Research Techniques Made Simple: Randomized Controlled Trials for Topical Drugs in Dermatology: When and How Should We Use a Within-Person Design?

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Topical drugs are often used as first-line treatment for dermatological conditions. Depending on the disease and the drug, three main designs can be used for randomized controlled trials assessing topical drugs: the classical individual parallel design, the cluster randomized design, and designs allowing within-individual comparisons, including the cross-over design (in which patients are randomized to a sequence of interventions) and the within-person design (also called the split-body design). Within-person design can be used to compare different drugs concomitantly in the same patient. Randomization does not concern patients but rather lesions or body sites within patients, and the drugs to be compared are applied to the different lesions (or sites). This design considerably reduces interobservation variability, and thus, the number of patients to be included in the trial (sample size). However, this design has major methodological constraints, especially the need to resolve the problem of a possible carry-across effect. First, we describe the specificities of randomized controlled trials evaluating a topical drug. Second, we present the different designs available and discuss the methodological points that should be considered, especially for a within-person design. Finally, we compare the relevance of the within-person design with that of other trial designs by considering three different scenarios.

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INTRODUCTION

Skin diseases are common in the general population. Clinical presentations are highly heterogeneous, depending on the disease, and management might involve surgery, physical therapy (lasers, phototherapy, etc.), systemic drugs, topical drugs, or devices.

Topical drugs are often used as first-line treatment. They are directly applied on the skin and have limited systemic effects in most cases. Currently, topical drugs represent a major cost to the public. For example, the US Medicare Part D expenditures for topical steroids between 2011 and 2015 were estimated at $2.3 billion (Song et al., 2017).

The most frequent classical design for trials is the individual parallel randomized control trial (RCT) design (Maruani et al., 2015). However, other designs are available (Figure 1; Table 1). Because topical drugs can be applied to only one or several lesions, different drugs can be compared in a single patient at the same time; this design is called the within-person RCT. Contrary to the individual parallel RCT, the randomization units and the assessment units can be the patient or each lesion, as reported in trials of vitiligo (Whitton et al., 2015).

In this article, we describe and discuss the specificities of these within-person RCTs and offer guidance for when and how to use them.

SPECIFICITIES OF TRIALS OF TOPICAL DRUGS

As in trials of systemic drugs, trials assessing topical drugs require a detailed description of all characteristics of the intervention, including the drug dosage, frequency of application, and duration of treatment as well as the galenic formulation and drug components (Box 1). In addition, concomitant topical drugs as well as cosmetics and hygiene care products, including the delay between drug applications and cleaning products, must be mentioned because they can interact. Another specificity is the difficulty in determining a standardized quantity of topical drug to apply (for example, the number of fingertip units by cutaneous area in centimeters

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Abbreviations: RCT, randomized controlled trial
Trials of topical drugs require a detailed description of all application modalities such as the amount of drug to apply, how to apply treatments, and the delay between drug application and use of hygiene products.

Three main designs can be used when assessing topical drugs: (i) designs allowing for comparison between parallel groups, including the classical individual parallel randomized controlled trial (RCT), in which patients are randomized and one assessment is available per patient, and the individual parallel RCT with clustering, in which patients are randomized and allocated to one treatment, but several lesions from the patient are separately assessed; (ii) the cluster design, in which clusters of patients are randomized and allocated to one treatment; and (iii) designs allowing for a within-individual comparison RCT, including the cross-over design, in which individuals switch from one treatment to another after a wash-out period, and the within-person design, in which lesions are separately randomized and concomitantly treated and assessed.

In the within-person RCT, also called split-body RCT, left and right comparisons RCT, or intraindividual comparison RCT, patients simultaneously receive topical experimental drugs and controls on different lesions or body sites, which reduces interobservation variability.

As compared with the individual parallel RCT design, the within-person design allows for reducing the number of patients to be included in the trial; thus, the design is well-adapted for rare diseases.

The main constraint of the within-person design is the need to control the risk of the carry-across effect, that is, leakage of the treatment effect from one site to another for a patient simultaneously receiving different drugs on different lesions.

The choice of design depends on the drug (systemic passage, etc.) and the disease (number and extension of lesions, prevalence, etc.).

