

BOX

Box 1. Items to be considered when designing and reporting a within-person randomized controlled trial involving a topical treatment in dermatology

Designing

- ✓ Existence of an extension period to increase patient adherence to the trial

In an extension period, all lesions/body sites receive the experimental treatment. This facilitates patient recruitment and adherence because of the certainty of having all lesions eventually treated by the new treatment by the end of the study

- ✓ Description of eligibility criteria for both patients and lesions/body sites
- ✓ Monitoring of compliance of the experimental and control treatment

Patients receive both experimental and control treatments at the same time, with a risk of administration errors.

- ✓ Use of a care provider for administering the experimental and control treatment

Simultaneously applying both treatments on a single patient may challenge compliance, and therefore, the use of a care provider such as a nurse will limit protocol deviations.

- ✓ Blinding of patients
- ✓ Blinding of care providers
- ✓ Blinding of outcome assessors
- ✓ Prevention and detection of a potential carry-across effect

Methods to prevent and detect a potential carry-across effect should be considered to ensure no group contamination.

- ✓ Objective primary outcome

The risk of unblinding can be increased because patients concomitantly receive both experimental and control treatments. Therefore, objective outcomes (e.g., spectrophotometry or blinded evaluation by an independent outcome assessor using photographs in case of subjective outcomes) are highly recommended.

- ✓ Sample size calculation

Intra-patient between-lesion correlation must be considered.

- ✓ Statistical analysis

Intra-patient between-lesion correlation must be considered.

Reporting

- ✓ Identification of the study as a within-person randomized controlled trial in the title, abstract and main text

- ✓ Design justification

Because of the constraints inherent to the design and the risk of a carry-across effect, justification for using a within-person design is desirable.

- ✓ Patients' acceptability of the design
- ✓ Assume a within-patient between-lesions correlation coefficient estimate used for the sample size calculation
- ✓ Flow chart of patients and lesions/body sites
- ✓ Baseline characteristics for both patients and lesions/body sites
- ✓ Within-patient between-lesions correlation coefficient estimate
- ✓ Local adverse events reported by lesions/body sites

TABLES

Table 1. General characteristics of included studies (n=54)

SETTING	
Subcontinent of study recruitment ¹	
Europe	20 (37.0)
Asia	17 (31.5)
North America	9 (16.7)
Middle East	5 (9.2)
South America	1 (1.9)
Oceania	1 (1.9)
Unclear	2 (3.7)
Number of centres	
Single-center study	31 (57.4)
Multicenter study	9 (16.7)
Unclear	14 (25.9)
POPULATION	
Dermatologic condition	
Acne	14 (25.9)
Acne rash-like induced by anti-epidermal growth factor	2 (3.7)
Actinic keratosis	11 (20.4)
Atopic dermatitis	8 (14.8)
Psoriasis and nail psoriasis	6 (11.1)
Rosacea	3 (5.6)
Vitiligo	2 (3.7)
Other ²	8 (14.8)
Type of population	
Adults	45 (83.3)
Children	1 (1.9)
Both	7 (12.9)
Unclear	1 (1.9)

Data are n (%).

¹Sum of the category is > 1 because for one study, the recruitment was conducted in both Europe and North America

²Other included CYLD cutaneous syndrome, disseminated superficial actinic porokeratosis, eyebrow hypotrichosis, facial angiofibromas, moderate to severe facial telangiectasia, primary amyloidosis macular, skin graft and superficial partial thickness burns

Table 2. Methodological characteristics of included within-person randomized controlled trials (n=54)

