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Guidelines for Designing and Reporting Clinical Trials in Vitiligo

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Objective: To create guidelines for randomized controlled trials (RCTs) investigating interventions used in the management of vitiligo.

Participants: Guideline developers included authors (clinicians, patient representatives, and a statistician) of the Cochrane systematic review "Interventions for Vitiligo" plus the coordinator of the vitiligo priority-setting partnership at the Centre of Evidence-Based Dermatology at the University of Nottingham.

Evidence: The guidelines are based on the assessment of the quality of design and reporting of RCTs evaluating interventions for vitiligo included in the 2010 update of the Cochrane systematic review "Interventions for Vitiligo."

Consensus Process: We reviewed and commented on the sources of bias in existing RCTs on interventions for vitiligo (selection bias, blinding assessment, attrition bias, characteristics of participants, interventions, and outcomes) based on the findings of the Cochrane review, and we used open discussion on guideline drafts focusing on the study question (participants, interventions, and outcomes), study design (research methods), and reporting.

Conclusions: Much opportunity exists for improving the design and reporting of vitiligo clinical trials. The proposed guidelines will help overcome methodologic challenges faced when conducting RCTs to answer treatment questions.

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VITILIGO IS AN ACQUIRED chronic pigmentation disorder that causes depigmentation of the skin corresponding to a substantial loss of functioning epidermal and sometimes hair follicle melanocytes. There are 2 main clinical variants of vitiligo: *generalized vitiligo*, characterized by symmetrical patchy white areas that may spread to any part of the body; and *segmental vitiligo*, defined by unilateral depigmented macules. There are several subtypes of vitiligo applicable to both variants. *Focal vitiligo* is characterized by 1 or few small macules; *periorificial vitiligo* involves skin around the eyes, nose, ears, mouth, and anus; *acrofacial vitiligo* affects periorificial facial areas and distal extremities; *mucosal vitiligo* affects the oral and/or genital mucosa; and *vitiligo universalis* refers to generalized vitiligo with complete or almost complete depigmentation. The cause of vitiligo is unknown, but research suggests that it may arise from autoimmune, genetic, oxidative stress, neural, or viral causes. The estimated prevalence of vitiligo worldwide is reported to be less than 1%.[1]

There is no definitive cure for vitiligo, but there are a number of treatments or interventions for this condition. However, to improve existing control of disease, evidence for the effectiveness of different interventions is needed. Sixty-eight different interventions (monotherapies and combinations) for vitiligo have been described.[2] Therefore, future intervention trials need to be designed in a manner that should be able to demonstrate the efficacy of the interventions tested. The rise of evidence-based medicine has highlighted the use of systematic reviews of the best evidence as fundamental tools for health care. The quality of randomized controlled trials (RCTs) is essential to determine what therapeutic interventions work and are safe for people with vitiligo. Special attention must be paid to the design, methodology, analysis, clinical relevance, and reporting of future trials; oth-

erwise, the conclusions derived from low-quality and biased trials will remain inconclusive and clinically irrelevant.

These guidelines are based on the assessment of the methodology of the RCTs included in the 2010 update of the Cochrane Systematic review "Interventions for Vitiligo"[2] (hereinafter, "the Cochrane review"). The guideline developers included authors (clinicians, patient representatives, and a statistician) of the Cochrane review plus the coordinator of the vitiligo priority-setting partnership at the Centre of Evidence-Based Dermatology at the University of Nottingham. Herein, we review and comment on the sources of bias in existing RCTs on interventions for vitiligo, and we use open discussion on guideline drafts focusing on the study question, study design, and reporting.

DESCRIPTION OF THE SOURCES OF BIAS IN EXISTING RCTS ON INTERVENTIONS FOR VITILIGO

The Cochrane review included a total of 57 RCTs,[3-59] which covered a wide range of interventions including topical and oral preparations, light therapy, surgical techniques, psychological therapy, and unconventional or complementary therapies (**Table 1**). The evidence from individual RCTs to support existing therapies for vitiligo was limited by the variations in the methodologic quality of trials. The reliability of the results of a randomized trial depends on the extent to which potential sources of bias have been avoided. A key part of the Cochrane review is the assessment of the risk of bias in the results of each of the eligible studies. We briefly describe herein 6 issues related to bias in RCTs of interventions for vitiligo.