The maximum quantity to be applied, the use of a glove or not, and the modalities of application should also be mentioned to be able to reproduce the protocol. Regarding controls, most trials use a topical inactive control even when it is not the most relevant (Wilkes et al., 2016). If an inactive control is chosen, the best one to use is the vehicle (i.e., the same components as the intervention except for the active product) and not an emollient, which can be slightly active for inflammatory skin diseases and would induce interpretation bias (Hon et al., 2013). Finally, topical drugs might have a slight systemic effect if there is enough percutaneous absorption.

**SUMMARY POINTS**

- Trials of topical drugs require a detailed description of all application modalities such as the amount of drug to apply, how to apply treatments, and the delay between drug application and use of hygiene products.
- Three main designs can be used when assessing topical drugs: (i) designs allowing for comparison between parallel groups, including the classical individual parallel randomized controlled trial (RCT), in which patients are randomized and one assessment is available per patient, and the individual parallel RCT with clustering, in which patients are randomized and allocated to one treatment, but several lesions from the patient are separately assessed; (ii) the cluster design, in which clusters of patients are randomized and allocated to one treatment; and (iii) designs allowing for a within-individual comparison RCT, including the cross-over design, in which individuals switch from one treatment to another after a wash-out period, and the within-person design, in which lesions are separately randomized and concomitantly treated and assessed.
- In the within-person RCT, also called split-body RCT, left and right comparisons RCT, or intraindividual comparison RCT, patients simultaneously receive topical experimental drugs and controls on different lesions or body sites, which reduces interobservation variability.
- As compared with the individual parallel RCT design, the within-person design allows for reducing the number of patients to be included in the trial; thus, the design is well-adapted for rare diseases.
- The main constraint of the within-person design is the need to control the risk of the carry-across effect, that is, leakage of the treatment effect from one site to another for a patient simultaneously receiving different drugs on different lesions.
- The choice of design depends on the drug (systemic passage, etc.) and the disease (number and extension of lesions, prevalence, etc.).

**WHICH DESIGNS TO BE USED WHEN ASSESSING A TOPICAL DRUG**

Skin conditions may present as a single lesion (a skin tumor, cutaneous malformation, etc.), multiple countable well-limited lesions (vitiligo, chronic plaque psoriasis, etc.), or multiple diffuse uncountable lesions (scabies, exanthema, etc.). According to these presentations, several distinctly designed trials can be considered (Figures 1 and 2):

1. The classic individual parallel RCT. Patients are randomized, and assessment involves the whole patient (Papp et al., 2016) or a single lesion on the patient.
2. The individual parallel group with clustering RCT. Patients are also randomized, but the treatment effect is assessed for each lesion treated with the topical drug. For example, the study by Cavalié et al. (2015), which evaluated 0.1% topical tacrolimus for vitiligo, included 35 randomized patients and 72 assessed lesions. Because each patient may have one or more lesions, the design is similar to a classical cluster RCT, in which patients are clusters, and vitiligo lesions are assessment units within the clusters. These units are correlated, as in cluster RCT.

These two designs above lead to interindividual comparisons, that is, between parallel groups of patients.

3. The classical cluster RCT. Groups (clusters) of patients are randomized and allocated to one topical treatment. For example, Madan et al. (2019) performed a cluster RCT to evaluate the efficacy of a behavior change package, including regular use of moisturizing cream to prevent hand dermatitis in nurses working in healthcare. In this trial, clusters were hospitals, and nurses, who corresponded to assessment units, were embedded within clusters.

4. The cross-over RCT. Patients are randomized to a sequence of interventions and switch from one topical treatment to another after a wash-out period. Therefore, patients act as their own control. This design is appropriate for chronic stable disease (e.g., recurrent aphthous stomatitis), in which topical treatments will have transient effects without carry-over effects between the two periods of treatment (Gorsky et al., 2007).

5. The within-person design. The lesions or body sites are randomized but the patient is not, and lesions or sites are further assessed. The patient concomitantly receives the topical intervention and the topical control. The within-person design is close to the cross-over design, but treatments are administered at the same time rather than consecutively. As for the cross-over design, the within-person RCT benefits from patients being compared with themselves. Thus, because each patient contributes to both groups and because it reduces interobservation variability, the required sample size greatly decreases. This design has
been used in studies of topical drugs for acne vulgaris, in which patients applied the experimental drug to the right or left side of the face and the control to the contralateral side, then each side was assessed. In such designs, assessment units within patients are correlated (Pandis et al., 2017).

