrounding normal skin; 3, severe, markedly darker than surrounding normal skin.

## Objective evaluation techniques

A variety of objective evaluation techniques are used in melasma trials (Box 3).

### Reflectance spectroscopy

Reflectance spectroscopy is an objective measure of skin colour, which involves measuring the intensity of reflected light of specific wavelengths. Accurate, reproducible readings are obtained using narrow-band reflectance spectrophotometers such as the DermaSpectrometer (Cortex Technologies), the Erythema/Melanin Meter (DiaStron) and the Mexameter (Courage-Khazaka) or hand-held tristimulus reflectance colorimeters such as the Photovolt ColorWalk colorimeter (Photovolt, UMM Electronics) and the Minolta Chromameter.

The principle of the narrow band instruments is based on the fact that the two main skin pigments, melanin and haemoglobin, absorb light differently.[9] Haemoglobin absorbs mainly in the green area of the spectrum, while melanin absorbs light of all wavelengths. The reflectance of narrow band light in the red spectrum therefore provides a reasonable estimate of the melanin content of a person's skin.

Tristimulus instruments measure the intensity of reflected light when a white light is shone on a particular area of skin/hair. Several standard colour systems can be used to describe the results. The most widely used is the Commission International d'Eclairage Laboratory system, in which colours are described by their lightness value ($L^*$), and the amounts of green or red ($a^*$) and yellow or blue ($b^*$) they contain. Colour is recorded in a three-dimensional space bounded by the

 

**Table 1.** Physician's global assessment

| Score | Description |
|---|---|
| 0 | Clear, except for possible residual discoloration |
| 1 | Almost clear, very significant clearance (*c.* 90%); only minor evidence of hyperpigmentation remains |
| 2 | Marked improvement, significant improvement (*c.* 75%); some disease evidence of hyperpigmentation remains |
| 3 | Moderate improvement, intermediate between slight and marked improvement; *c.* 50% improvement in appearance of hyperpigmentation |
| 4 | Slight improvement, some improvement (*c.* 25%); significant evidence of hyperpigmentation remains |
| 5 | No improvement; hyperpigmented condition unchanged |
| 6 | Worse; condition worse than at week 0 |

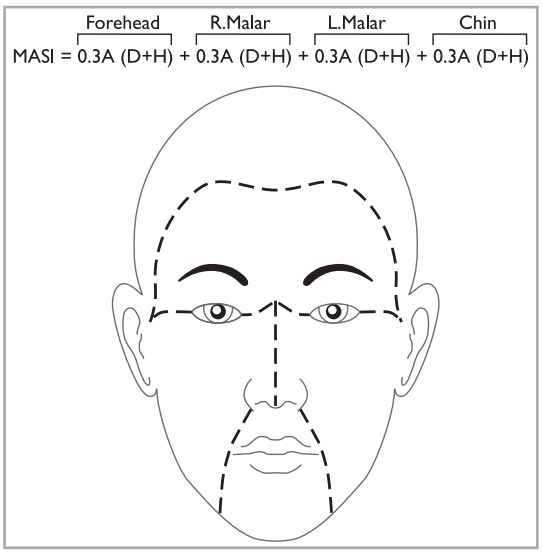


**Fig 1.** The Melasma Area and Severity Index (MASI).[8] Published with permission. Topical retinoic acid (tretinoin) for melasma in black patients. *Arch Dermatol* © 1994; 130: 727–33. American Medical Association. All rights reserved.

**Box 3.** Objective evaluation techniques

- Narrow-band reflectance spectroscopy (mexameter and dermaspectrometer)
- Hand-held tristimulus reflectance meter (minolta chromameter)
- Photography: UV and light
- Fluorescence video recording (video camera with UV light – allows determination of area of hyperpigmented compared to non-pigmented skin
- Corneomelametry
- Histology

L* (lightness–darkness) axis, a* (red–green) axis and b* (blue–yellow) axis and colour values can be plotted within that space. From a practical point of view, the L* value expresses the relative brightness of colour (ranging from black to white) and measures pigmentation; the a* value records erythema or skin redness; and the b* value records skin tanning responses. The Chromameter is probably the most widely used tristimulus instrument and has been shown to provide reliable, reproducible data.[10]

In order to obtain optimal results with these instruments a number of recommendations can be made. Ideally, each subject's position and the ambient temperature should be controlled. The subject should be at rest, away from direct sunlight, and should not be under the influence of any vasoactive substances. The use of cosmetics or topical medications by the subject is also to be avoided prior to measurements. With regard to technique, it is important for the operator to hold the probe perpendicular to the skin area to be assessed. Finally, repeat measurements should be obtained at the same time of day to negate the effect of any potential diurnal changes in skin coloration.