Selection Bias

In RCTs, *selection bias* refers to the possible differences between baseline characteristics in the groups under comparison. Investigators should devote appropriate resources for allocating interventions to participants on the basis of some chance (random) process and report their methods clearly, avoiding nonrandom methods of allocation.[60] Adequate generation of the randomization sequence takes little effort and enhances scientific accuracy and credibility. However, randomization continues to be the least understood feature of trials. All RCTs included in the Cochrane review stated or implied that treatment allocation was randomized; however, only 56% of the studies (32 of 57) clearly stated an adequate randomization method (eg, random number table, coin toss).

Proper randomization also relies on adequate allocation concealment, a process that keeps clinicians and participants unaware of upcoming assignments to intervention groups by preventing foreknowledge of the forthcoming allocations. Allocation concealment (eg, by using centralized randomization) is an essential step to secure strict implementation of that schedule of random assignments. Inadequate allocation concealment leads to either an underestimate or an overestimate of the treatment effect being investigated. However, only 24% of the studies in the Cochrane review (14 of 57) reported allocation concealment adequately.

Blinding Assessment

In clinical research, blinding is used to eliminate the risk of subjectivity in assessing outcomes.[61] Successful blinding is a fundamental issue in many clinical trials. In 12% of RCTs included in the Cochrane review (7 of 57), participants, clinicians, and assessors were all blinded. Many studies were within-participant comparisons of different interventions. This makes it difficult for participants (and sometimes clinicians) to be blinded, and so it is important to minimize bias through the use of a blinded outcome assessor. Blinding of participants was also not possible in those studies where 2 different modalities of intervention were being assessed (eg, oral vs topical interventions or surgical procedures). In 19% of studies (11 of 57), it was stated that the outcome assessor was blinded, but the participants and/or the clinicians were not blinded. In 25% of studies (14 of 57), blinding participants, clinicians, or outcome assessors was not reported.

Attrition Bias

Attrition bias is caused by a selective loss of participants (eg, withdrawals, dropouts, and protocol deviations) from the population that was initially selected. This bias can produce a deviation in the measure of the effect of the intervention from its true value due to different rates of loss of participants between the intervention and the comparison group. The overall number of participants lost to follow-up in the RCTs included in the Cochrane review was 16.6% of the total number of study participants included across all of the studies (521 of 3139). Forty percent of the included studies were analyzed on an intention-to-treat basis (23 of 57). This was either because there were no losses to follow-up in 28% of the studies (16 of 57) or because data from dropouts were included in an explicit intention-to-treat analysis.

Overall, we found only 3 trials in the Cochrane review that addressed randomization, allocation concealment, blinding, and assigned group analyses adequately.[28,41,55] In the Cochrane review, additional information about the following 3 key elements of the study question that could influence assessment of the quality of the RCT was also analyzed: participants, interventions, and outcomes.

Participants

The total number of participants in all of the RCTs included in the Cochrane review was 3171. Most RCTs recorded baseline characteristics of participants (68%) and defined the inclusion (81%) and exclusion criteria (67%). Almost 50% of RCTs included both children and adults in their studies (28 of 57); 7% of RCTs did not mention the age of participants (4 of 57); 5% studied only children (3 of 57); and 37% studied only adults (21 of 57). It was difficult to calculate the male-female ratio either because the researchers omitted this information (12% of RCTs; 7 of 57) or because sex was reported only for

