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ASPECTS MÉTHOLOGIQUES ET STATISTIQUES DES « WITHIN-PERSON RANDOMISED TRIALS » ÉVALUANT UN TRAITEMENT TOPIQUE EN DERMATOLOGIE

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Résumé

Lors de l'évaluation d'un traitement topique en dermatologie, on peut recourir à un « within-person design ». Les unités de randomisation ne sont alors pas les patients mais les lésions (ou régions anatomiques), et les traitements à comparer sont appliqués de façon concomitante sur les différentes lésions. Ce schéma d'étude réduit la variabilité inter-observations, et donc le nombre de patients à inclure dans l'essai. Cependant il présente des contraintes méthodologiques majeures, notamment la nécessité de s'assurer qu'il n'y a pas de risque de contamination intergroupe (« carry across effect »). L'objectif de cette thèse était d'étudier les aspects méthodologiques et statistiques des « within-person trials ». La 1ère partie de ce travail présente une synthèse des aspects méthodologiques à considérer lorsqu'on envisage ce type de schéma d'étude. Cette synthèse a été réalisée par un groupe de travail comportant des dermatologues et biostatisticiens. Dans la 2ème partie, nous avons réalisé une revue méthodologique des « within-person trials » publiés entre 2017 et 2021. Les aspects méthodologiques identifiés dans le 1er travail ont été recueillis et discutés dans cette revue. Le 3ème travail portait sur les méthodes d'analyse potentielles pour ce type d'essai. A l'aide d'une étude de simulation de Monte-Carlo, nous avons comparé les propriétés statistiques de plusieurs méthodes d'analyse (modèles mixtes et *generalized estimating equations*). Enfin, à titre d'illustration, la 4ème partie présente un protocole de « within-person trial » visant à évaluer le sirolimus topique dans les malformations lymphatiques superficielles. Le schéma d'étude en « within-person » présente de multiples spécificités à la fois méthodologiques et statistiques qui doivent être pris en compte lors de la planification et de l'analyse de l'étude. Les dermatologues et méthodologistes doivent également tenir compte de l'acceptabilité du patient.

Mots-clés : essai en comparaison intra-individuelle, *within-person design*, administration par voie topique, essai contrôlé randomisé, traitement topique, dermatologie, méthodologie, étude de simulation, modèles mixtes, *generalized estimation equations*

Abstract

To assess a topical treatment in dermatology, we may use a within-person (also called split-body) design. Randomization units are no longer patients but rather lesions or body sites. Experimental and control treatments are then applied simultaneously on the different lesions. This study design reduces the inter-observation variability, and therefore the number of patients to be included in the trial. However, this study design presents methodological constraints, notably a risk of intergroup contamination, named the "carry across effect". The objective of this PhD thesis was to study the methodological and statistical aspects of within-person randomized clinical trials. The first part of this work presents a synthesis of the methodological aspects to be considered when using this design. This work was conducted by a group associating dermatologists and biostatisticians. In the second part, we performed a methodological review of within-person randomized trials published between 2017 and 2021. The methodological aspects identified in the first work were assessed and discussed in this review. The third work focused on the statistical analysis. Using a Monte-Carlo simulation study, we compared the statistical properties of several analysis methods (mixed models and generalized estimating equations). Finally, as an illustration, the last part presents a within-person randomized trial protocol for evaluating topical sirolimus in superficial lymphatic malformations. The within-person design has multiple methodological and statistical specificities that must be taken into account when planning and analyzing the study. Dermatologists and methodologists must also consider patient acceptability.

Keywords: within-person, topical treatment, randomized clinical trial, local treatment, dermatology, methodology, simulation study, mixed models, generalized estimation equations

Productions scientifiques liées à la thèse

Articles publiés dans des revues internationales à comité de lecture

1. **Leducq S**, Caille A, Barbarot S, Bénéton N, Bessis D, Boccara O, Bursztejn AC, Chiaverini C, Dompmartin A, Droitcourt C, Gissot V, Goga D, Guibaud L, Herbreteau D, Le Touze A, Léauté-Labrèze C, Lorette G, Mallet S, Martin L, Mazereeuw-Hautier J, Phan A, Plantin P, Quéré I, Vabres P, Bourgoin H, Giraudeau B, Maruani A; Groupe de Recherche de la Société Française de Dermatologie Pédiatrique. Topical sirolimus 0.1% for treating cutaneous microcystic lymphatic malformations in children and adults (TOPICAL): protocol for a multicenter phase 2, within-person, randomized, double-blind, vehicle-controlled clinical trial. *Trials*. 2019;20:739.
2. **Leducq S**, Caille A, Le Cleach L, Samimi M, Tavernier E, Maruani A, Giraudeau B. Research Techniques Made Simple: Randomized controlled trials for topical drugs in dermatology: When and how should we use a within-person design? *J Invest Dermatol*. 2020;140:931-938.e1.
3. **Leducq S**, Dugard A, Allemang-Trivalle A, Giraudeau B, Maruani A. Design and methodological issues of within-person (split-body) randomized controlled trial evaluating a topical treatment: A systematic review. Soumis
4. **Leducq S**, Taljaard M, Passeron T, Fontas E, Maruani A, Giraudeau B. Comparison of statistical methods to analyze a within-person randomized trial evaluating a topical drug with a binary outcome: a simulation study. Soumis

Présentations orales à des congrès

1. **Leducq S**, Maruani A, Samimi M, Tavernier E, Passeron T, Fontas E, Le Cleach L, Caille A, Giraudeau B. Design issues when assessing a topical pharmacological treatment in dermatology. EPICLIN 27èmes Journées des statisticiens des CLCC (2020). Résumé dans *Revue d'Épidémiologie et de Santé Publique* 2020;68:S111-S112.

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1. **Leducq S**, Maruani A, Samimi M, Tavernier E, Passeron T, Fontas E, Le Cleach L, Caille A, Giraudeau B. Design issues when assessing a topical pharmacological treatment in dermatology. Journée de la Recherche Biomédicale des facultés d'Angers et Tours (Tours, 2019).
2. **Leducq S**, Maruani A, Samimi M, Tavernier E, Passeron T, Fontas E, Le Cleach L, Caille A, Giraudeau B. Design issues when assessing a topical pharmacological treatment in dermatology. Current developments in cluster randomised trials and stepped wedge designs (Londres, Angleterre, 2019).

Autres travaux scientifiques menés au cours de la thèse

1. Allemang-Trivalle A, **Leducq S**, Maruani A, Giraudeau B. Designs used in published therapeutic studies of rare superficial vascular anomalies: A systematic review. En cours de révision.

Environnement de la thèse

Cette thèse a été réalisée au sein de l'unité de recherche INSERM U1246 SPHERE (« methodS in Patient-centered issues & Health ResEarch ») des Universités de Nantes et Tours. Il s'agit d'une unité de recherche bi-site, créée en 2017 et co-dirigée par le Pr Véronique Sébille (Université de Nantes) et le Pr Bruno Giraudeau (Université de Tours). C'est une unité pluridisciplinaire composée de cliniciens, universitaires ou non (néphrologues, réanimateurs, dermatologues, psychiatres, etc) et d'enseignants-chercheurs non cliniciens (méthodologistes, biostatisticiens, économistes de la santé, etc) dont les objectifs sont le développement de méthodes pour la recherche en santé centrée sur le patient dans une perspective pluridisciplinaire impliquant la biostatistique, la santé publique et les disciplines cliniques.
J'ai été co-encadrée, pendant mon master 2 réalisé au sein de l'unité SPHERE en 2018 puis au cours de mes 3 années de thèse de 2019 à 2022, par le Pr Annabel Maruani, PU-PH de Dermatologie et membre de l'unité SPHERE, et par le Pr Bruno Giraudeau, méthodologiste et biostatisticien. Le travail de thèse a été réalisé pendant ces 3 années en parallèle de mon activité clinique (Chef de Clinique - Assistante des Hôpitaux de Tours, au sein du service de Dermatologie, dirigé par le Pr Laurent Machet) avec une activité de consultation dans le centre de référence des malformations vasculaires (centre MAGEC, Maladies rares de la peau et des muqueuses d'origine génétique, site constitutif Tours, coordonné par le Pr Annabel Maruani).

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Glossaire des abréviations

CONSORT	*Consolidated Standards of Reporting Trials*
CCI	Coefficient de Corrélation Intraclasse
DALY	*Disability-Adjusted Life Year*
DLQI	*Dermatology Life of Quality Index*
ECR	Essai Contrôlé Randomisé
GEE	*Generalized Estimating Equations*
MAGEC	Maladies rares de la peau et des muqueuses d'origine génétique
MCLM	Malformation cutanée lymphatique microkystique
mTOR	*mammalian Target Of Rapamycin*
PASI	*Psoriasis Area Severity Index*
PGA	*Physician Global Assessment*
PHRC	Programme Hospitalier de Recherche Clinique
SPHERE	*methodS in Patient-centered issues & Health ResEarch*
SPIRIT	*Standard Protocol Items Recommendations for Interventional Trials*
YLDs	*Years Lived with Disability*
YLLs	*Years of Life Lost*

I- Introduction

1. Les pathologies dermatologiques

1.1.Physiologie et épidémiologie

- *La peau : plus grand organe de l'être humain*

La peau est le plus grand organe de l'homme, en contact avec le milieu extérieur (surface de $2m^2$). Elle est organisée en 4 couches : l'épiderme (épithélium stratifié), surplombée par une couche cornée (*stratum corneum*), la jonction dermo-épidermique, le derme (tissu conjonctif) et l'hypoderme (tissu graisseux) (Figure 1). A la peau, sont annexées les phanères (follicules pileux et ongles) et les glandes cutanées (Arda, 2014).

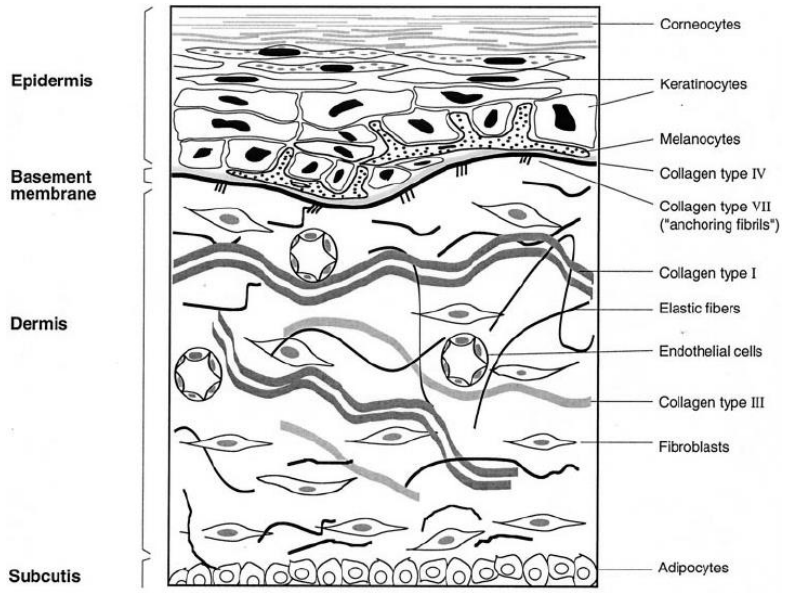


Figure 1 : Représentation schématisée des 4 couches de la peau (issue de Scharffetter-Kochanek et al, 2000)

Les fonctions de la peau sont multiples (Dréno, 2009) :

- protection contre les agressions extérieures et agents infectieux ;
- régulation thermique : la peau assure un effet barrière en permettant la régulation des échanges thermiques et le maintien de la température corporelle ;
- perception : la peau est le siège de différents types de terminaisons nerveuses et de récepteurs ;

- participation au système immunitaire : la peau est constituée principalement par des cellules présentatrices d'antigène ;
- et synthèse de la vitamine D.

En cas de maladies dermatologiques étendues, ces différentes fonctions peuvent être altérées.

- *Les pathologiques dermatologiques : une cause fréquente de morbidité*

Les maladies de la peau sont fréquentes chez les adultes et les enfants, avec une prévalence globale estimée entre 27 % et 55 % (Lim, 2017 ; Schofield, 2009). La classification internationale des maladies (11ème version, CIM-11), publiée par l'Organisation Mondiale de la Santé en 2019 recense plus de 2000 pathologiques dermatologiques (World Health Organization, 2021). Les pathologies les plus fréquentes en 2010 sont les infections fongiques (en 4ème position) et l'acné vulgaire (en 8ème position). L'impétigo, eczéma, prurit et gale sont également fréquents (Hay, 2014).

Le coût direct associé aux soins pour les maladies dermatologiques a été estimé à 75 milliards de dollars aux États-Unis et le coût indirect à 11 milliards de dollars (Lim, 2017). Les coûts sont comparables ou supérieurs à ceux d'autres maladies, telles que les maladies cardiovasculaires et le diabète (Lim, 2017).

Les symptômes liés aux dermatoses sont multiples (prurit, douleurs, etc) et constituent une des principales causes de morbidité. Du fait du caractère affichant des dermatoses, un impact important sur la qualité de vie est fréquent (Harlow, 2000). Le fardeau lié aux dermatoses peut être mesuré à l'aide du DALY (« Disability-Adjusted Life Year ») qui correspond à la somme des années de vie perdues en lien avec une maladie (YLLs, « Years of Life Lost ») et les années vécues avec handicap (YLDs, « Years Lived With Disability ») (Murray, 1994). Une « DALY » équivaut donc à une année de vie en bonne santé perdue. Les pathologies dermatologiques ont été responsables en 2013 de 41,6 millions de « DALY » (Karimkhani, 2013). Elles sont responsables de la 18ème cause de « DALY » dans le monde. A titre de comparaison, la tuberculose est responsable de 49,8 millions de « DALY » et la 1ère cause de « DALY » correspond aux maladies coronariennes (150,2 millions de « DALY »). Lorsqu'on considère uniquement les « YLDs », les pathologiques dermatologiques sont responsables de 36,4 millions de « YLDs » et sont plus importantes que les « YLDs » secondaires au diabète (29,5 millions) (Karimkhani, 2013).