## Photography

Some general recommendations can be made for all forms of photography in the assessment of skin pigmentation. Photographs should be standardized and reproducible, which is feasible if certain conditions are met. The patient should be placed in a fixed position at a fixed distance from the camera. The camera should have a fixed flash position and stop. Through-the-lens metering should be used as well as polarized filters to reduce glare.

Polarized light photography is useful in the assessment of dermal changes, particularly vascular changes and skin surface changes. In melasma studies, it is primarily used to reduce glare. The basis of this type of photography is the fact that light reflected from the skin comprises regular reflectance (glare) and light 'back-scattered' from within the tissue.[11] Visual information relating to the skin surface texture is contained within the regular reflectance (4–7% of incident light) while the back-scattered light contains information relating to intracutaneous structures, erythema, pigmentation, vascularity, etc. Reflected light preserves the plane of polarization of the incident light, while back-scattered light is depolarized. Separate surface and intracutaneous details can therefore be identified using polarizing filters that are parallel or perpendicular in orientation to each other. Surface details of the skin (texture, elevation and scaling) are enhanced and pigmentation, vascularity and colour are diminished if the filter covering the

 

camera lens is parallel to that of the filter covering the flash so that only the reflected polarized light passes through the lens filter. By contrast, if the lens filter is perpendicular to the flash filter, the regular reflectance is blocked and only the back-scattered light from the tissues reaches the lens.

Ultraviolet light examination can be used to distinguish between skin colour changes that are related to pigmentation and changes that result from other causes such as collagen deposition, scarring or vascularity. As UV light is absorbed by melanin, skin areas with high epidermal concentrations of this pigment – such as melasma and solar lentigines – show up as darker areas compared with normal skin. By contrast, hypo- or amelanotic areas such as vitiligo lesions do not absorb UV light and so show up as brighter areas on Wood's light examination as nearly all the light is reflected back from the epidermis (Fig. 2). By distinction, areas of skin that appear to be whitened in natural light due to scarring, collagen deposition or chemicals in the dermis do not show up under Wood's light (UV light) examination as their epidermal melanin content is not different from the surrounding skin. Similarly, areas where a colour change results from an increase or decrease in vascularity do not appear different from surrounding skin. Moreover, very little UV light penetrates the dermis. Consequently, Wood's light examination is useful for distinguishing between epidermal and dermal pigmentation. UV photography is 10 times more sensitive than visible light in detecting epidermal melanin.

### Fluorescent video recording and corneomelametry

Fluorescent video recording involves a video camera with UV light which determines the area of hyperpigmented skin compared with nonhyperpigmented skin. Corneomelametry is a technique for measuring the melanin content in the stratum corneum. The accuracy of this procedure has been compared with both fluorescent video recording and narrow band spectrophotometry in an analytical study of solar lentigines lightening by 2% hydroquinone-cyclodextrin.[12] Results indicate that corneomelametry identified improvements after 1 month of treatment compared with the other assessments which only reached significance at 2 months.

**Fig 2.** Appearance of melasma under Wood's light (UV). Note the melasma lesions appear darker than normal skin due to an increase in melanin content. Published with the permission of Dr Doris Hexsel.

### Histology

Although patients are often reluctant to consent to a biopsy of an involved area of melasma, histological evaluation of melasma can be very useful in determining activity of melanocytes, location of pigment and response to therapy. Kang *et al.*[13] have characterized the histopathological features of facial melasma skin by comparison with adjacent normal skin using biopsy sampling. A number of histological differences were observed including a significant increase in the amount of melanin in all epidermal layers in melasma skin as well as an increase in the staining intensity and number of epidermal melanocytes. Lesional skin showed more prominent solar elastosis compared with normal skin and melanosomes increased in number and were more widely dispersed in the keratinocytes of the lesional skin. In addition, lesional melanocytes had many more mitochondria, Golgi apparatus, rough endoplasmic reticulum and ribosomes in their cytoplasm.