Table 1. Interventions for Vitiligo Assessed in the RCTs of the Cochrane Review

Year of Publication	Country	Interventions
1967	Lebanon	PUVAsol vs topical PUVAsol vs PUVAsol plus oral triamcinolone[3]
1974	Kuwait	Topical betamethasone valerate vs placebo[4]
1975	Mexico	PUVAsol vs UV-A[5]
1979	India	Injections of triamcinolone acetonide vs placebo[6]
1984	India	8-MOP vs 4,5,8-trimethylpsoralen vs psoralen (and exposure to sunlight)[7]
1994	The Netherlands	*L*-phenylalanine plus UV-A vs placebo[8]
1995	Pakistan	Topical PUVAsol vs topical clobetasol propionate[9]
1995	Italy	Topical 3%-5% khellin plus UV-A vs UV-A[10]
1997	Brazil	Topical melagenina (human placental extract) vs placebo[11]
1998	India	Topical calcipotriol plus PUVAsol vs PUVAsol[12]
1999	The Netherlands	Topical fluticasone propionate and UV-A vs topical fluticasone propionate vs UV-A[13]
2001	Brazil	Topical 2% khellin plus UV-A vs topical khellin, 0.1%, plus UV-A[14]
2001	Turkey	Topical calcipotriol plus PUVA vs PUVA[15]
2002	Mexico	Skin minigraft plus 8-MOP vs skin minigraft vs 8-MOP (and exposure to sunlight?)[16]
2002	Turkey	Suction blister technique vs thin split-thickness graft technique[17]
2002	Israel	Climatotherapy vs topical pseudocatalase plus climatotherapy[18]
2002	The Netherlands	NB-UV-B vs oral vitamin B_{12} tablets and folic acid plus UV-B[19]
2003	Mexico	Topical tacrolimus vs topical clobetasol propionate[20]
2003	India	Oral ginkgo biloba vs placebo[21]
2004	India	PUVA vs topical fluocinolone acetonide (after punch grafting)[22]
2004	Poland	Cultured autologous melanocytes plus PUVA vs suction blister plus PUVA vs cryotherapy plus PUVA[23]
2004	Canada	NB-UV-B vs placebo[24]
2004	United States	Topical tacrolimus plus E laser vs E laser[25]
2004	United Kingdom	Cognitive behavioral therapy vs group therapy vs no counselling[26]
2004	France	E laser plus topical tacrolimus vs E laser[27]
2004	Belgium	Cellular (melanocytes) suspension vs placebo[28]
2005	India	Oral levamisole plus topical mometasone furoate vs topical mometasone furoate[29]
2005	Iran	Topical calcipotriol plus PUVA vs PUVA[30]
2005	Austria	E laser once a week vs twice a week vs 3 times a week[31]
2005	India	Minipunch grafting vs split-thickness skin grafting[32]
2005	Philippines	Topical clobetasol propionate plus NB-UV-B vs NB-UV-B[33]
2005	Iraq	Topical lactic acid vs UV-A vs topical lactic acid, 15%, plus UV-A[34]
2006	Turkey	NB-UV-B plus topical calcipotriol vs NB-UV-B[35]
2006	Austria	Topical pimecrolimus vs placebo[36]
2006	Egypt	UV-A 15 J/cm^2 vs UV-A 5 J/cm^2 [37]
2006	India	Topical betamethasone dipropionate vs topical calcipotriol vs topical betamethasone dipropionate and topical calcipotriol[38]
2006	Italy	Topical tacalcitol plus NB-UV-B vs NB-UV-B[39]
2006	China	Topical tacalcitol plus E light vs E light [40]
2006	United States	NB-UV-B plus topical tacrolimus vs NB-UV-B[41]
2006	Iran	PUVA plus azathioprine vs PUVA[42]
2006	Spain	PUVA plus *Polypodium leucotomos* vs PUVA[43]
2006	India	Autologous melanocyte transplantation from skin graft approximately one-third the size of the recipient area vs one-fifth the size of the recipient area[44]
2007	India	NB-UV-B vs PUVA[45]
2007	Italy/France	E light vs NB-UV-B[46]
2007	Italy/The Netherlands	NB-UV-B plus antioxidants vs NB-UV-B[47]
2007	Switzerland	E laser plus topical calcipotriol vs E laser plus verum[48]
2007	The Netherlands	*Polypodium leucotomos* plus NB-UV-B vs NB-UV-B[49]
2007	Venezuela	Topical antioxidants plus oral antioxidants and phenylalanine vs oral antioxidants and phenylalanine vs topical antioxidants[50]
2007	United Kingdom	PUVA vs NB-UV-B[51]
2008	Egypt	Laser ablation plus topical 5-fluorouracil plus NB-UV-B vs NB-UV-B[52]
2008	Thailand	BB-UV-B vs NB-UV-B[53]
2008	India	OMPB plus PUVA vs OMPB plus NB-UV-B vs OMPB plus BB-UV-B vs OMPB[54]
2008	Columbia	Topical betamethasone vs catalase/dismutase superoxide (and exposure to sunlight)[55]
2008	Italy	E laser plus topical hydrocortisone 17-butyrate vs E laser[56]
2008	China	Oral Chinese herbs and oral cobamamide vs oral cobamamide (and topical psoralen)[57]
2009	Iran	NB-UV-B plus topical pimecrolimus vs NB-UV-B[58]
2009	Spain	Topical tacalcitol vs placebo (and exposure to sunlight)[59]