**METHODOLOGICAL ISSUES THAT MUST BE CONSIDERED WHEN PLANNING A WITHIN-PERSON RCT**

*Figure 3 shows the advantages and limitations of the within-person RCT.*

**Eligibility criteria—for both patients and lesions**

Eligibility criteria need to be specified for patients as well as for lesions or body sites. For example, a trial on chronic plaque psoriasis also requires eligibility criteria for the plaque to avoid biased comparison. In addition, whether the dermatological condition involves a single lesion (e.g., a wide patch of alopecia areata), the within-person design requires that the size of the lesion be large enough to be divided into two homogeneous areas and to include an area separating the two areas to limit intercontamination of the topical drug applied. Similarly, baseline data must be collected for both patients and lesions or body sites.

**Interventions—the carry-across effect**

For a within-person RCT, the absence or negligible systemic passage of the topical experimental drug is required to avoid a carry-across effect. This effect can be defined as the potential leakage of the treatment effect from one site to another by direct contact or systemic passage (Lesaffre et al., 2009) (Figure 4). Systemic passage of a drug depends on its

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**Table 1. Glossary**

<table>
<thead>
<tr>
<th>Term</th>
<th>Description</th>
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<tr>
<td>Carry-across effect</td>
<td>The potential leakage of the treatment effect from one site to another in a patient receiving two or more topical treatments.</td>
</tr>
<tr>
<td>Cluster RCT</td>
<td>Trials in which clusters of patients, such as wards, practices, schools, or villages, are randomized rather than the patients themselves. They are usually used for evaluating health service organization and health policy, often with complex interventions targeted at the level of the cluster, the individual, or both.</td>
</tr>
<tr>
<td>Cross-over RCT</td>
<td>Patients are randomized to sequences of interventions and receive multiple interventions. Each patient receives each intervention in a separate period of time. There is usually a wash-out period between sequences. Each patient is in his or her own control.</td>
</tr>
<tr>
<td>Individual parallel RCT</td>
<td>Patients are randomized to intervention A (experimental treatment) or intervention B (control treatment). The objective of a superiority individual parallel RCT is to reveal that intervention A is superior to intervention B. The objective of a noninferiority individual RCT is to reveal that intervention A is at least as good as intervention B in terms of efficacy.</td>
</tr>
<tr>
<td>Individual parallel RCT with clustering</td>
<td>Patients with one or several lesions are randomized, but the treatment effect is assessed for each lesion treated with the topical drug. Because each patient may have one or more lesions, the design is similar to a cluster RCT, in which patients are clusters, and cutaneous lesions are assessment units within clusters. These units are correlated, as in any cluster RCT.</td>
</tr>
<tr>
<td>Within-person RCT</td>
<td>Patients receive two or more treatments to different body sites. The unit of randomization is not the patient but an organ or a lesion (cutaneous lesions, eye, teeth, etc.) or body area (arms, legs, etc.). The within-person design is also called the split-body design or intrapatient comparison design.</td>
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Abbreviation: RCT, randomized controlled trial.
molecular weight, its properties of retention in the dermis, its lateral diffusion by the dermal microvascular perfusion (blood and lymphatic vessels) and diffusion into tissue (Dancik et al., 2012), and the skin where the drug is applied (more systemic passage in case of wide area of application or severe alteration of the cutaneous barrier).

A carry-across effect would be associated with group contamination and therefore, an underestimated difference in treatment effect estimates. This situation would be conservative for a superiority RCT but would also inappropriately favor a noninferiority RCT. Methods to limit and detect the carry-across effect should be described in protocols. When a plasma dosage of the drug is feasible, blood samples for this dosage must be included in the protocol (Leducq et al., 2019).