1.2.Sémiologie

- *Différents types de dermatoses*

Les pathologies dermatologiques regroupent de nombreux domaines de maladies, telles que les infections, les cancers, les maladies auto-immunes, les maladies inflammatoires ou les génodermatoses. Les maladies dermatologiques peuvent être aiguës ou chroniques, rares ou au contraire très fréquentes, et peuvent affecter tous les âges de la vie. Parmi les maladies cutanées aiguës, les infections sont les plus fréquentes, par exemple la gale ou les infections cutanées virales, bactériennes ou fongiques. Les dermatoses chroniques les plus fréquentes sont l'eczéma, l'acné, le psoriasis, mais aussi les ulcères de jambe et les cancers cutanés chez le sujet adulte (Karimkhani, 2013).

- *Présentation clinique variée*

Le type de lésions et leur extension sur la surface corporelle sont très hétérogènes selon la maladie dermatologique.

Les maladies dermatologiques peuvent se présenter sous la forme :

- d'une lésion unique : par exemple, les cancers de la peau, les tumeurs ou anomalies vasculaires.

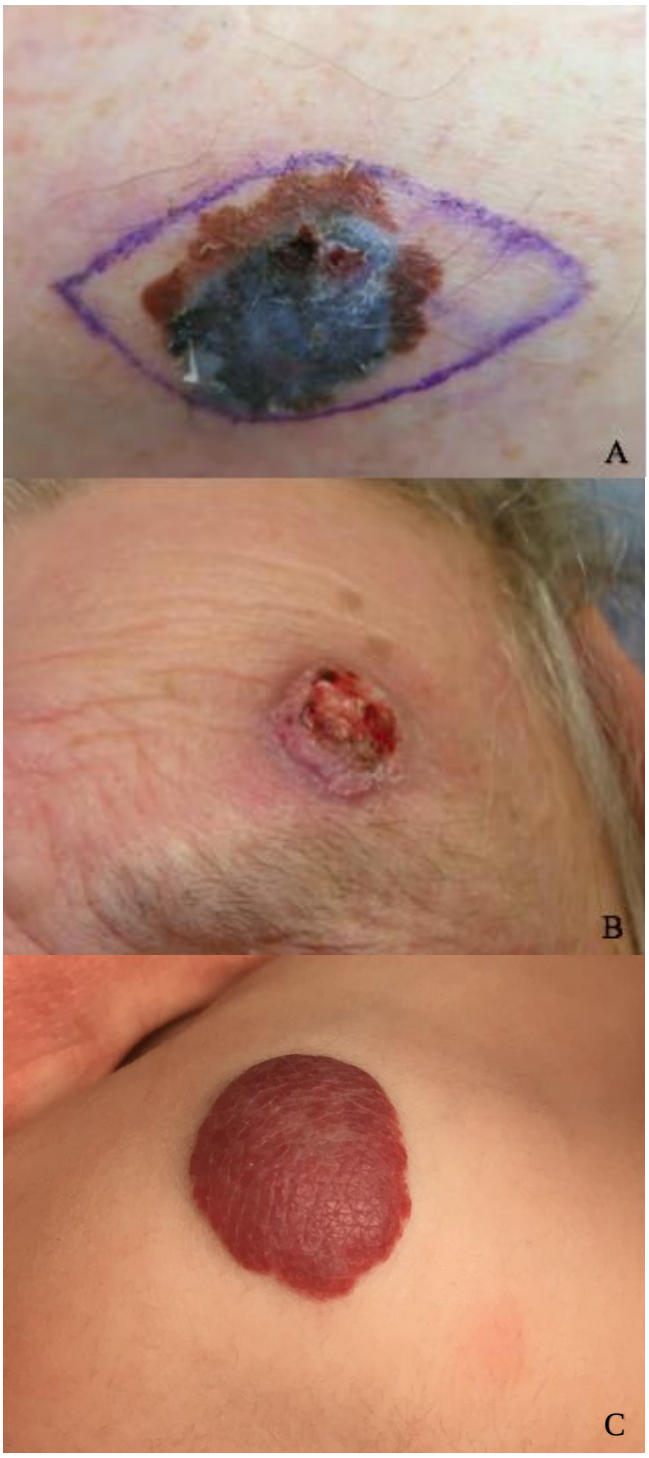


Figure 2 : Pathologies dermatologiques se présentant sous la forme d'une lésion unique, (A) mélanome, (B) carcinome épidermoïde, (C) tumeur vasculaire bénigne : hémangiome infantile

- de lésions multiples individualisables et dénombrables : par exemple, l'eczéma, le vitiligo et la pelade.



Figure 3 : Pathologies dermatologiques se présentant sous la forme de lésions multiples dénombrables, (A) eczéma (dermatite atopique), (B) vitiligo, (C) pelade en plaque

- ou de lésions diffuses multiples : par exemple, les infections virales, le psoriasis en goutte et les toxidermies.

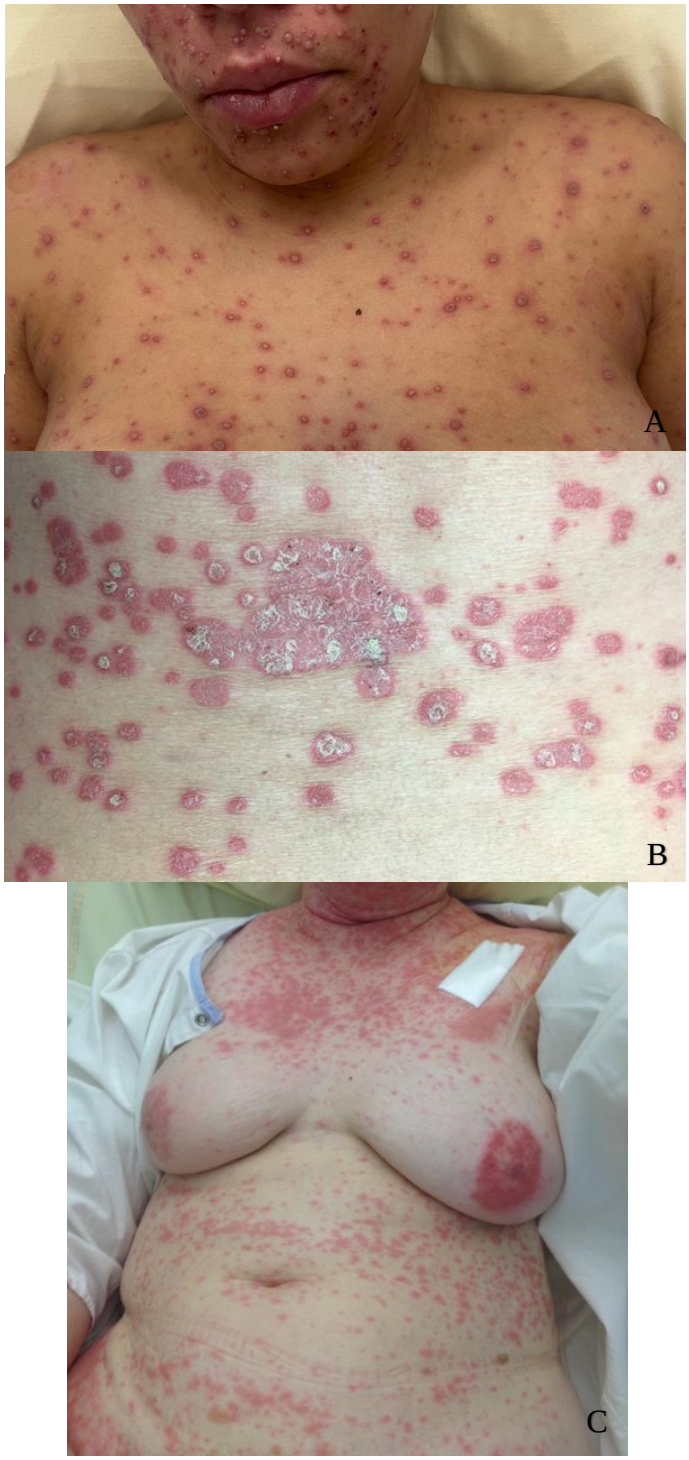


Figure 4 : Pathologies dermatologiques se manifestant par des lésions diffuses multiples, (A) varicelle, (B) psoriasis en goutte, (C) toxidermie de type exanthème maculo-papuleux

Selon la pathologie dermatologique, la prise en charge peut varier et se faire par une chirurgie, par un traitement physique (lasers, photothérapie dynamique…), ou par des médicaments par voie systémique (orale ou parentérale) ou par voie topique (locale).

2. Les traitements topiques

2.1. Les traitements topiques : axe thérapeutique majeur en dermatologie

Les médicaments topiques sont très courants en dermatologie et sont souvent utilisés comme traitements de première intention. Ils ont une action locale immédiate sur les lésions cutanées et permettent de limiter le risque de toxicité systémique du médicament (Maruani, 2015). Les pathologies dermatologiques avec une atteinte cutanée limitée et/ou une atteinte superficielle de la peau sont les indications principales. Dans une étude transversale de 2008 à 2010 aux USA, les traitements topiques constituaient 75% des prescriptions dans l'acné et la rosacée, par exemple (Zhang, 2017).

Le coût actuel des traitements topiques est évalué à 92,4 milliards de dollars américains en 2020 avec un coût estimé d'ici 2027 de 129,9 milliards de dollars américains (Global Topical Drug Delivery Industry, 2021).

Tous les médicaments ne peuvent pas être administrés par voie topique. Le principe actif, véhiculé par un excipient, mis au contact de la peau, doit pouvoir pénétrer à travers la couche cornée et exercer un effet pharmacologique suffisant. Actuellement, plus d'une centaine de traitements topiques sont recensés avec différentes galéniques (Agence Nationale de Santé et du Médicament).

2.2. Différents types de traitement topiques

Les traitements topiques comprennent les médicaments pharmacologiques topiques (corticoïdes, antibiotiques, antifongiques…), les émollients (utilisés pour maintenir l'hydratation et la douceur de la peau) et les dispositifs médicaux topiques (pansements).

Il existe différentes présentations dans les traitements topiques appelées galéniques : lotion, solution, crème, pommade, gel, poudre, pâte et talc. Le choix de la galénique se fera en fonction

de la disponibilité des galéniques, de la localisation des lésions, du type de lésions et de la préférence du patient.

L'administration par voie topique sur la peau n'est pas utilisée uniquement pour les maladies dermatologiques. Certains médicaments sont formulés de façon à avoir un passage transdermique qui évite notamment une dégradation importante lors du passage hépatique, ou peuvent permettre une administration prolongée du traitement, et dont le but est un effet systémique. Ces systèmes transdermiques, se présentant comme des patchs, concernent notamment les traitements pour la prévention de l'angor (nitroglycérine), les traitements hormonaux substitutifs, les traitements antalgiques (fentanyl par exemple) et les traitements anticholinergiques (scopolamine).

2.3.Absorption per cutanée

L'absorption percutanée d'une substance appliquée sur la peau correspond à son transport depuis la surface cutanée jusqu'aux vaisseaux dermiques. Le traitement topique est appliqué et va diffuser dans la couche cornée permettant une libération du traitement. L'absorption se fera avec la diffusion dans l'épiderme et le derme ; et enfin, une résorption et distribution par les capillaires dermiques (Figure 5) (Vaillant, 1995 ; de Monte, 2015).
La pénétration du principe actif véhiculé par un excipient se fait par deux voies simultanées : la voie trans-épidermique, à travers les cellules de la couche cornée et les espaces intercellullaires de la couche cornée ; et par la voie empruntant les annexes cutanées, à travers les follicules pilosébacés et glandes sudoripares (Schmieder, 2015).

Une des particularités de l'absorption percutanée est son effet de réservoir ; en effet, les composés du traitement actif peuvent s'accumuler dans la couche cornée qui libère au fur et à mesure les substances vers les couches profondes. Il n'est pas nécessaire de réaliser des applications itératives des traitements topiques.

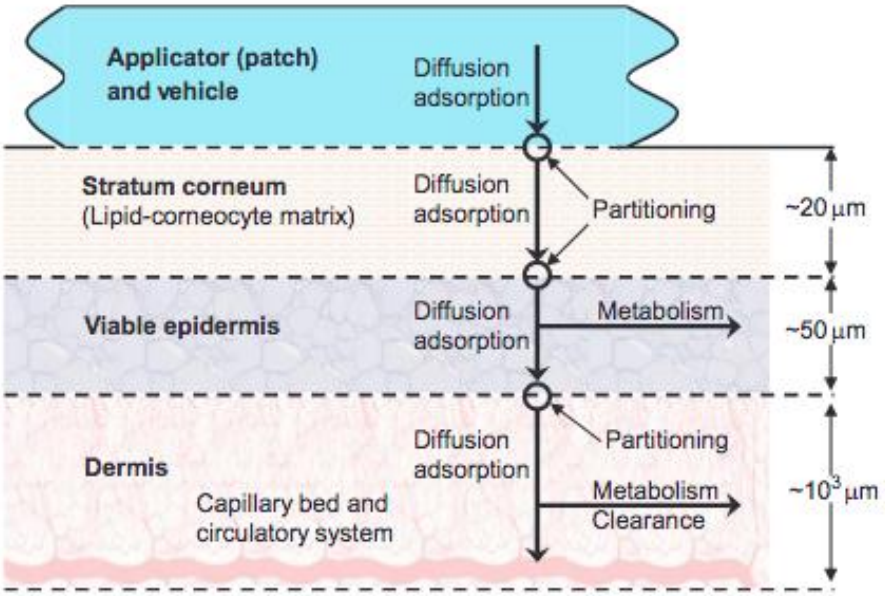


Figure 5 : Représentation schématisée illustrant les étapes intervenant lors de l'absorption cutanée (issue de de Monte et al, 2015)

L'absorption percutanée est conditionnée par le principe actif, mais également par la nature des excipients. Le rôle du véhicule est donc essentiel car la substance active seule ne pourra pas diffuser dans la couche cornée.