Abbreviations: BB-UV-B, broadband UV-B light; NB-UV-B, narrowband UV-B light; E, 308-nm monochromatic excimer; OMPB, oral minipulses of betamethasone; PUVAsol, psoralens before exposure to sunlight; RCT, randomized controlled trial; 8-MOP, 8-methoxypsoralen, 0.1%.

participants who were included in the final analysis, or rather for those who did not drop out (23% of RCTs; 13 of 57). Over a third of the studies reported skin phototype and the percentage of vitiliginous areas (21 of 57). However, only 54% of the studies reported the areas affected (31 of 57). Most RCTs (75%; 43 of 57) included participants who were affected with 1 type of vitiligo (eg, focal, generalized), but a minority (25%) included participants with more than 1 type of vitiligo (14 of 57), which included either a combination of acrofacial vitiligo, focal vitiligo, and vitiligo vulgaris or localized and generalized vitiligo. Unfortunately, many studies did not distinguish between segmental and nonsegmental or symmetrical and nonsymmetrical vitiligo but used the term *vitiligo* as an inclusion criterion with no further explanation.

Another important step in study design is the calculation of sample size; outcomes from studies with inadequate sample sizes are likely to be imprecise or provide false-negative values owing to a lack of statistical power. Only 12% of the RCTs in the Cochrane review (7 of 57) calculated the sample size required. The number of participants evaluated in the studies varied from 8 to 596. Sixty-seven percent of studies (38 of 57) consisted of a small sample size (fewer than 50 participants). Thirty-two percent of studies (18 of 57) contained a medium sample size (51-150 participants), and only 1 study[8] involved a large sample size (>150 participants).

Interventions

Randomized controlled trials included in the Cochrane review assessed a wide range of interventions including pharmacologic treatments (topical corticosteroids, immunomodulators, and oral treatments), various forms of UV-based therapy (UV-A, narrowband and broadband UV-B, psoralen and UV-A [PUVA], excimer laser, and monochromatic excimer light), surgical procedures (grafting and melanocyte transplantation), and psychological and complementary therapies. Several RCTs assessed combination therapies, most of which combined a light source (ranging from reliable forms of light therapy such as UV devices to sun exposure) with another form of treatment to enhance repigmentation. However, some interventions for vitiligo have not been well evaluated in RCTs. Only 1 study assessed psychological interventions despite the fact that vitiligo can have a devastating psychosocial impact on patients' lives.[26] In addition, there were no trials involving the use of cosmetic camouflage (which is widely used and is the only licensed treatment for vitiligo in some countries) or depigmenting agents. The most common intervention evaluated was light therapies (74% of RCTs; 42 of 57), in contrast to a small number of studies assessing the efficacy of surgical methods, such as skin grafts and cell transplants, which are more suitable for segmental or stable vitiligo.