Compliance—the use of a care provider optimizes the protocol

Simultaneously applying both treatments on the same patient may challenge compliance. Classically, despite several limitations (e.g., electronic caps do not guarantee that topical treatment is applied), medication electronic monitoring system caps, smartphone applications, motivational phone calls, weighting, and questionnaires have been used to enhance compliance (Svendsen et al., 2018). However, the very issue in a within-person RCT is contamination. Indeed, with evident superiority of one drug or in case of local side effects associated with a drug, patients might be tempted to apply the apparently best treatment to all lesions. The use of a care provider to apply the topical experimental drug and the control is expensive but allows for limiting this risk and optimizing compliance.

Outcomes and estimation

Within-person RCTs imply outcomes at the lesion level. For example, global patient-reported outcomes such as QOL, cannot be used for drug comparison. Similarly, the evaluation of general adverse events cannot be related to one of the drugs applied. Therefore, local adverse events (erythema, burning, and pruritus) are the most reliable.

Recruitment—patient must accept to receive both treatments

In within-person RCTs, each patient is assured of receiving the topical experimental drug and the control(s), which might be satisfying for patients who are reluctant to receive only a placebo as in individual parallel RCTs. However, all patients’ lesions do not receive the same topical drugs, which can lead to inhomogeneous aspects. A way to facilitate the patient’s agreement to be recruited is to provide the most effective topical drug for all lesions after the study has ended.

Blinding is more challenging

In within-person RCTs, the risk of unblinding can be increased because each patient receives both treatments, which allows for direct comparison of local effects. Therefore, as far as possible, objective outcomes are preferred, such as assessments of photographs or other systems.

Statistical methods

Statistical methods must take into account the correlation between the different lesions within a patient. With only two lesions (or body sites) per patient, paired tests should be used. If more than two lesions (or body sites) are included, linear or logistic mixed models should be used, as in a paired-matched cluster RCT. Otherwise, missing data must take into account this intrapatient correlation. In within-person RCTs, lost to follow-up and participant dropout will cause a loss of two observations but are expected to be balanced because each patient contributes to both the experimental and control groups.

WHEN TO USE A WITHIN-PERSON RCT

Here, we discuss the relevance of the within-person RCT by considering three different scenarios.

Scenario 1—an RCT of a dermatological condition that involves a single lesion (e.g., a wide patch of alopecia areata)

In an individual parallel RCT for a condition that involves a single lesion (e.g., alopecia areata) (Figure 5a), patients will be randomized and allocated to one treatment (topical experimental drug or control). The whole lesion will be treated with the allocated drug, and assessment will consist of one outcome measure per patient. With the within-person RCT, the lesion will be split into two homogeneous areas: one area randomly allocated to the topical experimental drug and the other to the control. Each area will be assessed, thus leading to two paired outcome measures per patient.

The individual parallel RCT is easier to conduct but requires a larger number of patients. The within-person RCT

### BOX 1. Items to be Specified for Randomized Controlled Trials Involving a Topical Drug

- Description of the characteristics of the topical drug
  - Dosage
  - Galenic formulation
  - Drug components
  - Frequency of application
  - Duration of treatment
- Definition of quantity of topical drug to apply
- Description of allowed concomitant topical drugs and cosmetics/hygiene care products
- Description of the delay between drug applications and cleaning products
- Description of potential systemic passage of the drug
- Description of the topical control and justification for the choice
Figure 2. Types of designs for trials assessing topical drugs according to the number of skin lesions.

<table>
<thead>
<tr>
<th>Randomization unit</th>
<th>Assessment unit (outcome for lesion severity)</th>
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<tbody>
<tr>
<td><strong>SINGLE LESION</strong></td>
<td></td>
</tr>
<tr>
<td>1A</td>
<td>Individual parallel randomized controlled trial</td>
</tr>
<tr>
<td>1B</td>
<td>Within-person randomized controlled trial</td>
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<tr>
<td><strong>MULTIPLE COUNTABLE LESIONS</strong></td>
<td></td>
</tr>
<tr>
<td>2A</td>
<td>Individual parallel randomized controlled trial</td>
</tr>
<tr>
<td>2B</td>
<td>Within-person randomized controlled trial</td>
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<td>2C</td>
<td></td>
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<tr>
<td>2D</td>
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<td>2E</td>
<td></td>
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<tr>
<td><strong>MULTIPLE DIFFUSE LESIONS</strong></td>
<td></td>
</tr>
<tr>
<td>3A</td>
<td>Individual parallel randomized controlled trial with clustering</td>
</tr>
<tr>
<td>3B</td>
<td>Within-person randomized controlled trial</td>
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<tr>
<td>3C</td>
<td></td>
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</tbody>
</table>