## Evaluation of treatment outcome: safety

The safety of a trial medication should be assessed in terms of local and systemic tolerance, adverse events and cosmetic appearance. The aspects that are reported by the patient and the physician are shown in Table 2.

## Evaluation of treatment outcome: quality of life

In view of the considerable effect melasma has on the quality of life of sufferers, an attempt has been made to assess the benefit of therapy on this parameter. A new HRQoL instrument for women with melasma, MELASQOL, has been developed.[6] The existing Dermatology Life Quality Index (DLQI) and SKINDEX-16 are general measures of the impact of skin disease on the HRQoL of patients with various skin disorders; they put equal weight on the physical and psychological

**Table 2.** Side effects of therapy from the perspective of the patient and the physician

| Patient | Physician |
|---|---|
| • Stinging/burning | • Erythema |
| • Itching | • Scaling |
| • Redness | • Erosions |
| • Scaling/dryness | • Crusting |
| | • Inflammation |
| | • Irritation |
| | • Hypopigmentation |
| | • Confetti-like pigmentation |
| | • Hyperpigmentation |
| | • Post-inflammatory hyperpigmentation |

 

effects of a dermatological condition. The MELASQOL uses items from the SKINDEX-16 as well as the skin discoloration questionnaire, which focus on items that would be more relevant to melasma-specific HRQoL. MELASQOL is a 10-question scale, which asks patients to rate how they feel about each issue on a scale of 1 (not bothered at all) to 7 (bothered all the time). The focus is on how the patients feel about their skin appearance and whether they have frustration, embarrassment or depression about their skin condition. The effect of their condition on interactions with family and friends and their desire to be with people has also been included. In addition, the MELASQOL asks if the melasma has an effect on the patient's ability to show affection, attractiveness, vitality, productivity and sense of freedom. The validation of the new instrument was conducted in a select sample of patients at Wake Forest University Health Sciences in North Carolina, the majority of whom were white, married and college educated. The MELASQOL has now been translated in Spanish in North America to characterize melasma's effect on Latino patients[14]. Further studies on patients from different racial groups, socioeconomic classes and marital status need to be done.

## Clinical trial design

Very few trials of a satisfactory standard have been conducted in patients with melasma. It is acknowledged that trial design is a key element in obtaining clinically relevant results. Three key elements of good clinical trial design can be identified:

1. Randomization of patients.
2. Inclusion of a control group.
3. Double-blinding.

In principle, parallel group, double-blind, vehicle and active comparator controlled studies are recommended. For trials aiming to demonstrate the superiority of a new therapy to the known active treatment, the need for a placebo arm will depend on the choice of an active comparator. Two-arm trials without a placebo control are acceptable if the efficacy of the active comparator is well established.

### Randomization of patients

Randomization of patients overcomes bias in patient selection and avoids the necessity to analyse outcome on a patient-by-patient basis.

### Control group

With regard to controls in clinical trials for melasma, there are a number of options that can be considered. The drug under study can be compared with a vehicle control, to dyads or to the opposite side of the face (split-face trial), which is not treated with the control drug. The use of historical controls is inferior to prospective trials, since the same conditions did not apply to both treated and control groups. The advantages of using a split-face trial design is that it is usually the only way to evaluate accurately treatment outcome with a study drug compared with vehicle to comparator drug in a small number of patients. The split-face design may be useful for comparisons between two active products where the test drug is compared with a known standard therapy, which is either approved for use or whose efficacy has been established in previous studies. The disadvantages of this design are that it may not be acceptable to regulatory authorities for test drug vs. placebo trials and that regulatory agencies are often not willing to accept a study design that does not correspond to the real life situation. There can also be errors in the application of specific medications and ethical considerations.

### Blinding

Blinding of the investigator and patient (double-blinding) is the optimal choice in a trial design, but patient blinding may not be possible with certain interventions such as chemical peels. Optimal frequency and concentration of topical drugs should be established in pilot studies.