Placebo-controlled studies constituted 51% of the RCTs (29 of 57), and the others used active controls. Regarding the study design, over the half of the studies were parallel group studies (35 of 57), but a third of the studies were within-participant and/or left-right comparison studies (31%; 18 of 57).

Outcomes

Efforts have been made to develop a standardized way to classify and measure vitiligo.[62] However, many studies still use their own scales to measure repigmentation, which is arguably the most important outcome when assessing interventions for vitiligo. The heterogeneity of outcomes measures makes it very difficult to make general statements regarding the efficacy of particular interventions. The outcomes of interest for the Cochrane review were prespecified as either primary outcomes or secondary outcomes.

Primary Outcomes. We determined that the primary outcomes should be patient quality of life and percentage of skin repigmentation. *Quality of life* should be measured using validated tools such as the Dermatology Life Quality Index (DLQI),[63] the Children's Dermatology Life Quality Index (CDLQI),[64] or Skindex-29.[65] For *percentage of repigmentation* of vitiliginous skin (restoration of normal skin color), success rate should be evaluated in terms of more than 75% repigmentation of individual patches or of total body surface area as measured by objective means (eg, photographs, rule of nines).

Secondary Outcomes. Secondary outcomes should include (1) *cessation of spread of vitiligo* or *stabilization of the disease* as no increase in the size of individual vitiligo patches (measured objectively with a Wood light, photography, or other objective means within a period of either less than 1 year or 1 year or more) or no new lesions appearing despite no improvement in existing patches resulting from treatment (within a period of less than 1 year or 1 year or more); (2) *long-term permanence of repigmentation* resulting from treatment (at least 2 years' follow-up); and (3) *adverse effects*.

Only 9% of the RCTs reported quality of life as an outcome (5 of 57). Although all RCTs assessed repigmentation as an outcome, no 2 RCTs used exactly the same method of measuring repigmentation. Only half of them (29 of 57) measured success rate in terms of more than 75% repigmentation of vitiliginous lesions. Only 10% (6 of 57) assessed the cessation of spread as an outcome measure, and none of the included RCTs assessed long-term repigmentation. The follow-up duration of the RCTs varied widely from 3 months to 3 years. However, none of the RCTs followed up with their patients for an adequate period. Finally, most of the trials (80%) reported the adverse effects of various interventions.

Outcomes were not always assessed by an independent outcome assessor. In fact, only 30% of the RCTs used an independent outcome assessor who was also blinded (17 of 57). The remaining 70% of the RCTs included in the review did not use an independent outcome assessor or did not include sufficient information to determine whether the assessor was independent (40 of 57).

GUIDELINES FOR DESIGNING AND REPORTING RCTS ON INTERVENTIONS FOR VITILIGO

To have properly designed RCTs aimed at the development of effective interventions for vitiligo, it is necessary to establish standard clinical trial designs and rig-

orous peer review processes in journals and to enhance the capacity for high-quality trials. Given the gaps and potential biases found in the designs and reporting practices of trials published to date, we propose guidelines for authors who plan to conduct RCTs on interventions for vitiligo (**Table 2**).

The Study Question

Participants. Patient information should be provided in a format that makes the nature and purpose of the study comprehensible to its participants and answers their queries. In addition, a general overview of interventions available for vitiligo should be included in the written information provided to the patient. Standardized methods for describing and classifying vitiligo need to be used by trial investigators. Study design should take into account variations in participant features including skin color, duration of disease, extent and type of vitiligo, and affected sites. These factors may determine the applicability of results in particular clinical settings and may cause variations in the response to treatment. The consensus statement report of the Vitiligo European Task Force (VETF)[62] is a good source of information about definition and assessment of patients with vitiligo.