La diffusion du produit est définie par la loi de diffusion passive de Fick (Jain, 2008) :

$$J = K_p \times \Delta C \quad (1)$$

avec J : quantité qui diffuse par unité de surface et de temps (flux percutané)

K_p : coefficient de perméabilité (Kp) lié aux caractéristiques physico-chimiques du principe actif

ΔC : concentration du principe actif dans son véhicule.

L'absorption du principe actif dépend donc de son poids moléculaire. Pour l'administration des traitements par voie topique, le poids moléculaire doit être inférieur à 500 Dalton pour permettre l'absorption percutanée (Bos, 2000). A titre d'exemple, le propionate de clobétasol a un poids moléculaire de 467 Dalton et le poids moléculaire de la trétinoïne est de 300 Dalton (PubChem, 2022 ; PubChem, 2022).

2.4.Facteurs modifiant l'absorption percutanée

Il existe de multiples facteurs pouvant faire varier l'absorption percutanée des traitements topiques :

- l'administration du traitement topique doit tenir compte de l'âge : chez les nourrissons par exemple, l'absorption cutanée est modifiée par la surface cutanée/poids, la localisation de certaines dermatoses, la toxicité de certains produits et l'immaturité de la couche cornée chez les prématurés (Amoric, 2000). Le vieillissement cutané modifie également l'absorption percutanée ;
- l'absorption va varier selon le site : la pénétration du produit sera le plus faible au niveau des lésions situées sur les zones palmoplantaires et l'absorption sera maximale au niveau des lésions sur le scrotum chez un homme (Wester, 1999). Cette variation d'absorption est expliquée par la composition de la couche cornée et la densité des annexes (follicules pileux et glandes sébacées) ;
- le mode d'administration : dans certaines dermatoses, une administration sous occlusif peut être proposée pour augmenter l'absorption percutanée, en particulier dans les dermatoses à localisation palmo-plantaire (Zhai, 2001) ;
- l'altération de la barrière cutanée est également un facteur modifiant l'absorption percutanée. En effet, en cas de peau lésée (par exemple, érosion ou ulcération), compliquant la pathologie dermatologique ou secondaire à un traumatisme externe, l'absorption du traitement topique appliqué sur la lésion est augmentée, du fait de l'altération de l'épiderme ne jouant plus son rôle de barrière (Kezic, 2009) ;
- le rythme et la durée d'application ;
- la température cutanée : lors de l'augmentation de la température cutanée, par exemple lors d'un effort physique, l'augmentation de l'absorption est observée (Danon, 1986) ;
- les promoteurs chimiques dont le but est d'accroitre l'absorption cutanée (solvants, surfactants kératolytiques) (Vaillant, 1997) ;
- les promoteurs physiques tels que la ionophorèse, l'électroporation et la sonophorèse (ultrasons de haute et basse fréquence appliqués sur la peau (Maruani, 2010).

Certains moyens ont été étudiés pour augmenter le passage transcutané de substances par voie topique, telles que l'occlusion, la ionophorèse ou la sonophorèse (Machet, 1996, Maruani, 2010).

Pour les traitements par voie orale, la posologie du traitement est précisée et est exprimé en dose poids. Pour les traitements topiques, il est important également de préciser la posologie à appliquer pour éviter des effets secondaires liés à une application trop importante ou au contraire, à une « sous-utilisation » du traitement pouvant entrainer un échec. Pour cela, l'unité phalangette (« fingertip unit ») peut être utilisée (Long, 1991). Cette unité de mesure est largement utilisée en dermatologie. Une unité phalangette correspond à 20-25 mm de crème déposée sur la dernière phalange d'un adulte. Une unité phalangette équivaut à 0,5 g de crème et est suffisante pour traiter les deux paumes (incluant les doigts) de la main d'un adulte. Le nombre d'unités phalangettes est donc précisé aux patients/parents et est adapté à la surface cutanée à traiter (Figure 6).

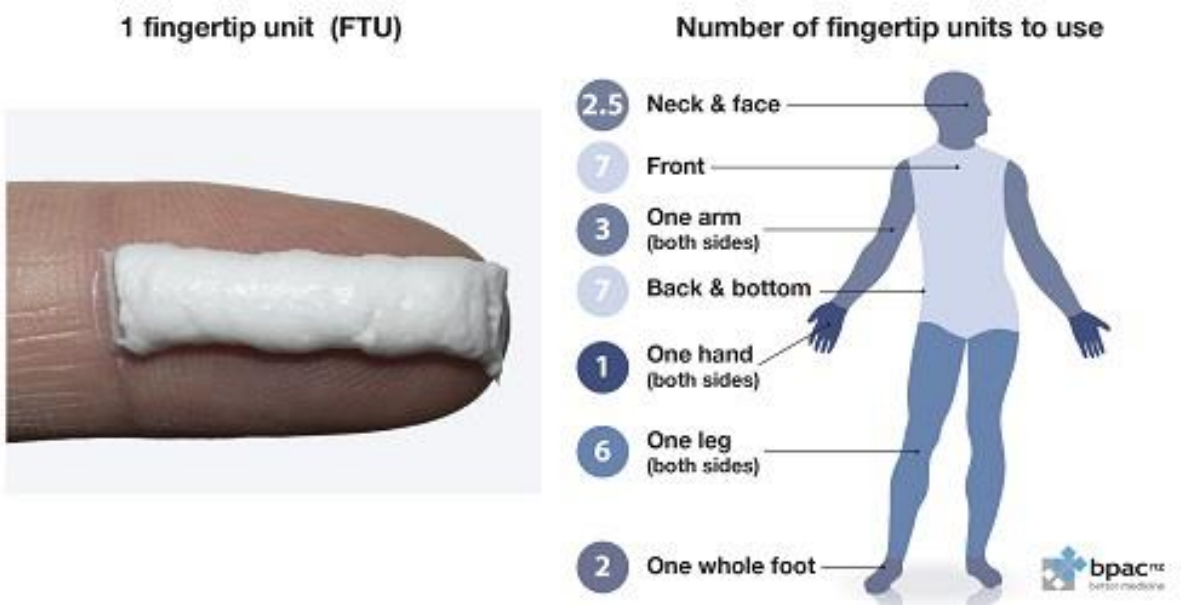


Figure 6 : L'unité phalangette et le nombre d'unités phalangettes à utiliser en fonction de la surface cutanée (illustration issue de New Zealand Formulary Patient Information, disponible sur https://www.mymedicines.nz/home/Sheet/zGBkEHsAbk0%3D)

En plus de la posologie de traitement à appliquer, certaines précautions sont nécessaires et spécifiques aux traitements topiques et sont fournies au patient lors de la prescription. Par exemple, l'application du traitement topique est réalisée à distance des bains ou douches, le lavage pouvant entrainer une diminution de l'absorption car le produit est enlevé.

3. L'évaluation des traitements topiques en dermatologie

Pour évaluer, en recherche clinique, des traitements appliqués localement sur les maladies dermatologiques, différents schémas d'études sont possibles et vont dépendre de la pathologie (nombre de lésions, caractère aigu ou chronique) et du traitement expérimental.

3.1.Les schémas d'études classiques

- *Essai contrôlé randomisé (ECR) classique en groupes parallèles*

Dans l'ECR en groupes parallèles, deux ou plusieurs groupes recevant les différentes modalités, sont comparés. Les unités de randomisation sont les patients et l'évaluation est réalisée au niveau du patient. Cela signifie que pour chaque patient une seule lésion n'est considérée. Si plusieurs lésions doivent être considérées, on parle alors d'essai randomisé avec « clustering » (cf infra). Le patient reçoit le traitement expérimental ou le traitement contrôle qui est appliqué sur la lésion (Seneschal, 2021). Le critère de jugement peut être mesuré au niveau du patient (par exemple la qualité de vie en utilisant l'échelle *Dermatology Life of Quality Index* [DLQI]) (Finlay, 1994), ou au niveau de la lésion (par exemple, en utilisant le score *Physician Global Assessment* [PGA]) (Garduno, 2007).

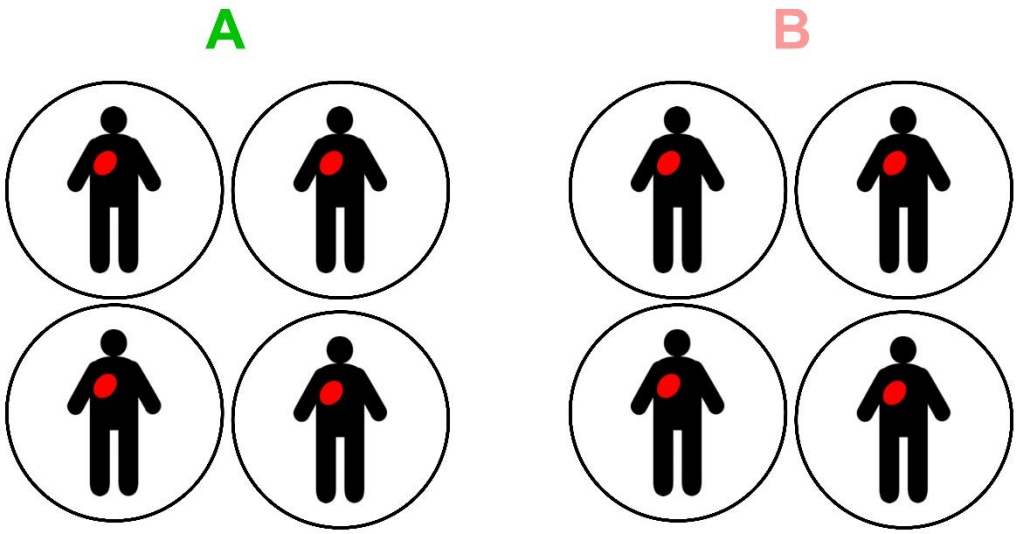


Figure 7 : Représentation schématisée d'un ECR classique en groupes parallèles

- *ECR en comparaison intra-individuelle : essai en cross-over*

Dans l'ECR en cross-over, deux ou plusieurs groupes recevant les différentes modalités, sont comparés et le traitement expérimental et contrôle sont administrés de façon séquentielle et dans un ordre aléatoire chez tous les patients (Jones, 2003). Ce schéma permet une comparaison intra-individuelle. Il peut être utilisé dans l'évaluation des traitements topiques en dermatologie, mais s'appliquera uniquement aux pathologies chroniques avec poussées régulières (par exemple, la dermatite atopique) (Hon et al).

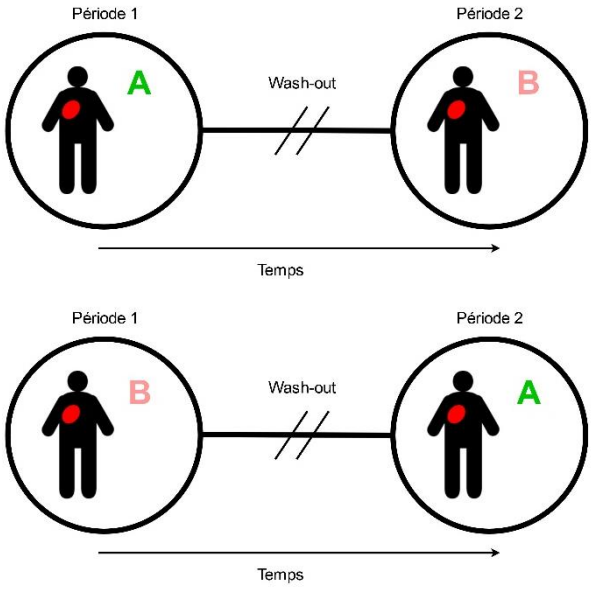


Figure 8 : Représentation schématisée d'un ECR en cross-over

- *ECR en cluster*

Dans l'ECR en cluster, l'attribution des traitements se fait au niveau du cluster et non des patients. Ainsi, un groupe de patients reçoit l'ensemble du traitement auquel il a été alloué. L'évaluation est faite au niveau individuel (du patient) ou au niveau du cluster (Caille, 2014). Dans les traitements topiques en dermatologie, il peut s'agir d'un essai randomisé évaluant un traitement anti-parasitaire topique dans le traitement de la pédiculose. Le cluster est alors la famille, chaque membre de la famille recevant le traitement expérimental ou le traitement contrôle (Chosidow, 2010).

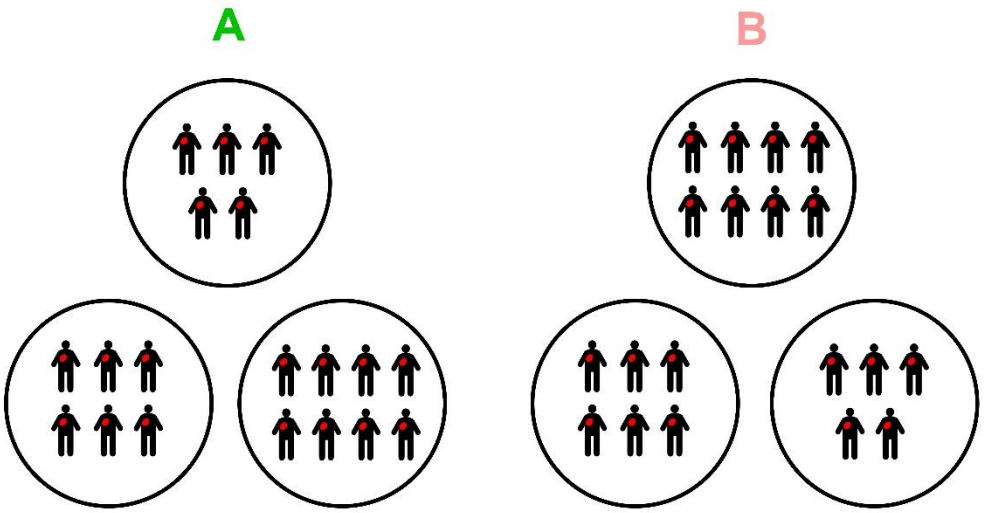


Figure 9 : Représentation schématisée d'un ECR en cluster

3.2.Les schémas d'étude spécifiques liées aux dermatoses

La multiplicité des lésions dans les pathologies dermatologiques permet d'envisager d'autres schémas d'étude.