- **1A**: Patients are randomized and lesions (one per patient) are assessed.
- **1B**: The lesion is divided into 2 areas, each area randomly allocated to the experimental or control group.
- **2A**: Patients are randomized; all lesions are treated, each lesion is assessed, but a summary statistic (e.g., sum or mean) is used such that there is only one global assessment per patient. This comes down to a cluster randomized trial with a cluster level outcome.
- **2B**: All lesions or one lesion are included and receive the experimental topical drug or control. Evaluation is of one unique lesion, and thus, one measure per patient is available.
- **2C**: Patients are randomized; all lesions are treated with the experimental topical drug or control and assessed. For each patient, we have as many evaluation units as number of lesions. This design is similar to a classical cluster RCT in which patients are clusters, and lesions are assessment units within clusters. These units are correlated, as in cluster RCT.
- **2D**: Two lesions or two body sites are randomly allocated to the 2 groups and assessed. Only two lesions per patient are considered.
- **2E**: Lesions or body sites are randomized (for an individual patient, there may be several lesions or body sites in the same group) and assessed.
- **3A**: Patients are randomized, all lesions are treated in the same way, and assessment is at the patient level by use of a global assessment tool.
- **3B**: Body sites are randomized and assessment is at the body site level, considering all lesions of the body sites.
- **3C**: For lesions of the face, the face can be divided into 2 areas and each face half is randomly allocated to the experimental or control group. Assessment is at the face half level.
allows for reducing the number of patients as well as inter-observational variability in a pathology with significant disparity among patients. However, with the within-person RCT, the risk of carry-across effect is high for this condition, especially by direct contact. One way to limit the effect is to define a large buffer zone between both areas (i.e., an area where no drug is applied) to avoid interarea drug contamination. Finally, we must consider patients’ acceptability of the within-person RCT regarding the potential hair regrowth on only one half of the patch of alopecia.

Scenario 2—an RCT of a dermatological condition involving several countable lesions (e.g., vitiligo)

In an individual parallel RCT for a condition involving several countable lesions (e.g., vitiligo) (Figure 5c, d), patients are randomized, but three situations can be considered for outcome assessment: (i) all lesions receive the same topical treatment (experimental drug or control), each lesion is assessed, and a summary statistic is used for only one global evaluation per patient (e.g., the Vitiligo Area Scoring Index); (ii) one lesion, several lesions, or all lesions receive the topical treatment, but assessment focuses on only one lesion, thus, one measure per patient is available; or (iii) all lesions receive the same topical treatment to which the patient was randomly allocated, but each lesion is separately assessed. Therefore, for one patient, there are as many assessment units as the number of treated lesions. This design is considered as an individual parallel RCT with clustering.

In contrast, we can use a within-person RCT, in which randomization is not at the patient level but at the lesion or body site level. Lesions are randomly allocated to receive the

![Figure 4. Two ways to induce a carry-across effect. (a) Direct contact between the two topical drugs. (b) Systemic passage of the experimental topical treatment.](image-url)
In this vitiligo scenario, the individual parallel RCT with clustering is an appealing design because it has the advantage to increase statistical power by using the maximum potential amount of data. The within-person RCT also has advantages because it allows for reducing the sample size and limiting interobservation variability. However, it can be considered only if the carry-across effect is controlled; that is, the treated lesions must not be too close to one another, and the experimental drug must have negligible systemic passage (which should be controlled by blood sampling).

Scenario 3—an RCT of a dermatological condition involving multiple diffuse lesions (e.g., guttate psoriasis)
In this scenario, patients (individual parallel RCT) or body sites that include a large number of guttate psoriasis lesions (within-person RCT) (Figure 5b) can be randomized. In the first case, the unit of randomization is the patient, and all lesions are treated in the same way; assessment is at the patient level by use of a global evaluation tool. If body sites are randomized, assessment is at the body site level, considering an overall evaluation of lesions at each site. Global assessment such as QOL cannot be used for drug comparison because each patient receives both treatments. If we consider that QOL is the most relevant outcome for guttate psoriasis, the individual parallel RCT would be preferred to the within-person RCT.