Inclusion criteria are important to define the trial participants. A minimum list for definition of participants needs to include a description of the type of vitiligo (authors of RCTs should say what they mean), the inclusion of more than 1 type of vitiligo (authors of RCTs should provide separate data for nonsegmental and segmental vitiligo), disease activity (progressive, regressive, or stable over the last 6 months), affected sites, disease duration or duration of the lesions treated, and whether vitiligo was diagnosed by a dermatologist or other health care professionals (eg, nurse or general practitioner). It is always important to specify criteria for exclusion, such as patients with other hypopigmentation and depigmentation disorders.

The main selection biases in RCTs are found in the description of baseline characteristics, which need to be fully detailed to ensure homogeneity and comparability between groups. It is strongly recommended that investigators fully report baseline characteristics in a table describing age, sex, ethnic background, duration of disease, number and morphologic characteristics of lesions, sites and severity of lesions, previous treatment received and cotreatments, and medical history including autoimmune diseases and others.[62]

Interventions. The studies should provide an adequate description of the intervention (name, trademark, route of administration, doses, and regimen schedule). In the case of combination therapies with a light source, it is important to use reliable forms of light therapy such as UV devices. These are better than natural phototherapy or sun exposure because variable factors including the compliance of the participant, the degree of exposure, and the country where the trial is conducted can limit the interpretation and applicability of results. Treatment duration and follow-up periods should be clearly defined in the study protocol.

Table 2. Summary of the Guidelines for Conducting RCTs on Interventions for Vitiligo

Study Question	Level of Description in Reviewed RCTs
Participants	
Description of inclusion/exclusion criteria	+++
Description of baseline characteristics of the participants by group; authors should take into account variations in participant features, including skin color, duration of the disease, extent and type of vitiligo, and affected sites	++
Study setting (eg, primary or secondary care, country, number of centers)	+++
Interventions	
Adequate description of the intervention (name, trademark, route of administration, doses, and regimen schedule)	+++
Adequate choice and description of the control group	++
Adherence to treatment or compliance should be measurable, measured, and reported	+
Outcomes	
Adequate follow-up and frequency of data recording; we suggest a minimum time period of 1 year	+
Standardized definition of treatment effect and measurement scales (especially for combination therapies)	+
Define primary patient-centered outcomes (suggested):	
Quality of life measured using a validated tool	+
More than 75% repigmentation of individual patches or of total body surface area, measured by objective means	++
Define secondary outcomes (suggested):	
Cessation of spread of vitiligo or stabilization of the disease defined as no increase in the size of individual vitiligo patches measured objectively; or no new lesions appearing, despite no improvement in existing patches resulting from treatment	+
Long-term permanence of repigmentation resulting from treatment (at least 2 years of follow-up)	+
Adverse effects	+++
Study Design	
Criteria for adequate generation of randomization sequence: random numbers generated by computer or table of random numbers or other unbiased methods of allocation	++
Criteria for adequate allocation concealment: participants and investigators enrolling participants cannot foresee assignment (eg, central allocation, including telephone, Web-based or pharmacy-controlled randomization; *a priori* third-party sequentially numbered or coded drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes; or other descriptions that contain convincing elements of concealment)	+
Blinding (detailed description of methodology of assessors and participants blinding)	++
Calculation of the sample size	+
Losses to follow-up per arm (when and why) and analysis of the total number of randomized participants	++
Data Reporting	
Follow CONSORT guidelines[66] (authors, journals, and referees)	+

Abbreviations: RCT, randomized controlled trial; +++, more than 75% of RCTs; ++, 25% to 75% of RCTs; +, fewer than 25% of RCTs.

A placebo control group is not always feasible, not only because the nature of some interventions hampers the

design of a placebo-controlled trial, but also because of specific situations where an active control intervention group may be ethically required to protect the participants' well-being.