- *ECR en groupes parallèles avec « clustering »*

Dans l'ECR en groupes parallèles avec « clustering », deux ou plusieurs groupes recevant les différentes modalités, sont comparés et chaque patient peut contribuer à hauteur d'une ou plusieurs lésions. Le critère de jugement ne sera alors pas évalué au niveau du patient, mais au niveau de la lésion. S'il existe plusieurs lésions chez un même patient qui ont été inclues et traitées par le traitement (expérimental ou contrôle), alors ces différentes lésions correspondent à des unités d'analyse distinctes. Ainsi, si un patient présente 4 lésions traitées par le groupe expérimental, alors l'évaluation sera faite au niveau de chacune des lésions, fournissant ainsi 4 observations. Ceci permet d'augmenter le nombre d'observations et donc la puissance de l'étude (Cavalié, 2015).

L'analyse de ce type d'étude doit cependant tenir compte de la corrélation qui existe entre les lésions. En effet, les observations ne sont pas indépendantes : les lésions issues d'un même patient et traitées par le même traitement (expérimental ou contrôle) ont des réponses corrélées.

Cette corrélation est illustrée sur la Figure 10. L'essai, en termes de structures de données, s'apparente alors à un essai en cluster : le patient est le cluster, et les lésions sont les unités au sein du cluster. Cette corrélation correspond au coefficient de corrélation intraclasse (CCI), est notée ρ et elle quantifie le degré de similitude entre les réponses observées sur les différentes lésions d'un même patient.

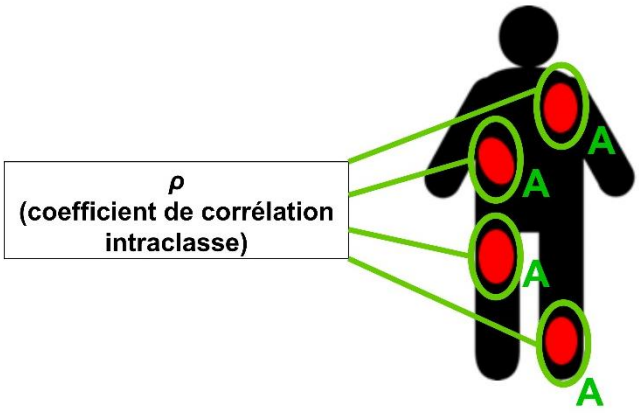


Figure 10 : Représentation schématisée d'un patient (cluster) avec plusieurs lésions cutanées (observations) toutes traitées par le traitement A. La corrélation entre les réponses observées sur les différentes lésions est définie par ρ.

Le CCI admet une définition duale. Il peut être défini comme la corrélation entre les réponses observées sur deux lésions d'un même patient, quelles que soient les lésions, et quel que soit le patient. Il peut également être défini comme la proportion de la variance totale liée à la variabilité inter-clusters (Eldridge, 2012) :

$$\rho = \frac{\sigma_b^2}{(\sigma_b^2 + \sigma_w^2)} \qquad (2)$$

avec σ_b^2 la variance inter-cluster

σ_w^2 la variance intra-cluster

Le CCI varie donc entre 0 et 1. S'il est égal à 1 (situation théorique), cela signifie que toutes les observations d'un même cluster sont identiques. Dans notre cas, cela signifierait que les réponses au traitement de toutes les lésions d'un sujet sont toujours identiques. Si le CCI est égal à 0, cela signifie qu'il y a indépendance entre les observations d'un même cluster. Dans notre cas, cela signifierait qu'il n'y aurait pas plus de similitude de réponse entre deux lésions d'un même patient qu'entre deux lésions de deux patients distincts. Disposer d'une estimation

du CCI est nécessaire pour le calcul d'effectif. Cette estimation peut être obtenue à partir de publications antérieures, bien que peu d'ECR en cluster rapportent les valeurs de CCI (Adams, 2004). Dans un essai randomisé en cluster, les valeurs classiques de CCI sont bien souvent de l'ordre de 1 à 5.10^{-2} Dans le contexte spécifique du traitement topique, on s'attend à ce que les valeurs de CCI soient plus élevées car deux lésions (= observations) chez un même patient (= cluster) sont sûrement plus similaires que deux personnes appartenant à une unité sociale commune.

Les méthodes d'analyse des essais en groupes parallèles avec « clustering » sont donc les mêmes que pour les essais en cluster. Elles peuvent se faire au niveau du cluster (observations résumées pour chaque cluster) ou au niveau de la lésion.

- *ECR en comparaison intra individuelle : « within-person »*

Les essais contrôlés randomisés en comparaison intra-individuelle en « within-person », également appelés en « split-body », sont utilisés en dermatologie mais également dans d'autres spécialités : en ophtalmologie (deux yeux), orthopédie (deux membres) et dentisterie principalement (Lee, 2012 ; Pfannensteil, 2022 ; Bryant, 2006). Dans ce type d'essai, le traitement contrôle et expérimental est administré au patient de façon concomitante (à la différence du cross-over où ce sont deux périodes de traitement successives avec le traitement expérimental ou le traitement contrôle). Ainsi, en dermatologie, on peut considérer et randomiser deux lésions ou sites anatomiques. Pour chaque patient, le traitement expérimental est administré sur une lésion et le traitement contrôle sur l'autre lésion. Le patient est donc son propre contrôle. Il est possible également d'inclure plus de deux lésions par patient : une partie des lésions est allouée au groupe expérimental et l'autre partie au groupe contrôle. En augmentant le nombre de lésions on augmentera la puissance de l'essai.

La corrélation entre les lésions est à prendre en compte pour le calcul d'effectif et l'analyse statistique. Dans le cas où 2 lésions par patient sont inclues, la taille de l'échantillon est équivalente à la taille de l'échantillon utilisée pour les groupes appariés (Machin, 2009). Dans le cas où plus de 2 lésions par patient sont inclues, il existe deux corrélations : une corrélation entre 2 lésions d'un patient allouées au même groupe de traitement (correspondant au CCI) et une corrélation entre deux lésions allouées à 2 groupes différents (ce qui correspond à la corrélation intergroupe dénotée η) (Figure 11). On s'attend à ce que cette dernière corrélation (entre les groupes) soit inférieure aux corrélations intra-groupe (définies par les corrélations intraclasses).

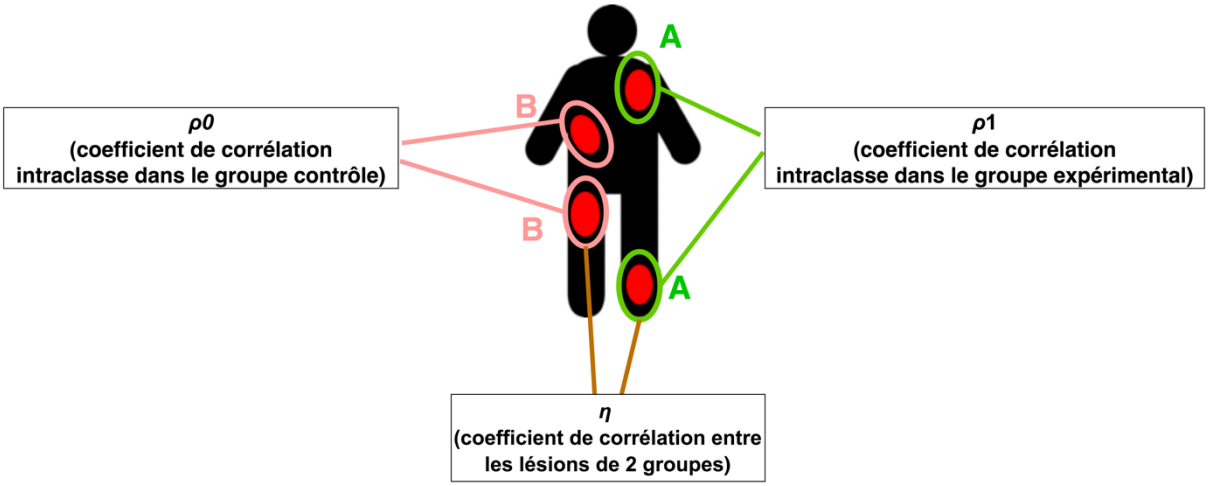


Figure 11 : Représentation schématisée d'un patient avec plusieurs lésions cutanées (observations), certaines traitées par le traitement A et d'autres par le traitement B. La corrélation des lésions traitées par le traitement A est définie par ρ_0 et la corrélation des lésions traitées par le traitement B, ρ_1. La corrélation entre les lésions des deux groupes est définie par η.

L'utilisation d'un schéma en « within-person » en dermatologie pour l'évaluation d'un traitement topique comporte donc des aspects méthodologiques et statistiques particuliers liés aux spécificités du traitement topique et aux corrélations, supposées élevées, entre les lésions d'un même patient.

4. Objectifs de la thèse

Les objectifs de ce travail de thèse ont été :

- d'une part, de développer les aspects méthodologiques propres au design en « within-person » évaluant un traitement topique en dermatologie et de réaliser une revue systématique méthodologique de la littérature des essais en dermatologie utilisant ce schéma d'étude afin de vérifier comment ces aspects méthodologiques identifiés et synthétisés avaient été appréhendés par les auteurs des essais.
- d'autre part, d'étudier les propriétés statistiques des modèles statistiques pouvant être utilisés pour l'analyse d'essais en « within-person » considérant plus de 2 lésions par patient.

Enfin, pour illustrer nos propos, nous fournirons l'exemple d'un essai en « within-person » pour l'évaluation du sirolimus topique dans les malformations vasculaires de type malformations lymphatiques microkystiques cutanées.

II- Travaux et résultats

1. Aspects méthodologiques des essais contrôlés randomisés pour les traitements topiques en dermatologie : spécificités du « within-person design »

1.1.Présentation du travail

Lors de l'évaluation d'un traitement topique en dermatologie, trois schémas d'étude peuvent être utilisés : un schéma d'étude classique en randomisation individuelle, un schéma d'étude avec du clustering (i.e., les patients sont randomisés, et pour chaque patient, un « cluster » de lésions sont traitées) et les schémas d'études permettant des comparaisons intra-individuelles comprenant les schémas en cross-over et les essais en « within-person » (également appelé « split-body »). Le schéma en « within-person » peut être utilisé pour comparer simultanément différents traitements chez un même patient. La randomisation ne concerne pas les patients mais les lésions ou régions anatomiques, et les traitements à comparer sont appliqués de façon concomitante sur les différentes lésions (ou régions anatomiques). Ce schéma d'étude réduit considérablement la variabilité inter-observations, et donc le nombre de patients à inclure dans l'essai (taille de l'échantillon). Cependant, ce schéma d'étude présente des contraintes méthodologiques majeures, notamment la nécessité de résoudre le problème d'une contamination intergroupe (« carry across effect »).

Nous avons constitué un groupe de travail comprenant sept dermatologues et statisticiens qui ont déjà participé à la planification, à l'analyse et à la rédaction d'ECR en dermatologie. En juillet 2019, ce groupe de travail s'est réuni durant une journée pour discuter des points méthodologiques spécifiques au « within-person design ». La liste des points méthodologique avait été établie à l'aide des recommandations CONSORT (*Consolidated Standards of Reporting Trials*) et SPIRIT (*Standard Protocol Items Recommendations for Interventional Trials*) (Schulz, 2010 ; Chan, 2013).

Premièrement, pour un essai contrôlé randomisé en « within-person », l'absence de passage systémique du traitement expérimental et l'absence de contact direct entre les 2 traitements évalués sont une condition nécessaire pour éviter une contamination intergroupes qui pourrait conduire à une sous-estimation de l'effet du traitement. Deuxièmement, appliquer simultanément les deux traitements chez un même patient peut compromettre l'observance du

patient et augmenter le risque de lever de l'aveugle. L'utilisation d'un « care-provider » (par exemple, application du traitement par une infirmière) permet de garantir la compliance du patient au traitement. De plus, les critères de jugement objectifs (par exemple, évaluation sur photographies) seront à privilégier. En effet, chaque patient recevant les traitements comparés de façon concomitante, il y a un risque de biais d'évaluation plus important encore que dans un essai classique, ce que seul le caractère objectif du critère de jugement peut contribuer à limiter. Par ailleurs, les essais contrôlés randomisés en « within-person » font que l'unité d'évaluation est la lésion ; dès lors, des critères de jugement globaux tels que la qualité de vie ne pourront pas être évalués. Enfin, l'analyse statistique d'un essai en « within-person » doit prendre en compte la corrélation entre les différentes lésions d'un même patient.

Le choix du schéma d'étude le plus adéquat lors de la planification d'un protocole doit tenir compte du type de maladie (nombre de lésions), de la prévalence de la maladie, du critère de jugement principal, du risque de contamination intergroupe et de l'acceptabilité du patient. Il n'y a pas de règle unique à suivre et les discussions devraient impliquer les dermatologues, les méthodologistes et les patients.