### Inter-trial variables

A number of variables within a clinical trial need to be controlled for. These include the enrolment of a single phototype or a mixed phototype group of patients, since outcome has been shown to vary in different phototypes. The time of the year during which the clinical trial is conducted also has to be accounted for to allow for the degree of sun exposure. One method would be to have an internal control whereby the sun-exposed suprasternal notch is assessed but not treated. Another option would be to include a patient completed questionnaire that focuses on length of sun exposure during a study. The educational and socioeconomic class of the patients within the study should be considered with regard to compliance; understanding instructions; affordability of sunscreens, cleansers, etc.; and inability to avoid sun exposure, such as in outdoor workers. Language and cultural practices must also be taken into account when using consent forms and providing instructions on medication. Cultural practices are also important as 'home remedies' might conflict with the study medication.

### Study size

In terms of patient numbers, it is recommended that the total number of enrolled patients be determined by statistical methods. Pilot, proof-of-concept studies on a few patients can be done first in order to predict the response to a particular therapy. The predicted difference between the study and control populations can then be used to calculate the number of patients that will be needed in a randomized controlled trial in order to demonstrate a difference between the two groups. This 'powering' of a study is a useful and crucial exercise prior to starting a therapeutic trial. Once a study has begun, any patients that withdraw from the study should not be substituted for, and should be included in the final results – the

 

**Box 4.** Examples of inclusion criteria for patients enrolled in clinical trials in melasma

- Female subjects aged 18–50 years with moderate-to-severe hypermelanosis consistent with the diagnosis of melasma
- Subjects with Fitzpatrick skin types III, IV and V
- Female subjects of childbearing potential using a reliable from of contraception during the course of the study excluding oral contraceptive pills at the time of the study or in the past 6 months (intrauterine device or condoms) or female of nonchildbearing potential (hysterectomy, bilateral ovariectomy or tubal section/ligation)
- Female subjects of childbearing potential with a negative urine pregnancy test before inclusion in the study
- Subjects in good health, with normal findings in the medical history and the physician examination
- Subjects who are willing to sign the written consent form prior to participation in the study

**Box 5.** Examples of exclusion criteria for patients enrolled in clinical trials in melasma

- Pregnant women, nursing mothers
- Subjects suffering from other pigmentation disorders
- Subject having used any cosmetic depigmenting agent within 2 weeks prior to inclusion
- Subjects who have used a topical or inhaled corticosteroid or systemic steroids within 1 month prior to inclusion in the study
- Subjects having used topical tretinoin within 3 months or topical hydroquinone within 6 months prior to inclusion
- Subjects with history of endocrinopathies
- Subjects who have a known history or clinically relevant allergy, in particular to components to the study treatments
- Subjects with a history of significant drug or alcohol abuse
- Subjects who are in a situation which, in the opinion of the investigator, may interfere with optimal participation in the study
- Subjects participating or having participated in a clinical trial within 1 month before the enrolment in the study
- Subjects who cannot communicate reliably with the investigator or who are unlikely to cooperate with the requirements of the study

so-called 'intention-to-treat analysis'. In selecting the study population, inclusion and exclusion criteria should be carefully considered. Some examples of these criteria are shown in Boxes 4 and 5.

## Study objectives

The objectives of the trial, i.e. efficacy, local and general safety, or remission, should be clearly stated. Recommended primary criteria of efficacy for a melasma trial are

- Physician and/or patient overall response global assessment (PGA).
- Clinical scores.
- Improvement in colour.

**Box 6.** Endpoints for a trial in melasma

Overall improvement at the end of treatment using one of the following scoring systems:

- Melasma area and severity index (MASI)
- Melasma severity scale from 0 to 3
- Much worse (−2) to much improved (+2)
- Munsell colour chart
- Hyperpigmentation scale from 1 to 10
- Total improvement vs. partial improvement vs. failure
- Target lesion assessment compared with surrounding skin
- Linear analogue scale
- Chromametry values (L*, a*, b* system)
- Autoquestionnaire (patient's opinion on efficacy and skin acceptability)
- Quality of Life (MELASQOL and DLQI)

## Endpoints

Efficacy endpoints that can be used in trials on melasma are shown in Box 6.