CONCLUSION
The choice of the most adequate design when planning a protocol must take into account the type of disease (number of lesions), disease prevalence, the relevant primary outcome, the risk for the carry-across effect, and patient’s acceptability. There is no unique rule to follow, and discussions should optimally involve dermatologists, methodologists, and patients.

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CONFLICT OF INTEREST
The authors state no conflict of interest.

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SL had a role as trainee author; AC and ET had a role as faculty advisor; LLC, MS, AM, and BG had a role as subject matter experts.

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Conceptualization: SL, AC, LLC, MS, ET, AM, BG; Supervision: SL, AM, BG; Visualization: SL; Writing - Original Draft Preparation: SL, AM, BG; Writing - Review and Editing: SL, AC, LLC, MS, ET, AM, BG
MULTIPLE CHOICE QUESTIONS

1. In a trial evaluating a topical drug, dermatological departments are randomly allocated to the experimental or control group (all patients from a department receive the same treatment). What is the randomized control trial (RCT) design?
   A. Within-person RCT
   B. Cluster RCT
   C. Classical individual parallel RCT
   D. Cross-over RCT

2. For a within-person RCT, what are the correct answers?
   A. The unit of randomization is the patient
   B. The unit of randomization is the lesion
   C. The unit of assessment is the patient
   D. The unit of assessment is the lesion

3. The carry-across effect depends on
   A. The skin condition
   B. The drug properties
   C. Molecular weight of the drug
   D. All of the above

4. When should a within-person RCT be avoided?
   A. For rare diseases
   B. If the relevant primary outcome is QOL
   C. If the best control is another active topical drug and not a placebo
   D. Dermatological conditions with facial involvement

5. For which dermatological condition should a within-person RCT not be used?
   A. Acne vulgaris
   B. Acral melanoma
   C. Plaque of vitiligo
   D. None of the above

SUPPLEMENTARY MATERIAL

Supplementary material is linked to this paper. Teaching slides are available as supplementary material.

REFERENCES


1. In a trial evaluating a topical drug, dermatological departments are randomly allocated to the experimental or control group (all patients from a department receive the same treatment). What is the randomized controlled trial (RCT) design?

**CORRECT ANSWER:** B. Cluster RCT

In cluster RCTs, groups (clusters) of patients are randomized and allocated to one topical treatment. For example, Madan et al. (2019) performed a cluster RCT to evaluate the efficacy of a behavior change package, including regular use of moisturizing cream to prevent hand dermatitis in nurses working in healthcare. In this trial, hospitals were clusters, and nurses constituted the assessment units within clusters.

2. In a within-person RCT, what are the correct answers?

**CORRECT ANSWER:** B. The unit of randomization is the lesion; D. The unit of assessment is the lesion.

In a within-person RCT, the lesions or body sites but not the patient are randomized, and these randomization units are further assessed.

3. The carry-across effect depends on

**CORRECT ANSWER:** D. All of the above

The carry-across effect depends on numerous variables, including the molecular weight of the drug and its afterglow in the dermis (depends on systemic passage of the drug), the drug properties (anti-inflammatory properties can have local extension), and the skin where the drug is applied (more systemic passage with wide area of application or severe alteration of the cutaneous barrier).

4. When should a within-person RCT be avoided?

**CORRECT ANSWER:** B. If the relevant primary outcome is QOL

Patient-reported outcomes such as QOL cannot be assessed in a within-person RCT because the patient receives both topical drugs simultaneously. For pathologies with facial involvement (acne for example), a within-person RCT could be used, although the investigator should keep in mind that aesthetic consequences are possible and could cause inconvenience to the patient.

5. In which dermatological condition should a within-person RCT not be used?

**CORRECT ANSWER:** B. Acral melanoma

A within-person design could be chosen for acne vulgaris (split-face design), and for plaque of vitiligo (several lesions can be randomized and included in different groups of treatment). Surgery is the recommended treatment of acral melanoma and not topical treatments.