Compliance should be measured and reported to ensure adherence to treatment regimen and can be assessed using many standardized methods, such as requesting the return of unused medication; counting remaining capsules or sachets or tablets; or interviewing patients. However, the period of time and the best method to measure compliance remain unclear. Dropouts and the flow of participants should be clearly recorded in each intervention group. The impact of missing data should be fully explored within the statistical analysis of the trial and within the interpretation of the results of the trial.

Outcome Measures

Patient response to treatment varies depending on the areas affected and the extent of the disease as well as how aggressively it is spreading. Diffuse type of repigmentation, which is also the least stable, occurs earlier than follicular-type repigmentation. In fact, the speed of repigmentation and retention of pigment in vitiliginous patches seem to depend on the type of intervention given. As an example, a diffuse type of repigmentation is reported to occur more quickly with topical treatment than with phototherapy, but it is short lasting. Once the stimulus ceases, the lesion reverts back to the depigmented state.[67] It is therefore difficult to make firm recommendations regarding the optimum duration for studies. This is an area that needs more research, but trials should last at least 6 months and ideally for 1 year. Long-term efficacy of interventions and sustainability of responses may be determined with extended follow-up period of patients after termination of therapy.

The definition of the outcomes needs to be sufficiently rigorous to make clinical sense and to allow reproducibility by other investigators. Therefore, standardized methodology for assessing the effect of interventions should be developed and used by trial investigators. To this end, attempts have been made by the VETF[68] to create standardized measures of outcomes such as repigmentation, which can be used by investigators when they conduct vitiligo RCTs in the future.

It is preferable to randomize and analyze participants rather than individual lesions because it is more clinically relevant to determine the proportion of participants who achieved the stipulated outcome. Ideally, the severity of vitiligo should be allowed for within the randomization method, if possible using stratification, to minimize the potential for baseline differences between the intervention groups. To overcome the issue of different body sites responding differently to different interventions, it would be preferable for studies to also perform stratified analyses based on body sites, so that comparisons of different studies can be made. Outcomes should be reported in all groups. Because vitiligo is a chronic disease and frequently recurs after treatment, outcome measures should be reported at regular intervals to establish whether an intervention demonstrates a gradual and sustained improvement or whether extensive fluctuations occur over the course of the study.

Patient-centered outcomes should be incorporated into the design of future studies. Primary outcome measures should include the use of quality of life measures using a validated tool such as the DLQI,[63] CDLQI,[64] or Skindex-29.[65] This would not only improve the relevance of trials but could allow comparison between trials using different interventions. Another important primary outcome, which should be reported in the trials, is the percentage of repigmentation (restoration of normal skin color) of vitiliginous skin, especially a success rate in terms of more than 75% repigmentation of individual patches or of total body surface area, measured by objective means (eg, photographs or rule of nines).[62,68] However, we would emphasize that there is no firm evidence to support the use of 75% repigmentation or more as a measure of treatment success; this is based on empirical evidence and specialist consensus. More research is needed to address the definition of successful repigmentation from the perspective of clinicians and patients.

Secondary outcomes, in particular long-term permanence of repigmentation and adverse effects, are very important indeed, especially from the patient point of view and also for developing the evidence base for treatment maintenance regimens. The unpredictability of vitiligo is one of the disease's most challenging features, and permanence of repigmentation is an important outcome for informing patients what to expect from treatment in the longer term.

Treatments for vitiligo should arrest the progression of the disease and induce repigmentation. Both outcomes are equally important from the patient's perspective. Therefore, future studies should also evaluate cessation of spread of vitiligo or stabilization of the disease. However, currently there are no validated scales to assess disease activity and to estimate cessation of spread of vitiligo in clinical trials. Only 2 unvalidated scoring systems are available to help monitor vitiligo: the vitiligo area severity index (VASI)[24] and the vitiligo disease activity (VIDA) score[69] based on the patient's perspective. Further research is needed to devise a standardized, objective method of ascertaining disease activity, bearing in mind the difficulty of achieving and measuring repigmentation while lesions are actively spreading.