## Duration of treatment

In order to determine the duration of any individual test therapy it is important to consider its mechanism and rapidity of action. The duration of the study should be sufficient to allow time for an accurate assessment of efficacy and should generally vary from 8 to 16 weeks, dependent on the agent being tested. Suggested assessment points are at 0, 4, 8 and 12 weeks; an additional 12 week assessment point should be included for poorly responding patients. Additional time may be useful to identify relapsing patients with those drugs that have previously reached a plateau.

## Adherence

The issue of adherence should be addressed in a clinical trial with an assessment made of the amount of study drug used per patients, i.e. number of tubes, weight of drug.

## Maintenance treatment

The results from a short-term trial may not always be extrapolated to maintenance therapies. Studies are required that

 

**Table 3.** CONSORT recommendations on items to include when reporting a randomized clinical trial[2]

| Paper section and topic | Item | Description |
|---|---|---|
| Title and abstract | 1 | How participants were allocated to interventions (e.g. 'random allocation', 'randomized', or 'randomly assigned') |
| Introduction background | 2 | Scientific background and explanation of rationale |
| Methods participants | 3 | Eligibility criteria for participants and the settings and locations where the data were collected |
| Interventions | 4 | Precise details of the interventions intended for each group and how and when they were actually administered |
| Objectives | 5 | Specific objectives and hypotheses |
| Outcomes | 6 | Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g. multiple observations, training of assessors) |
| Sample size | 7 | How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules |
| Randomization – sequence generation | 8 | Method used to implement the random allocation sequence (e.g. numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned |
| Randomization – allocation concealment | 9 | Method used to implement the random allocation sequence (e.g. numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned |
| Randomization – implementation | 10 | Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups |
| Blinding (masking) | 11 | Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment. When relevant, how the success of blinding was evaluated |
| Statistical methods | 12 | Statistical methods used to compare groups for primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses |
| Results Participant flow | 13 | Flow of participants through each stage (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analysed for the primary outcome. Describe protocol deviations from study as planned, together with reasons |
| Recruitment | 14 | Dates defining the periods of recruitment and follow up |
| Baseline data | 15 | Baseline demographic and clinical characteristics of each group |
| Numbers analysed | 16 | Number of participants (denominator) in each group included in each analysis and whether the analysis was by 'intention-to-treat'. State the results in absolute numbers when feasible (e.g. 10/20, not 50%) |
| Outcomes and estimation | 17 | For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (e.g. 95% confidence interval) |
| Ancillary analyses | 18 | Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory |
| Adverse events | 19 | All important adverse events or side effects in each intervention group |
| Discussion interpretation | 20 | Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes |
| Generalizability | 21 | Generalizability (external validity) of the trial findings |
| Overall evidence | 22 | General interpretation of the results in the context of current evidence |

examine the long-term management of melasma using maintenance therapy after the initial improvement achieved with primary/secondary therapy; these should be for at least 3 months duration.

### Follow-up after cessation of treatment

A follow-up period of at least 8 weeks following cessation of treatment is recommended in order to identify potential relapse.

## Clinical trial reporting: the CONSORT Guidelines

The CONSORT guidelines were developed in 1996 to improve the sub-optimal reporting of randomized control trials. The aim of these guidelines is to assist health-care providers to make informed inferences about the validity of the studies upon which they base their clinical practice. Eleven key methodological factors important in reporting a randomized control trial

were identified. Several journals accepted these recommendations, with the exception of the *New England Journal of Medicine*. The second edition of CONSORT established a 22-item checklist, which emphasized the need for the word 'randomized' to appear in the title in order to allow literature searches to identify the paper (Table 3).[2] The CONSORT statement is an important research tool that takes an evidence-based approach to improve the quality of reports of randomized trials and is available in several languages.

The randomized controlled trial provides medicine with its main source of evidence for supporting the use of a particular therapy or medical practice, yet many of these trials are open to criticism on a number of counts. Many clinical situations, such as cardiac arrest and pain relief, do not lend themselves to randomization. In addition, trials seldom study the effects seen in different subgroups of patients, nor can the results from a small group of study patients always be extrapolated to larger populations. Short-term outcomes do not always translate into long-term outcomes for any particular treatment, necessitating specific clinical trials conducted over long periods of time. Age is another factor to consider when assessing the risk-to-benefit of a particular therapy; this can often be overlooked in the randomized clinical trial. Reporting of outcomes is crucial so that the medical profession can scrutinize all of the data and not just positive outcomes. Despite these problems, the randomized, controlled, blinded trial, and the CONSORT guidelines represent a significant advance in standardizing clinical trials and future trials in patients with melasma should be designed according to these guidelines.