1.2.Article 1

Ce travail a fait l'objet d'une publication dans le journal *Journal of Investigative Dermatology* : Leducq S, Caille A, Le Cleach L, Samimi M, Tavernier E, Maruani A, Giraudeau B. Research Techniques Made Simple: Randomized Controlled Trials for Topical Drugs in Dermatology: When and How Should We Use a Within-Person Design? *J Invest Dermatol*. 2020;140:931-938.e1.

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

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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.).

has been used). 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.

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

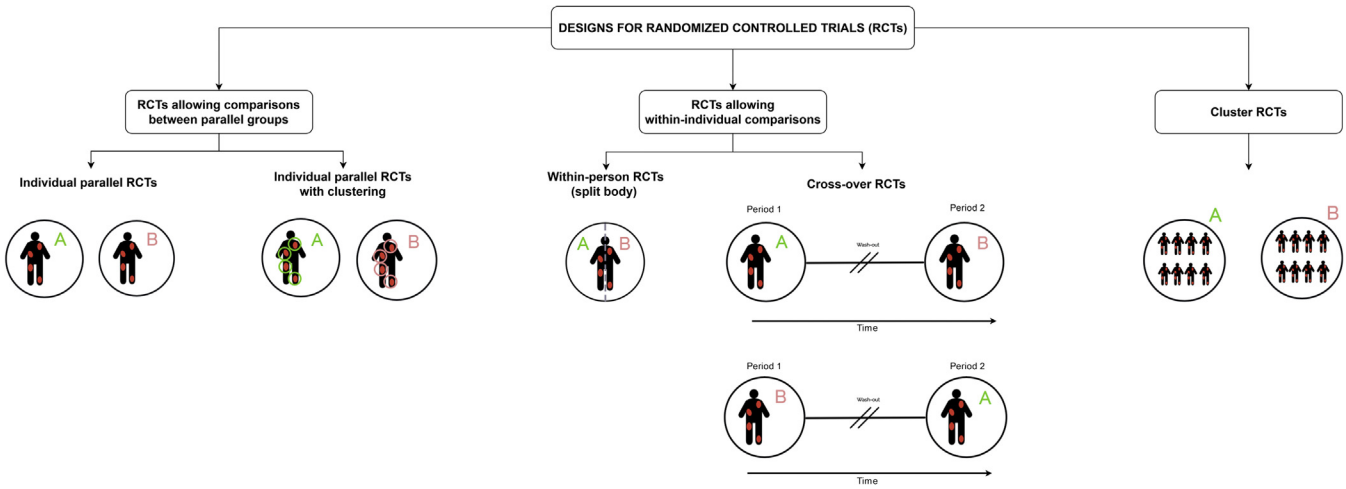


Figure 1. Available designs for randomized controlled trials (RCTs).

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

Table 1. Glossary

Term	Description
Carry-across effect	The potential leakage of the treatment effect from one site to another in a patient receiving two or more topical treatments.
Cluster RCT	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.
Cross-over RCT	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.
Individual parallel RCT	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.
Individual parallel RCT with clustering	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.
Within-person RCT	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 intraindividual comparison design.

Abbreviation: RCT, randomized controlled trial.

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

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.

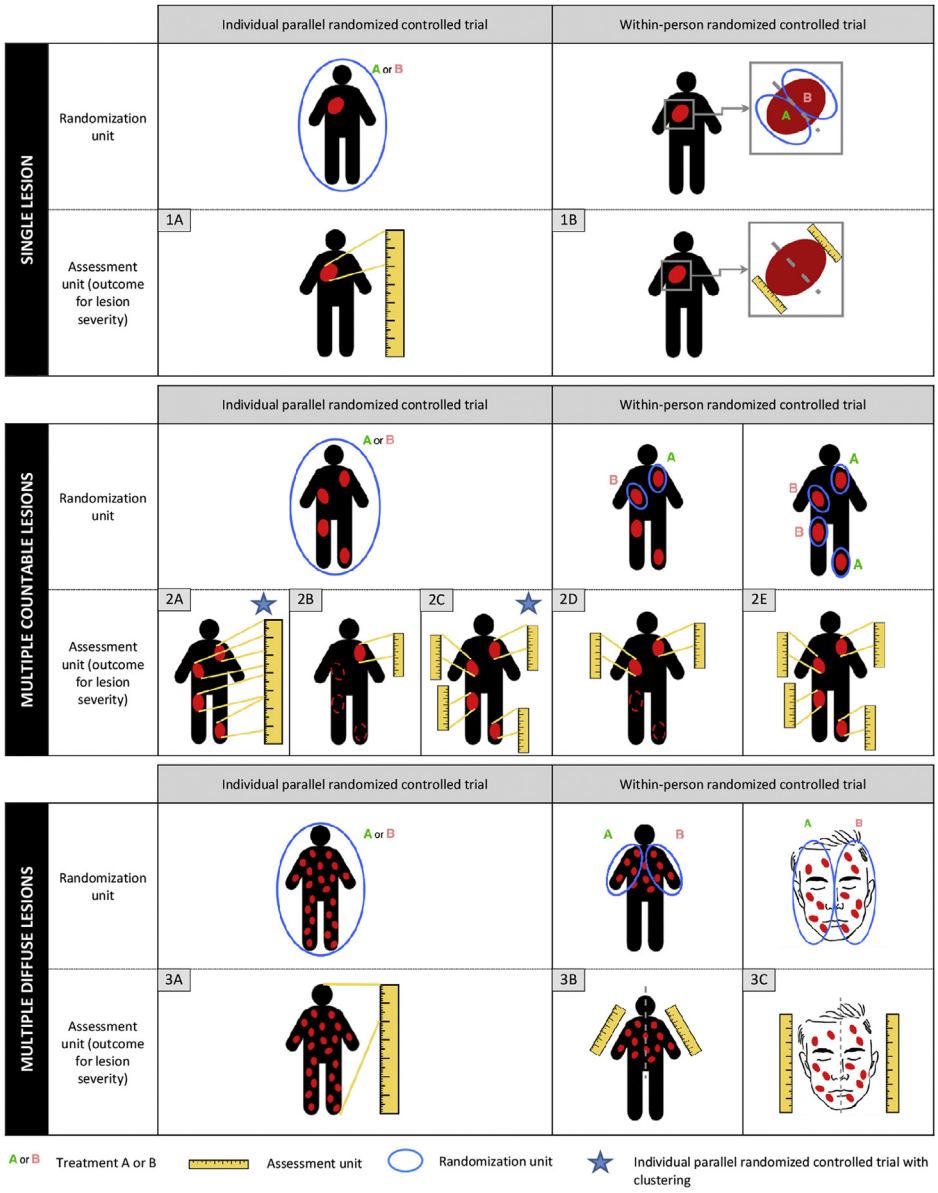
WHEN TO USE A WITHIN-PERSON RCT

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



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 be 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.

Figure 2. Types of designs for trials assessing topical drugs according to the number of skin lesions.

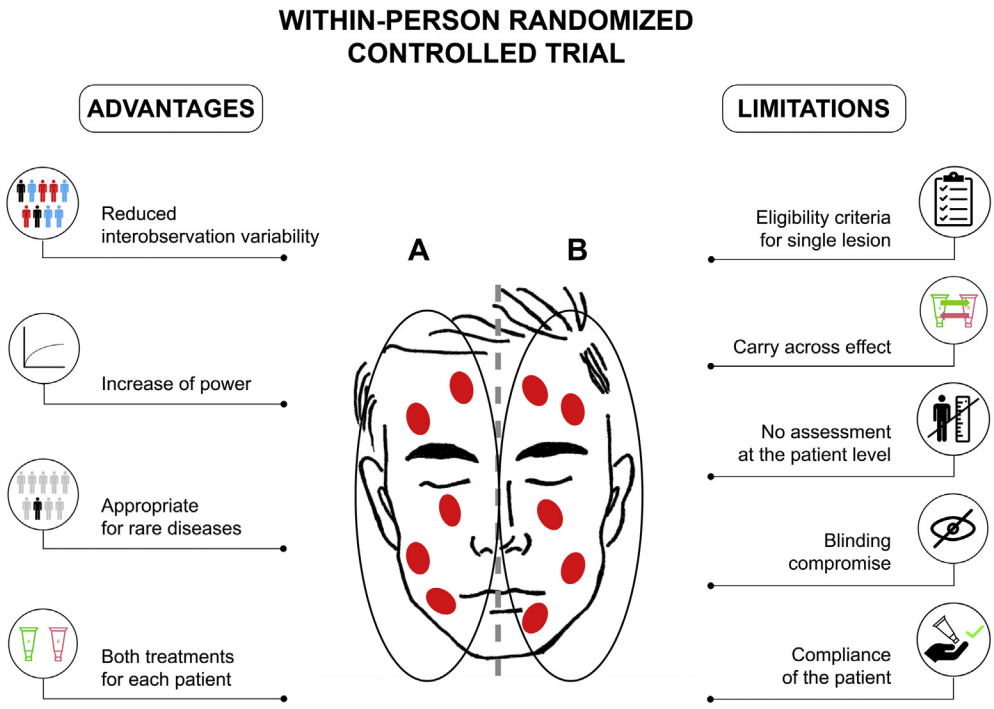


Figure 3. Advantages and limitations of the within-person randomized controlled trial design.

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

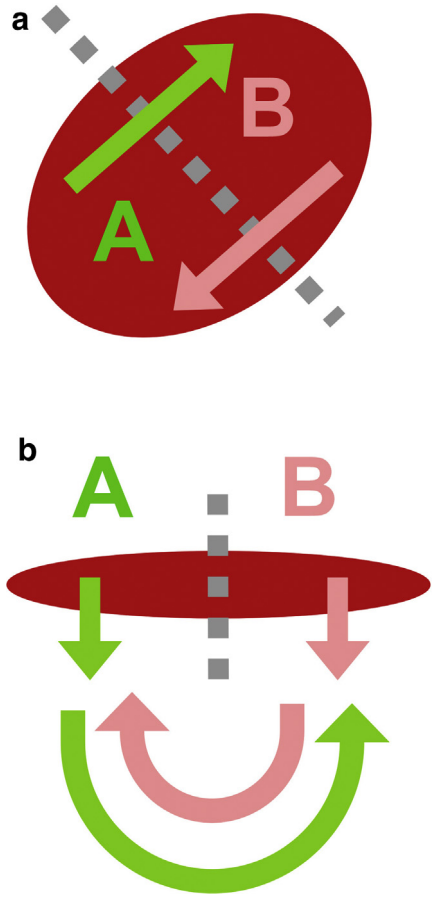


Figure 4. Two ways to induce a carry-across effect. (**a**) Direct contact between the two topical drugs. (**b**) Systemic passage of the experimental topical treatment.

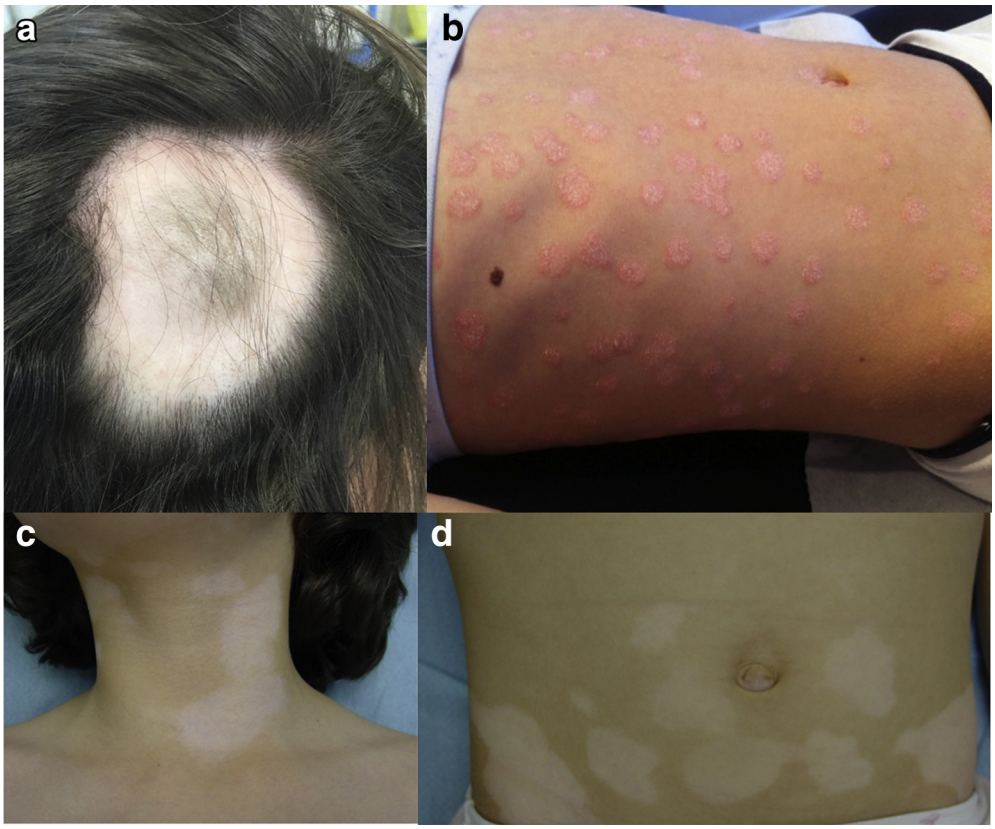


Figure 5. Skin conditions used for scenarios. (**a**) Alopecia areata. (**b**) Guttate psoriasis. (**c** and **d**) Patches of vitiligo. The patients whose pictures are shown or their parents and/or guardians consented to the publication of the image.

experimental drug or the control, so the patient receives both treatments.

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.

AUTHOR CONTRIBUTIONS

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

Cavalié M, Ezzedine K, Fontas E, Montaudié H, Castela E, Bahadoran P, et al. Maintenance therapy of adult vitiligo with 0.1% tacrolimus ointment: a randomized, double blind, placebo–controlled study. J Invest Dermatol 2015;135:970–4.