The Study Design

The methodology used for the generation of randomization sequence and the allocation concealment, as well as the blinding method, should be adequate and clearly described. Although some studies randomize by individual vitiligo lesions, especially those assessing topical and surgical interventions, it makes more sense clinically to randomize participants, particularly in nonblinded trials. In studies where investigator and participant blinding is not possible because the comparison is between topical and light-based interventions, for example, an independent blinded assessor is essential.

The main focus of any RCT assessing interventions for vitiligo should be the primary outcome, which should also form the basis of the general conclusion of the study.

Secondary outcomes may help to support the direction and magnitude of the primary outcome such as comparing the adverse effects and the rate of repigmentation of a treatment and considering the permanence of gained repigmentation for establishing maintenance regimen of this treatment. All outcomes need to be reported with the estimated effect of the intervention and the 95% confidence intervals to allow further meta-analysis (eg, the mean and the standard deviation for each group).[70]

Sample size needs to be calculated to ensure sufficient statistical power to appropriately evaluate the primary outcome measure. The rationale used for the calculation of sample size should be specified in the study protocol. Small sample size, a source of potential imprecision, does not necessarily mean that such studies cannot provide some useful information about intervention efficacy. In addition, the statistical analysis should be based on full reporting of any reasons for withdrawals and the timeline during which they occurred. Because a large proportion of missing data (eg, withdrawals) will diminish the credibility of a study, the best practice is to minimize the chance of withdrawals at the design stage or during the trial.[71] To minimize the effect of attrition bias, 2 possible analysis plans can be used: an available-case analysis or an intention-to-treat analysis. An *available-case analysis* includes only participants with complete outcome data in the analysis. An *intention-to-treat analysis*, which is often recommended as the least biased way to estimate intervention effects,[72] uses a process called imputation to replace missing data.

The investigation of treatment strategies using patient satisfaction outcomes would be invaluable in future RCTs, but more research needs to be done to define outcomes important to both patients and clinicians. In addition, current evidence for vitiligo in pediatric patients is lacking, which emphasizes the need for more research.[73]

Reporting

Adequate reporting of RCTs improves transparency and enables the interpretation and replication of studies. Many journals require that reports of RCTs conform to the guidelines in the Consolidated Standards of Reporting Trials (CONSORT) statement.[66] Rigorous peer review in journals is another way of ensuring that RCTs are well reported. Studies demonstrating more positive treatment effects are more likely to be published than those with less conclusive results, many of which may remain unpublished altogether. This may be because authors decide not to submit reports of such studies to journals or because journals are more interested in studies with "positive" findings[74] or because studies are written in languages other than English.[75] The first study to be published on a particular intervention is more likely to show positive results.[76] However, it is unethical not to publish RCTs with negative results.[77] Fortunately, most RCTs are currently registered in public databases (eg, www.clinicaltrials.gov) at the start of the trial, enabling identification of, as well as any discrepancies between, the registered protocol and the methods used in the published trial.

The CONSORT statement also requires that data from a new trial should be interpreted in the light of the totality of the available evidence.[66] Accurate representation of the prior cumulative research including clinical trial registration information is necessary to ethically justify a trial, to make proper inferences, and to better address any gaps in the evidence.

CONCLUSION

A more evidence-based, strategic approach based on the findings of the updated Cochrane systematic review "Interventions for Vitiligo"[73] may help to plan and prioritize global treatment recommendations and clinical research in the field of vitiligo. There is much scope for improving the design and reporting of RCTs. This can be encouraged by adopting general guidelines and by ensuring rigorous peer review in journals. Factors that will improve the validity of vitiligo RCTs include longer duration of trials with adequate follow-up periods and clinically relevant, patient-orientated outcome measures.

It is our hope that the recommendations in this report will help in the process of overcoming the methodologic challenges faced when conducting RCTs on interventions for vitiligo. This report on the methodology of vitiligo RCTs and our proposed guidelines should assist with the design and execution of high-quality, multicenter RCTs that attempt to answer treatment questions of importance to both clinicians and patients.[73]

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