DESIGN	
Identification as a within-person randomized controlled trial	52 (96.3)
Identification in both title, abstract (if required) and manuscript	26 (48.2)
Design justification by the authors ¹	10 (18.5)
To limit inter-individual variability	9 (90.0)
To reduce the number of patients to be included	5 (50.0)
To improve treatment adherence	1 (10.0)
Rare skin disease	1 (10.0)
Objective	
Superiority	50 (92.6)
Non-inferiority/equivalence	4 (7.4)
Add-on design	21 (38.9)
Standard treatment	
Physical treatment ²	13 (61.9)
Topical treatment	5 (23.8)
Topical medical devices	1 (4.8)
Oral treatment	1 (4.8)
Topical treatment and oral treatment	1 (4.8)
Existence of an extension period	5 (9.3)
ETHICAL ASPECTS	
Patient's acceptability of the design reported	1 (1.9)
Ethical aspects evoked	1 (1.9)
ELIGIBILITY CRITERIA	
Description of eligibility criteria for	
Patients	35 (64.8)
Body sites/lesions	0 (0.0)
Both	18 (33.3)
Unclear	1 (1.9)
Required number of units (lesions) per patient	
2	52 (96.3)
> 2 ³	2 (3.7)
INTERVENTIONS	
Methods to enhance compliance	
Person in charge of the application of the topical treatment	
Patient	26 (48.2)
Care provider	12 (22.2)
Family caregiver	0 (0.0)
Not described	16 (29.6)
Monitoring that the assigned treatment is applied to the correct site	2 (3.7)
Blinding of one of these actors	
Patients ⁴	25/46 (54.3)
Care provider ⁵	2/9 (22.2)
Outcome assessor ⁶	39/45 (86.7)

<i>Detection of carry-across effect</i>	0 (0.0)
OUTCOME	
Outcome clearly identified	44 (81.5)
Type of outcome (n=44)	
Objective outcome	8 (18.2)
Subjective outcome	32 (72.7)
Mixed outcome (objective and subjective)	4 (9.1)
Level of the primary outcome (n=44)	
Lesion/body site	44 (100.0)
Patient	0 (0.0)
RANDOMIZATION	
Unit of randomization	
Lesion	5 (9.3)
Anatomic site ⁷	41 (75.9)
Upper limb	7 (17.1)
Lower limb	2 (4.9)
Trunk part	3 (7.3)
Face/neck	31 (75.6)
Pelvis area	0 (0.0)
Hands/feet	3 (7.3)
Other ⁸	5 (9.3)
Unclear	3 (5.5)
STATISTICAL CONSIDERATIONS	
Planned required patient sample size	
Not estimated	21 (38.9)
< 25	8 (14.8)
25-49	16 (29.6)
≥ 50	9 (16.7)
Within patient correlation accounted for in the sample size (n=21)	
No	5 (15.1)
Yes	6 (18.2)
Unclear	22 (66.7)
Statistical methods for analysis	
For trials with 2 units (lesions) per patient (n=52)	
Not described	3 (5.8)
Paired test for 2 lesions	33 (63.5)
Conditional models/mixed models	1 (1.9)
Statistical methods for independent data	15 (28.8)
For trials with > 2 units (lesions) per patient (n=2)	
Descriptive statistics	1 (50.0)
Mixed models for repeated data ⁹	1 (50.0)
FUNDING BODY	
Private	18 (33.3)
Public ¹⁰	18 (33.3)
Both private and public	1 (1.9)
No specific funding ¹⁰	7 (13.0)
Not reported	10 (18.5)

Data are n (%).

WP-RCT: within-person randomized controlled trial

¹Sum of the category is > 1 because one study may have had several design justifications

²Photodynamic therapy for 10 studies, phototherapy for 1 study, excimer light lamp for 1 study and air cooling for 1 study

³Minimal number of units (lesions) per patient for these 2 trials were 4 and 10

⁴Unclear for 8 trials, ⁵unclear for 3, ⁶unclear for 9 trials

⁷Sum of the category is > 1 because one study may have had several anatomic sites

⁸Other included for 2 trials 2 study areas in a same anatomic site, for 2 trials 2 hemibodies and for 1 trial 2 distinct anatomic sites

⁹Mixed models account for the correlation between repeated data but not the correlation between lesions

¹⁰For 2 trials, experimental treatment was given by industry

Table 3. Characteristics of intervention and control treatments (n=54)