Dancik Y, Anissimov YG, Jepps OG, Roberts MS. Convective transport of highly plasma protein bound drugs facilitates direct penetration into deep tissues after topical application. Br J Clin Pharmacol 2012;73:564–78.

Gorsky M, Epstein JB, Rabenstein S, Elishoov H, Yarom N. Topical minocycline and tetracycline rinses in treatment of recurrent aphthous stomatitis: a randomized cross-over study. Dermatol Online J 2007;13:1.

Hon KL, Pong NH, Wang SS, Lee VW, Luk NM, Leung TF. Acceptability and efficacy of an emollient containing ceramide-precursor lipids and moisturizing factors for atopic dermatitis in pediatric patients. Drugs R D 2013;13:37–42.

Leducq S, Caille A, Barbarot S, Bénéton N, Bessis D, Boccara O, et al. Topical sirolimus 0.1% for treating cutaneous microcystic lymphatic malformations in children and adults (TOPICAL): protocol for a multicenter phase 2, within-person, randomized, double-blind, vehicle-controlled clinical trial. Trials 2019;20:739.

Lesaffre E, Philstrom B, Needleman I, Worthington H. The design and analysis of split-mouth studies: what statisticians and clinicians should know. Stat Med 2009;28:3470–82.

Madan I, Parsons V, Ntani G, Wright A, English J, Coggon D, et al. A behaviour change package to prevent hand dermatitis in nurses working in health care: the SCIN cluster RCT. Health Technol Assess 2019;23:1–92.

Maruani A, Samimi M, Lorette G, Le Cleach L. Comparative effectiveness of topical drugs in dermatologic priority diseases: geometry of randomized trial networks. J Invest Dermatol 2015;135:76–83.

Pandis N, Chung B, Scherer RW, Elbourne D, Altman DG. CONSORT 2010 statement: extension checklist for reporting within person randomised trials. BMJ 2017;357:j2835.

Papp KA, Bissonnette R, Gooderham M, Feldman SR, Iversen L, Soung J, et al. Treatment of plaque psoriasis with an ointment formulation of the Janus kinase inhibitor, tofacitinib: a phase 2b randomized clinical trial. BMC Dermatol 2016;16:15.

Song H, Adamson A, Mostaghimi A. Medicare Part D payments for topical steroids: rising costs and potential savings. JAMA Dermatol 2017;153:755–9.

Svendsen MT, Andersen F, Andersen KH, Pottegård A, Johannessen H, Möller S, et al. A smartphone application supporting patients with psoriasis improves adherence to topical treatment: a randomized controlled trial. Br J Dermatol 2018;179:1062–71.

Whitton ME, Pinart M, Batchelor J, Leonardi-Bee J, González U, Jiyad Z, et al. Interventions for vitiligo. Cochrane Database Syst Rev 2015:CD003263.

Wilkes SR, Nankervis H, Tavernier E, Maruani A, Williams HC. How clinically relevant are treatment comparisons of topical calcineurin inhibitor trials for atopic eczema? J Invest Dermatol 2016;136:1944–9.

DETAILED ANSWERS

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.

Supplemental file. Teaching slides

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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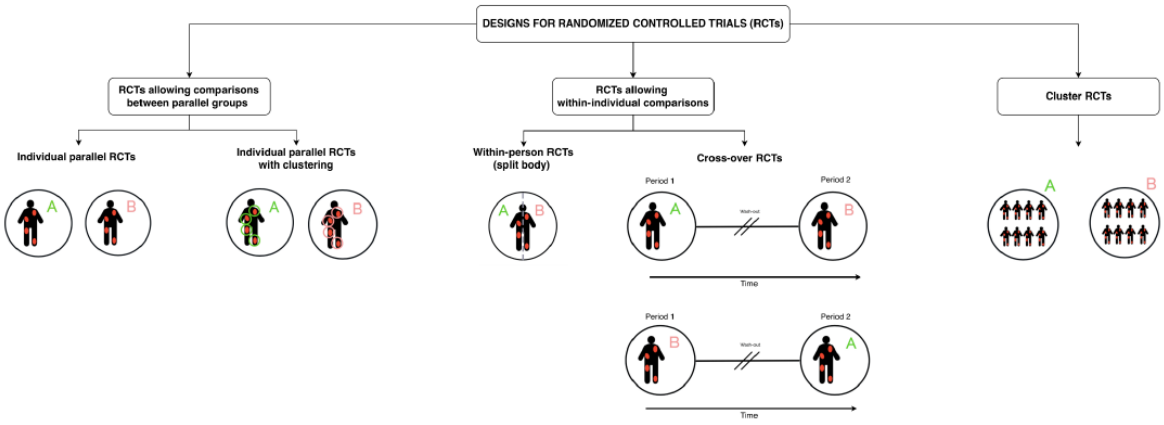
JOURNAL OF INVESTIGATIVE DERMATOLOGY

Introduction

- Skin diseases are common in the general population
- Clinical presentations are highly heterogeneous depending on the disease, including variability in number of lesions (from a single lesion to multiple diffuse ones)
- Topical drugs are often used as first-line treatment
- Randomized clinical trials (RCTs) assessing topical drugs for dermatology conditions offer different possible designs

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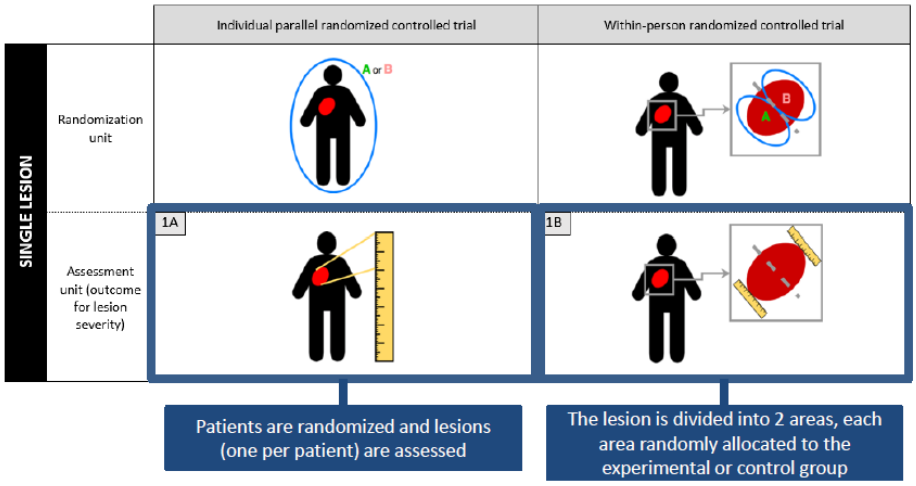
The main possible designs



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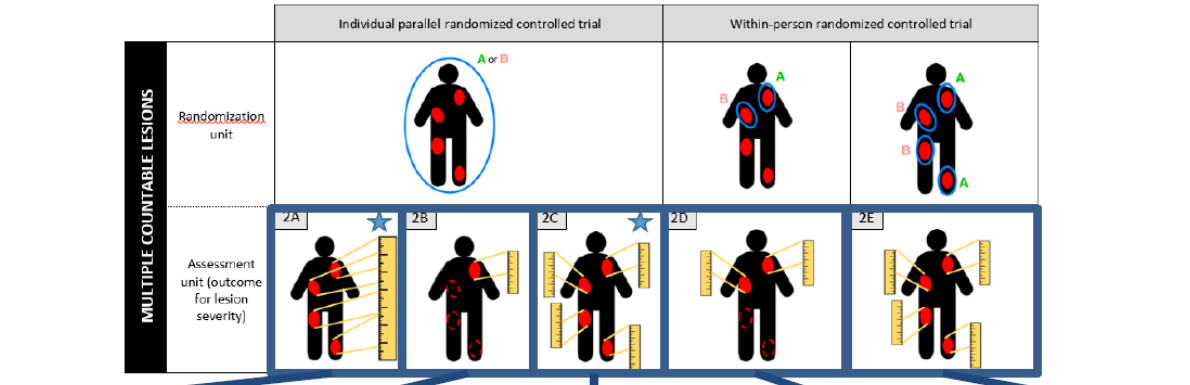
Methodological issues for RCTs of a disease that involves a single lesion



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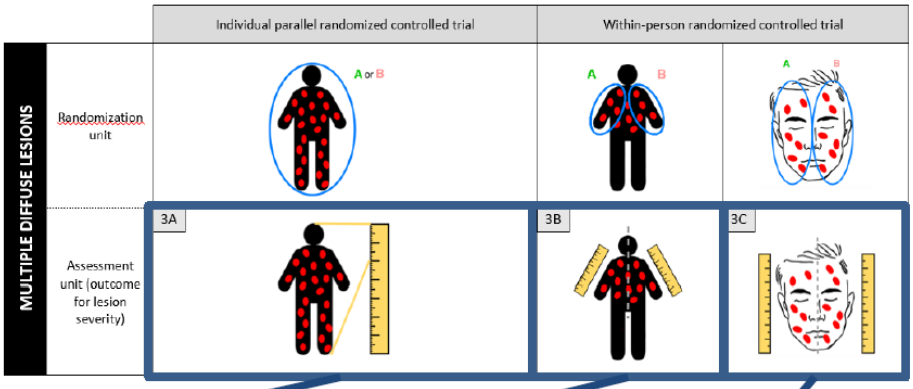
Methodological issues for RCTs of a disease that involves countable lesions



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Methodological issues for RCTs of a disease that involves multiple lesions



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Specificities of the within-person design

Patients simultaneously receive the topical experimental drug(s) and topical control(s) on different lesions/body sites

Reduced required number of patients to be included → well-adapted for rare diseases

→ The absence or negligible systemic passage of the topical experimental drugs is required (risk of carry-across effect)

→ Use of a care provider to optimize the adherence to the protocol

→ Risk of unblinding can be increased

→ No assessment possible at the patient level (such as quality of life)

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Examples – Scenario 1: an RCT of a dermatologic condition that involves a single lesion



Wide plaque of alopecia areata

Individual parallel RCT

\+ Easier to conduct

− Large number of patients

Within-person RCT

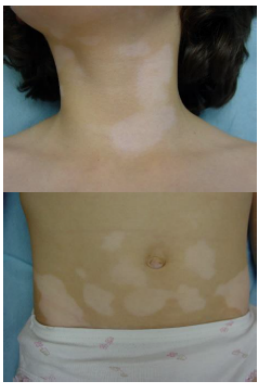
\+ Reduce sample size
Limit inter-individual variability

− Risk of carry-across effect by direct contact
Patients may not agree to have the topical drug and control on the same area

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Examples – Scenario 2: an RCT of a dermatologic condition that involves several countable lesions



Vitiligo

Individual parallel RCT

- ✚ Easier to conduct
- ▬ Large number of patients

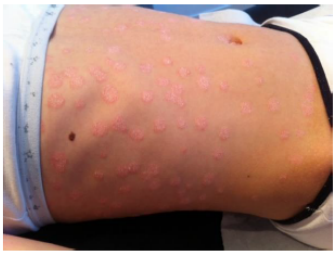
Individual parallel RCT with clustering

- ✚ Increase statistical power by using the maximal potential amount of data

Within-person RCT

- ✚ Reduce sample size
  Limit inter-individual variability
- ▬ Risk of carry-across effect by direct contact: treated lesions cannot be too close to one another

Examples – Scenario 3: an RCT of a dermatologic condition that involves multiple diffuse lesions



Guttate psoriasis

Individual parallel RCT

- ✚ To evaluate quality of life as the primary outcome
  Easier to conduct
- ▬ Large number of patients

Within-person RCT

- ✚ Reduce sample size
  Limit inter-individual variability
- ▬ Risk of carry-across effect by direct contact or by systemic passage of the drug

Conclusion

- Several designs might be chosen for RCTs of topical drugs
- Within-person RCT
  - increases the power
  - ⚠ carry-across effect
- Methodological choices must take into account:
  - the type of disease (number of lesions)
  - prevalence of the disease
  - the relevant primary outcome (whether at the level of the participant or lesion)
  - the risk of a carry-across effect
  - the expected acceptance of the protocol and compliance of participants

2. Revue systématique méthodologique des essais randomisés utilisant un schéma d'étude en « within-person » en dermatologie

2.1.Présentation du travail

Nous avons réalisé dans un 2ème temps une revue méthodologique de la littérature incluant les essais contrôlés randomisés en « within-person » évaluant un traitement topique en dermatologie. L'objectif de cette revue était de vérifier comment les aspects méthodologiques identifiés et synthétisés dans le 1er travail pour la planification, l'analyse et la rédaction des essais en « within-person » avaient été appréhendés par les auteurs des essais.

La recherche documentaire a été faite en juillet 2021 à l'aide de MEDLINE, Embase et Central dans les revues de dermatologie et dans les 6 revues généralistes aux « impact factors » les plus élevés. Était éligible tout essai contrôlé randomisé évaluant un traitement topique en dermatologie et utilisant un schéma d'étude en « within-person » publié entre Juillet 2017 (date de publication de la CONSORT checklist pour les essais en « within-person ») et Juillet 2021 (Pandis, 2017). Deux auteurs ont sélectionné les publications et ont extrait les données de manière indépendante.