## Conclusion

Very few well-conducted trials have been conducted in patients with melasma, and further effort is required to standardize such trials, from the viewpoints of both how study drugs are to be applied to the assessment of outcome and which patient populations are included. This process will allow accurate comparisons of outcomes between different therapeutic clinical trials to be made. Dermatologists and researchers will be greatly assisted in this endeavour by the establishment of accepted clinical trial guidelines, the process for which has been initiated in this paper.

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## Conflicts of interest

A Pandya has received an honorarium to attend the annual meetings of the Pigmentary Disorders Academy (PDA). M Berneburg has received an honorarium to attend an annual meeting of the PDA and to advise on the content and structure of the PDA website. J-P Ortonne has acted as a paid consultant to l'OREAL, Galderma, Pierre Fabre, Abbott, UCB and a paid speaker for Serono, Wyeth, Biogen, Schering-Plough, 3M, IBSA, Merk-Familial, Roche-Posay. M Picardo has been reimbursed for attendance and given an honorarium for participation at the 2005 PDA conference by Galderma International.

## References

1 Altman DG, Schulz KF, Moher D *et al.* The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Int Med* 2001; **134**:663–94.

2 Moher D, Schultz KF, Altman DG, for the CONSORT Group.The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. *Lancet* 2001; **357**:1191–4.

3 Grimes PE. Melasma: etiologic and therapeutic considerations. *Arch Dermatol* 1995; **131**:1453–7.

4 Grimes PE, Kelly P, Totok H, Willis I. Community-based trial of a triple combination agent for the treatment of facial melasma. *Cutis* 2006; **77**:177–84.

5 Im S, Kim J, On WY, Kang WH. Increased expression of a melanocytes-stimulating hormone in the lesional skin of melasma. *Br J Dermatol* 2002; **146**:165–7.

6 Balkrishnan R, McMichael AJ, Camacho FT *et al.* Development and validation of a health-related quality of life instrument for women with melasma. *Br J Dermatol* 2003; **149**:572–7.

7 Fleischer AB Jr, Schwartzel EH, Colby SI, Altman DJ. The combination of 2% 4-hydroxyanisole (Mequinol) and 0.01% tretinoin is effective in improving the appearance of solar lentigines and related hyperpigmented lesions in two double-blind multicenter clinical studies. *J Am Acad Dermatol* 2000; **42**:459–67.

8 Kimbrough-Green CK, Griffiths CEM, Finkel LJ *et al.* Topical retinoic acid (tretinoin) for melasma in black patients. *Arch Dermatol* 1994; **130**:727–33.

9 Diffey BL, Oliver RJ, Farr PM. A portable instrument for quantifying erythema induced by ultraviolet radiation. *Br J Dermatol* 1984; **3**:663–72.

10 Van den Kerckhove E, Staes F, Flour M *et al.* Reproducibility of repeated measurements on healthy skin with Minolta Chromameter CR-300. *Skin Res Tech* 2001; **7**:56–9.

11 Anderson RR. Polarized light examination and photography of the skin. *Arch Dermatol* 1991; **127**:1000–5.

12 Petit L, Piérard GE. Analytic quantification of solar lentigines lightening by a 2% hydroquinone–cyclodextrin formulation. *Eur Acad Dermatol Venereol* 2003; **17**:546–9.

13 Kang WH, Yoon KH, Lee ES *et al.* Melasma: histopathological characteristics in 56 Korean patients. *Br J Dermatol* 2002; **146**:228–37.

14 Dominguez AR, Balkrishnan R, Elizey AR, Pandya AG. Melasma in Latina patients: cross-cultural adaptation and validation of a quality-of-life questionnaire in Spanish language. *J Am Acad Dermatol* 2006; **55**:59–66.

15 Im S, Hann S-K, Kang W-H. (eds) *New Concepts of Melasma and Postinflammatory Hyperpigmentation*. Seoul, South Korea: Dongil Publishing Company, 2002.

 