Number of treatments compared	
1	1 (1.8)
2	48 (88.9)
3	3 (5.6)
4	2 (3.7)
Experimental treatment ¹	
Emollient	10 (18.5)
Corticosteroids	8 (14.8)
Photosensibilizer	8 (14.8)
Herbs/plants	8 (14.8)
Immunosuppressive drugs	4 (7.4)
Vitamin B12	3 (5.6)
Anti inflammatory drugs	2 (3.7)
Peeling	2 (3.7)
Retinoids	2 (3.7)
Beta-blockers	1 (1.9)
Retinoids + benzoyl peroxide	1 (1.9)
Corticosteroids + immunosuppressive drugs	1 (1.9)
Other ²	10 (18.5)
Type of experimental treatment ¹	
Cream	20 (37.0)
Gel	15 (27.8)
Ointment	8 (14.8)
Solution	3 (5.6)
Emulsion	2 (3.7)
Vaseline	2 (3.7)
Peels	2 (3.7)
Patch	1 (1.9)
Paraffin	1 (1.9)
Nanolipid carrier	1 (1.9)
Control group (n=53)	
Active drug	23 (43.4)
Emollient cream	12 (22.6)
Vehicle	8 (15.1)
Other	8 (15.1)
No treatment	2 (3.8)
Unclear	1 (1.9)
Duration of the treatment	
One session of treatment	5 (9.3)
< 15 days	9 (16.7)
15-29 days	17 (31.5)
30-60 days	6 (11.1)
> 60 days	14 (25.9)
Unclear	3 (5.5)
Number of applications	
One session of treatment	3 (5.6)
≤ 1 application/week	7 (13.0)
3-4 applications/week	7 (13.0)
1 application/day	15 (27.8)
1-2 applications/day	2 (3.7)
2 applications/day	18 (33.3)

2-3 applications/day	1 (1.8)
Unclear	1 (1.8)

Data are n (%).

¹Sum of the category is > 1 because one study may have had several experimental treatments

²Other includes moisturizer containing lidochalcone A, decanediol, Lcarnitine, 1% salicylic acid, lidochalcone l carnitine decanediol, salicylic acid, agonist alpha2 adrenergic receptor, synthetic prostaglandine (bimatoprost), solution topical dimethyl sulfoxide, vitamin D, sodium bicarbonate, PDE4 inhibitor, 2% simvastatine 2% cholesterol

Table 4. Description of results of included studies (n=54)

<i>PATIENT FLOW</i>	
Flow chart with number of patients only	17 (31.5)
Flow chart with number of lesions/body sites only	0 (0.0)
Flow chart with number of patients and lesions/body sites	2 (3.7)
<i>PATIENTS AND LESIONS</i>	
Number of patients included	
< 25	20 (37.0)
25-49	22 (40.8)
≥ 50	12 (22.2)
Patients lost to follow-up/dropped out	
Yes	34 (63.0)
No	13 (24.0)
Unclear	7 (13.0)
<i>BASELINE DATA</i>	
Baseline characteristics are reported for	
Patients only	26 (48.2)
Body sites/lesions only	1 (1.9)
Both	24 (44.4)
None	3 (5.5)
<i>HARMS</i>	
General adverse events/patient level	
Yes	14 (25.9)
No	15 (27.8)
Unclear	9 (16.7)
Not reported	16 (29.6)
Reporting of number of adverse events/patient level	
Number of general adverse events/patient level	5/14 (35.7)
Reporting of local adverse events/lesion/body site level	
Yes	43 (79.6)
No	6 (11.1)
Unclear	1 (1.9)
Not specified	4 (7.4)
Reporting of number of local adverse events in experimental group	
Number of lesions/body sites	15/43 (34.9)
Number of lesions/body sites	5.0 [3.0-9.5]
Reporting of number of local adverse events in control group ¹	
Number of lesions/body sites	14/43 (32.6)
Number of lesions/body sites	3.0 [0.0-5.75]
<i>REPORTING IN REGISTER</i>	
Number of trials registered	
Results published in registers	27 (50.0)
Results published in registers	8 (29.6)

Data are n (%) or median [interquartile range].

¹In one trial, the number of local adverse events for control group was not reported