Sur 1034 articles identifiés, nous avons inclus 54 essais. Les pathologies dermatologiques étaient majoritairement l'acné vulgaire, le psoriasis, les kératoses actiniques et la dermatite atopique. Dans la majorité des essais, les patients n'avaient que deux lésions/sites anatomiques évalués. Dans aucun des essais, les auteurs ne rapportent avoir cherché à détecter un potentiel *carry-accros effect* (contamination inter-groupe). Environ un tiers seulement des études décrivaient les critères d'éligibilité à la fois pour les patients et pour les lésions/sites anatomiques. Dans 52 (96,3%) essais, le nombre requis de lésion par patient était limité à 2. Le recours à un *care provider* (par exemple, l'application du traitement par une infirmière) a été rapporté dans 12 études alors que pour 26 autres études, le traitement a été appliqué par le patient lui-même. Les effets secondaires locaux ont été rapportés dans 43 études (79,6%), mais seules 14 études ont rapporté les effets secondaires locaux par groupe. Concernant les aspects statistiques, le calcul d'effectif était rapporté dans 33 études (61,1%), mais seules 6 études tenaient compte de la corrélation des lésions d'un même patient. Pour l'analyse statistique, dans les 52 essais incluant 2 lésions/sites anatomiques par patient, 33 études (63,5%) ont utilisé un

test pour séries appariées. Enfin, les aspects éthiques et d'acceptabilité pour le patient et l'investigateur n'ont été évoqués que dans un essai.
Notre revue souligne que, malgré la publication de CONSORT check-list en 2017 pour les essais contrôlés randomisés en « within-person », ce schéma d'étude est rarement utilisé et, lorsqu'il l'est, la méthodologie, l'analyse et la rédaction ne sont pas optimales.

2.2.Article 2

Ce travail a été soumis en Août 2022 : Leducq S, Dugard A, Allemang-Trivalle A, Giraudeau B, Maruani A. Design and methodological issues of within-person (split-body) randomized controlled trial evaluating a topical treatment: A systematic review.

TITLE PAGE

Design and methodological issues of within-person (split-body) randomized controlled trials evaluating a topical treatment: A systematic review

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ABBREVIATIONS USED:

AE: adverse event

RCT: randomized controlled trial

WP-RCT: within-person randomized trial

ABSTRACT

Topical drugs are often used as first-line treatment for dermatological conditions. A within-person design may then be well adapted: it consists of randomizing lesions/body sites rather than patients, which are then concomitantly treated by the different drugs compared. The aim of this review was to provide a methodological overview of within-person randomized trials (WP-RCTs) in dermatology. We searched for eligible trials published between 2017 and 2021 in MEDLINE, Embase and Central in dermatology journals and the 6 highest-impact-factor general medical journals. Two authors selected publications and extracted data independently. From 1034 articles identified, we included 54 WP-RCTs, mainly for acne vulgaris, psoriasis, actinic keratosis and atopic dermatitis. In most of the trials, patients had only 2 lesions/body sites. In none of the trials did we detect a potential carry-across effect (known to be the major methodological problem in WP-RCTs). Twelve studies reported a care provider applying the treatment, and in 26 studies, the patients themselves applied the treatment. Our systematic review highlights that despite the publication of the CONSORT checklist extension for WP-RCTs in 2017, this design is rarely used, and when it is, there are methodological and reporting concerns.

INTRODUCTION

Topical treatments are of major importance in dermatology and are the most prevalent drugs used for skin conditions (de Lusignan et al., 2021; Menter et al., 2009; Powell et al., 2018; Song et al., 2017). They have an immediate local effect on skin lesions and are often used as first-line treatments to avoid systemic effects (Maruani et al., 2015; Zhang et al., 2017). They can be administered alone or in combination with other topical or systemic treatments. Therapies with topical administration are of 3 subgroups: topical pharmacological drugs (e.g., topical corticosteroids, antibiotics, anti-inflammatory), emollients and cosmetics, and topical medical devices (e.g., bandages for leg ulcers). The choice of using a topical rather than a systemic treatment in skin conditions depends on several factors such as the severity of the disease and its extension.

Indeed, skin diseases might be classified according to the types of lesions and their extension to the body as 1) conditions that present as a single lesion (e.g., skin cancers); 2) conditions with multiple countable lesions (e.g., plaque psoriasis, eczema, vitiligo); and 3) multiple diffuse lesions extended to the body surface (e.g., scabies, viral exanthema). Thus, variability in the number and topography of skin lesions offers different methodological possibilities for randomized controlled trials (RCTs) assessing topical treatments (Leducq et al., 2020). The design of RCTs depends on the unit of randomization chosen (i.e., whether patients or lesions are randomized) but also whether a unique lesion or several lesions per patient are considered. According to these choices, RCTs of topical treatments might be designed as classical individual parallel RCTs (Ho et al., 2011), individual parallel group with clustering RCTs (whereby patients, considered as clusters of lesions, are randomized, with several lesions per patient treated) (Cavalié et al., 2015), or within-person RCTs (WP-RCTs), also called split-body RCTs or the intra-individual comparison design (Lepé et al., 2003). In WP-RCTs, lesions rather than patients are randomized and different drugs are concomitantly administered to the

same patient. This design is different from the cross-over design because distinct lesions are treated with distinct drugs administered at the same time rather than sequentially. By reducing inter-group variability (as in cross-over RCTs), the WP-RCT gains in efficiency and therefore requires fewer patients than the classical parallel-group trial.

However, the WP-RCT design has specific methodological issues. The main one is the risk of a carry-across effect, defined as the leakage of the treatment from one site (or lesion) to another that has another treatment or is not treated. Moreover, because lesions from an individual patient are more similar than lesions from different patients, there exists a correlation between assessment units (i.e., lesions) that must be considered in WP-RCTs, both for sample size calculation and data analyses. Other specificities must be considered and are summarized in **Box 1** (Leducq et al., 2020). Therefore, WP-RCTs are interesting designs for assessing topical drugs in skin conditions but are challenging to be set up; reporting guidelines (CONSORT extension) were elaborated for WP-RCTs (Pandis et al., 2017).

Here, by performing a systematic review, we aimed to assess whether trialists who conducted WP-RCTs considered all methodological and reporting specificities in order to highlight the points remaining to be improved.

RESULTS

The results of this systematic review have been structured in line with the methodological points raised by Leducq et al. (2020).

Study selection

The PRISMA flow diagram summarizing the screening process is in **Figure 1**. Of 1 034 references identified, 54 publications met the inclusion criteria.

General characteristics of included studies (**Tables 1 and 2**)

Most of the trials were single centre (n=31, 57.4%) and were superiority designed RCTs (n=50, 92.6%). The most frequent dermatological conditions were acne (n=14, 25.9%), actinic keratosis (n=11, 20.4%), atopic dermatitis (n=8, 14.8%) and psoriasis (n=6, 11.1%). Most of the trials included adults only (n=45, 83.3%).

General characteristics specifically related to the within-person design (**Table 2**)

Identification and justification for using a WP-RCT

Trials were generally identified as a WP-RCT (n=52, 96.3%). Identification of the trial as a WP-RCT was included in the title for 31 (57.4%) articles, in the abstract for 44 (88.0%, no abstract available for 5 articles) and in the manuscript for 48 (88.9%). However, different terms were used to describe this design, and several could be used in the same article: split-body/split-face/split-side (n=31, 59.6%), intra-individual/intra-subject/intra-patient (n=23, 44.2%), within-person/within-patient/within-subject (n=4, 7.7%), left to right/left vs right/right-left comparison/left right comparative (n=7, 13.5%), bilateral controlled clinical trial (n=1, 1.9%), per-patient (half face) (n=1, 1.9%), concurrent bilateral (n=1, 1.9%), side by side (n=1, 1.9%) and forearm controlled (n=1, 1.9%). Only 10 (18.5%) studies reported the rationale and justification for using a within-person design. Reasons evoked were to limit inter-individual variability (9 studies, 90.0%); reduce the number of patients to be included (5 studies, 50.0%); improve treatment adherence, without more explanation (one study); and because of the disease prevalence (rare skin disease for one study).

Methods for optimizing recruitment

Five (9.3%) studies planned an extension period (i.e., a period when all lesions/body sites were treated with the experimental treatment after a first period during which the experimental and control treatment were assessed). Such an extension period is expected to facilitate the recruitment of patients as well as their adherence to the study protocol, which allows for

explaining to them that eventually, all their lesions will be treated by the experimental treatment.

Ethical aspects

One trial reported the patient's acceptability of the design and ethical aspects, and these concerned ethical and cosmetic issues because the patients received a placebo on one side (Saki et al., 2020).

Characteristics of the topical drugs (**Tables 2 and 3**)

Most studies compared 2 treatments (n=48, 88.9%) and in 21 (38.9%) studies, the topical treatment assessed in the WP-RCT was an add-on treatment. The most frequent formulation of experimental treatment was cream (n=20, 37.0%). For the control group, an active drug was used in 23/53 (43.4%) studies, emollient cream in 12 (22.6%) and vehicle in 8 (15.1%). The most frequent regimen was 2 applications per day (n=18, 33.3%) for 15 to 29 days (n=17, 31.5%). In 21 (38.9%) studies, the topical treatment assessed was an add-on treatment. The standard treatment was a physical treatment in 14 (66.7%) studies, a topical treatment in 5 (23.8%) studies or a topical medical device, an oral treatment and a combination of a topical treatment and an oral treatment in 1 (4.8%) study each.

Methodological characteristics of included studies (**Tables 2 and 4**)

Eligibility criteria

Eligibility criteria were specified for both patients and body sites/lesions in 18 (33.3%) studies and for patients only in 35 (64.8%). Most of the studies included 2 units (lesions) per patient (n=52, 96.3%). No trial featured a single lesion split into 2 areas.

Compliance

Twelve (22.2%) studies involved a care provider in charge of applying the treatments, whereas for 26 (48.2%) studies, treatments were applied by the patients themselves. Two (3.7%) studies reported monitoring of treatment application.

Blinding

The following actors were blinded: patients in 25 trials (54.3%, unclear for 8 trials), care providers in 2 (22.2%, unclear for 8 trials and not applicable for 24) and outcome assessors in 39 (86.7%, unclear for 9 trials). For 23 trials (53.5%, unclear for 11 trials), both patients and outcome assessors were blinded.

Detection of a potential carry-across effect

None of the 54 included studies reported the detection of a potential carry-across effect.

Outcomes

A primary outcome was clearly defined for 44 (81.5%) studies and was mostly a subjective outcome (n=32/44, 72.7%), such as physician global assessment or psoriasis area severity index, quality of life etc. (Savović et al., 2012).

Randomization

Most studies randomized 2 different anatomic areas (n=41, 75.9%) or 2 distinct lesions (n=5, 9.3%).

Statistical methods

A total of 33 (61.1%) articles described a sample size calculation. Six (11.1%) studies accounted for a within-patient between-lesions correlation, without reporting the value of the assuming correlation.

For trials with 2 units per patient (n=52), 32 (61.6%) performed a paired test, and one study fitted a mixed effects model to take into account between-lesion correlation. No study reported the within-patient between-lesions correlation coefficient estimate. Overall, 14 (26.9%) studies used a test for independent observations, thus ignoring the between-lesion correlation. For the 2 trials with > 2 units (lesions) per patient, in one (Guttman-Yasski et al., 2017), the statistical analysis did not take into account the within-lesion correlation and the other used only a descriptive statistical analysis (Danilenko et al., 2018).

Reporting characteristics of the included studies

Patient flow and baseline characteristics

Only 17 (31.5%) studies provided a patient flow chart with number of patients. Only 2 other (3.7%) studies reported lesions/body sites numbers associated with patient numbers. Overall, 34 (63%) articles reported lost to follow-up and dropout. Baseline data were described for patients in only 48.2% (n=26) of the articles, for body sites/lesions in only one (1.9%) article and for both patients and body sites/lesions in 24 (n=44) articles.

Harms

Local adverse events were reported in 43 (79.6%) articles and general adverse events in 14 (25.9%); one study reported only general adverse events without reporting local adverse events. The median number of lesions/body sites with local adverse events was 5.0 (interquartile range, 3.0-9.5) and 3.0 (interquartile range, 0.0-5.75) in the experimental and control group, respectively.

Summary of methodological aspects to consider in WP-RCTs across all included studies (Figure 2)

In **Figure 2**, we synthesize the quality of the methodological items to consider (**Box 1**) for planning and reporting WP-RCTs presented as percentages across all included studies.

DISCUSSION

In this methodological systematic review, we included 54 trials using a within-person design. Dermatology conditions were mostly non-rare skin diseases in adults with multiple countable lesions with involvement of at least 2 different anatomical sites. Only about one third of the trials specified eligibility criteria for both patients and body sites/lesions. Most trials involved 2 lesions per patient. Twelve studies used a care provider for applying the treatments (which

may enhance compliance and limit group contamination), and in 26 studies, the treatment was applied by patients themselves. None of the trials assessed a potential carry-across effect.

No trial included a single lesion divided into 2 areas, although this type of design may be particularly interesting in rare skin diseases (Leducq et al., 2018). Indeed, because of the low prevalence of rare diseases, classical individual parallel RCTs are not adapted, and therefore, specific designs adapted to rare diseases might be considered, such as cross-over designs or stepped-wedge designs (Cornu et al., 2013). Also, the within-person design might be preferred to reduce the number of patients to be included. Similarly, few trials included > 2 lesions per patient even though this type of design allows for reducing the number of patients to be included by increasing the number of observations (lesions/body sites) per patient.

Regarding modalities of administration of treatment, because patients receive both treatments concomitantly, the use of an intervention care provider who applies the treatments, such a nurse, can limit if not avoid intergroup contamination. However, only a few trials used a care provider, and monitoring of treatment application was rarely reported. Moreover, the absence or negligible systemic passage of the experimental treatment is mandatory to avoid a carry-across effect. Avoiding a carry-across effect is a necessary prerequisite for using a within-person design. However, in our review, no study reported methods to detect a carry-across effect, such as plasma dosage of the drug, which, however, is not systematically available. Other factors should be considered for the risk of systemic passage of the experimental treatment such as the molecular weight of the experimental treatment (Bos et al., 2000), the surface to be treated and the alteration of the skin barrier, which may increase dermal absorption and therefore systemic passage (Kezic et al., 2009). However, in the end, having so few studies reporting the use of a care provider and none testing for a potential carry-across effect questions whether trialists have well appreciated the risk of between-group contamination in a WP-RCT.

Local side effects were commonly described, as for any time a topical treatment is assessed, and were reported for 43 studies. In a WP-RCT, such side effects may compromise blinding as well as compliance because each patient (who receives both treatments concomitantly) can directly compare the adverse events occurrence (but also efficacy) and therefore guess which lesion received the experimental/control treatment. In such a situation, an objective outcome is mandatory to limit a potential exaggeration of treatment effects (Hróbjartsson et al., 2014). Outcomes such as spectrophotometry or blinded evaluation by an independent outcome assessor using photographs in case of subjective outcomes is highly recommended (Savović et al., 2012).

Our study highlights a lack of quality for reporting despite the publication of the CONSORT extension for WP-RCTs in 2017. This lack of reporting concerned common items related to RCTs (e.g., 39% of the studies did not report a sample size) but also specific items related to WP-RCTs. Several studies have assessed the quality of reports of RCTs and the findings are similar regardless of the study design and condition. For example, a systematic review performed in 2013 that described non-pharmacological interventions of RCTs found that of 137 interventions included, only 53 (39%) were adequately described (Hoffmann et al., 2014). More recently, in a study of interventional trials studying colorectal cancer, only 5/101 (5%) trials reported all selected CONSORT items completely (Pellat et al., 2022).

Only one article reported the ethical aspects of the within-person design, although it actually refers more to the equipoise principle than the within-person design. Indeed, in this study, the authors mentioned that using a placebo "*brings ethical and cosmetic issues, because the patients cannot be deprived of the treatment in one side*" and thus decided to use an active comparator.

Finally, we also highlight statistical issues for both sample size calculation and the statistical analysis. These findings were similar to previous publications of WP-RCTs in dentistry or ophthalmology (Koletsi et al., 2014; Lee et al., 2012; Lesaffre et al., 2007). When 2 lesions per

patient were included, a classical pair-matched test was used, which is correct. Some trials (9, 16.7 %) used mixed models, but this was to consider intra-lesion correlation between repeated assessments, not within-patient between-lesion correlation. Such an approach is incorrect.

This systematic review has some limitations. First, we limited the eligibility criteria to reports published only in English and between 2017 and 2021. Therefore, this review is not extensive but provides a recent description of published WP-RCTs. Second, the identification of trials as WP-RCTs was heterogenous and therefore, with our selection of key words, we might have missed some WP-RCTs. Finally, we did not contact the first authors to deal with missing data.

In conclusion, the WP-RCT is an interesting design and an alternative to the classical individual parallel RCT for investigating topical drugs. Although this design is well adapted for evaluating topical treatment in skin conditions, only 54 trials were published between 2017 and 2021, with methodological and reporting concerns.

METHODS

We conducted a methodological systematic review and followed the standard Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines (**Supplemental file 1**). The protocol was registered in the International Prospective Register of Systematic Review (PROSPERO record: CRD42022315516).

Eligibility criteria

We included only RCTs published in dermatology journals defined by the National Library of Medicine Catalog (journals referenced in the NCBI Databases) or in the 6 highest-impact-factor general medical journals. Congress abstracts and protocols were excluded. All RCTs evaluating a topical drug and using a within-person design for cutaneous diseases were included. We excluded studies of physiologic skin changes (e.g., melasma, scars, xerosis and folds), oral and ophthalmology pathologies, and anti-aging and cosmetic treatments. We included studies of

topical treatments (e.g., cream, gel, solution) with an active drug, emollient, herbal and plant local treatment and medical devices with an active substance but excluded those assessing physical treatment (e.g., laser, phototherapy).

Information sources and search strategy

We searched MEDLINE, Embase and Central from 01/07/2017 (date of publication of the CONSORT checklist extension for reporting WP-RCTs) (Pandis et al., 2017) to 31/07/2021 for all RCTs evaluating a topical drug and using a within-person design in dermatology. Search algorithms were refined in collaboration with an expert methodologist (BG) and are presented in **Supplemental file 2**. We restricted the inclusion of articles to those published in English. The data on characteristics of patients, outcomes and adverse events were also collected from the results published at ClinicalTrials.gov (www.ClinicalTrials.gov) or any other register specified in the publication.

Selection process

Two reviewers (SL and AAT) selected the studies independently according to both the title and abstract and then the full text according to previously established inclusion criteria. In case of disagreement, consensus was determined by a discussion between the 2 reviewers or by consulting a third reviewer (BG/AM) if needed.

Data extraction

We designed a structured data extraction form using AirTable (**Supplemental file 3)** and extracted the following characteristics: name of the first author, publication year, journal, study recruitment characteristics (subcontinent and multicenter study), identification as a within-person design and term used by the authors, study design (objective, design justification by the authors, type of experimental and control treatment, type and level of outcome, blinding, prevention of carry-across effect, use of an intervention care provider), characteristics of patients (dermatologic condition, type of population, eligibility criteria for patients and lesions),

statistical considerations (estimated sample size, statistical methods for analysis), report of results (number of patients and lesions included, patient flow chart, description of baseline characteristics, number of lost to follow-up, reporting of adverse events [adverse events, by body sites/areas or by patients]), ethical aspects (patient acceptability, methods to facilitate recruitment) and funding. Data were extracted by 2 reviewers (SL, AD) individually with blinding to each other's decisions. Disagreements between individual judgements were resolved by consulting 2 other reviewers (AM, BG) as for the study selection.

Synthesis methods

Data are summarized as number (percentage) for categorical data and median (interquartile range) for continuous data. Statistical analyses were performed with R 4.1.2.

DATA AVAILABILITY STATEMENT

The data extracted from included studies are available from the corresponding author on reasonable request.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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AUTHORS CONTRIBUTIONS STATEMENT (CREDIT STATEMENT)

Conceptualization: SL, BG and AM

Data Curation: SL, AD and AAT

Formal Analysis: SL

Methodology: SL, BG and AM

Software: SL

Supervision: BG and AM

Visualization: SL

Writing - Original Draft Preparation: SL, BG and AM

Writing - Review and Editing: SL, AD, AAT, BG and AM

REFERENCES

1. Bos JD, Meinardi MM. The 500 Dalton rule for the skin penetration of chemical compounds and drugs. Exp Dermatol 2000;9:165-9.
2. Cavalié M, Ezzedine K, Fontas E, Montaudié H, Castela E, Bahadoran P, et al. Maintenance therapy of adult vitiligo with 0.1% tacrolimus ointment: a randomized, double blind, placebo–controlled study. J Invest Dermatol 2015;135:970-4.
3. Chan AW, Altman DG. Epidemiology and reporting of randomised trials published in PubMed journals. Lancet 2005;365:1159-62.
4. Cornu C, Kassai B, Fisch R, et al. Experimental designs for small randomised clinical trials: an algorithm for choice. Orphanet J Rare Dis 2013;8:48.
5. Danilenko M, Stamp E, Stocken DD, et al. Targeting Tropomyosin Receptor Kinase in Cutaneous CYLD Defective Tumors With Pegcantratinib: The TRAC Randomized Clinical Trial. JAMA Dermatol 2018;154:913-921.
6. Ho N, Pope E, Weinstein M, Greenberg S, Webster C, Krafchik BR. A double-blind, randomized, placebo-controlled trial of topical tacrolimus 0·1% vs. clobetasol propionate 0·05% in childhood vitiligo. Br J Dermatol 2011;165:626-32.
7. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. BMJ 2014;348:g1687.
8. Hróbjartsson A, Emanuelsson F, Skou Thomsen AS, Hilden J, Brorson S. Bias due to lack of patient blinding in clinical trials. A systematic review of trials randomizing patients to blind and nonblind sub-studies. Int J Epidemiol 2014;43:1272-83.
9. Guttman-Yassky E, Ungar B, Malik K, et al. Molecular signatures order the potency of topically applied anti-inflammatory drugs in patients with atopic dermatitis. J Allergy Clin Immunol 2017;140:1032-1042.e13.

10. Kezic S, Nielsen JB. Absorption of chemicals through compromised skin. Int Arch Occup Environ Health 2009;82:677-88.
11. Koletsi D, Fleming PS, Seehra J, Bagos PG, Pandis N. Are sample sizes clear and justified in RCTs published in dental journals? PLoS One 2014;9:e85949
12. Lee CF, Cheng AC, Fong DY. Eyes or subjects: are ophthalmic randomized controlled trials properly designed and analyzed? Ophthalmology 2012;119:869-72.
13. Leducq S, Caille A, Le Cleach L, Samimi M, Tavernier E, Maruani A, et al (2020). Research techniques made simple: randomized controlled trials for topical drugs in Dermatology: when and how should we use a within-person design? J Invest Dermatol 140:931-938.e1.
14. Leducq S, Caille A, Barbarot S, Beneton N, Bessis D, Boccara O, et al (2019). Topical sirolimus 0.1% for treating cutaneous microcystic lymphatic malformations in children and adults (TOPICAL): protocol for a multicenter phase 2, within-person, randomized, double-blind, vehicle-controlled clinical trial. Trials 20:739.
15. Lepe V, Moncada B, Castanedo-Cazares JP, Torres-Alvarez MB, Ortiz CA, Torres-Rubalcava AB. A double-blind randomized trial of 0.1% tacrolimus vs 0.05% clobetasol for the treatment of childhood vitiligo. Arch Dermatol 2003;139:581-5.
16. Lesaffre E, Garcia Zattera MJ, Redmond C, Huber H, Needleman I; ISCB Subcommittee on Dentistry. Reported methodological quality of split-mouth studies. J Clin Periodontol 2007;34:756-61.
17. Lesaffre E, Philstrom B, Needleman I, Worthington H. The design and analysis of split-mouth studies: what statisticians and clinicians should know. Stat Med 2009;28:3470-82.

18. de Lusignan S, Alexander H, Broderick C, Dennis J, McGovern A, Feeney C, et al. Patterns and trends in eczema management in UK primary care (2009-2018): A population-based cohort study. Clin Exp Allergy 2021;51:483-494.
19. Maruani A, Samimi M, Lorette G, Le Cleach L. Comparative effectiveness of topical drugs in dermatologic priority diseases: geometry of randomized trial networks. J Invest Dermatol 2015;135:76-83.
20. Menter A, Korman NJ, Elmets CA, Feldman SR, Gelfand JM, Gordon KB, et al. Guidelines of care for the management of psoriasis and psoriatic arthritis. Section 3. Guidelines of care for the management and treatment of psoriasis with topical therapies. J Am Acad Dermatol 2009;60:643-59.
21. Pandis N, Chung B, Scherer RW, Elbourne D, Altman DG. CONSORT 2010 statement: extension checklist for reporting within person randomised trials. BMJ 2017;357:j2835.
22. Pellat A, Boutron I, Ravaud P. Assessment of transparency and selective reporting of interventional trials studying colorectal cancer. BMC Cancer 2022;22:278.
23. Powell HB, Adamson AS. Medicare Part D payments for brand and generic drugs prescribed by dermatologists. J Am Acad Dermatol 2018;79:575-577.
24. Saki N, Ahramiyanpour N, Heiran A, Alipour S, Parvizi MM. Efficacy of topical dimethyl sulfoxide (DMSO) 50% solution vs tretinoin 0.5% cream in treatment of patients with primary macular amyloidosis: A split-side single-blinded randomized clinical trial. Dermatol Ther 2020;33:e13305.
25. Savović J, Jones H, Altman D, Harris R, Jűni P, Pildal J et al. Influence of reported study design characteristics on intervention effect estimates from randomised controlled trials: combined analysis of meta-epidemiological studies. Health Technol Assess 2012;16:1-82.

26. Song H, Adamson A, Mostaghimi A. Medicare Part D payments for topical steroids: Rising costs and potential savings. JAMA Dermatol 2017;153:755-759.
27. Zhang M, Silverberg JI, Kaffenberger BH. Prescription patterns and costs of acne/rosacea medications in Medicare patients vary by prescriber specialty. J Am Acad Dermatol 2017;77:448-455.e2.

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 (%).

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

[2]Other 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)
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)

Detection of carry-across effect	0 (0.0)
OUTCOME	
Outcome clearly identified	44 (81.5)
Type of outcome	
Objective outcome	8 (18.2)
Subjective outcome	32 (72.7)
Mixed outcome (objective and subjective)	4 (9.1)
Level of the primary outcome	
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	
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
[1]*Sum of the category is > 1 because one study may have had several design justifications*
[2]*Photodynamic therapy for 10 studies, phototherapy for 1 study, excimer light lamp for 1 study and air cooling for 1 study*
[3]*Minimal number of units (lesions) per patient for these 2 trials were 4 and 10*
[4]*Unclear for 8 trials,* [5]*unclear for 21 and not applicable for 24 trials,* [6]*unclear for 9 trials*
[7]*Sum of the category is > 1 because one study may have had several anatomic sites*
[8]*Other 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*
[9]*Mixed models account for the correlation between repeated data but no the correlation between lesions*
[10]*For 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	
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 (%).

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

[2]*Other includes moisturizer containing lidochalcone A, decanediol, Lcarnitine, 1% salicylic acid, lidochalcone lcarnitine 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)

PATIENT FLOW	
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)
PATIENTS AND LESIONS	
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)
BASELINE DATA	
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)
HARMS	
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	5/14 (35.7)
Number of general adverse events/patient level	4.0 [1.0-5.0]
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	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]	14/43 (32.6)
Number of lesions/body sites	3.0 [0.0-5.75]
REPORTING IN REGISTER	
Number of trials registered	27 (50.0)
Results published in registers	8 (29.6)

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

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

FIGURE LEGENDS

Figure 1. Prisma flow chart

Figure 2. Authors' judgements about each of the methodological items to consider for planning and reporting presented as percentages across all included studies.

SUPPLEMENTAL FILES

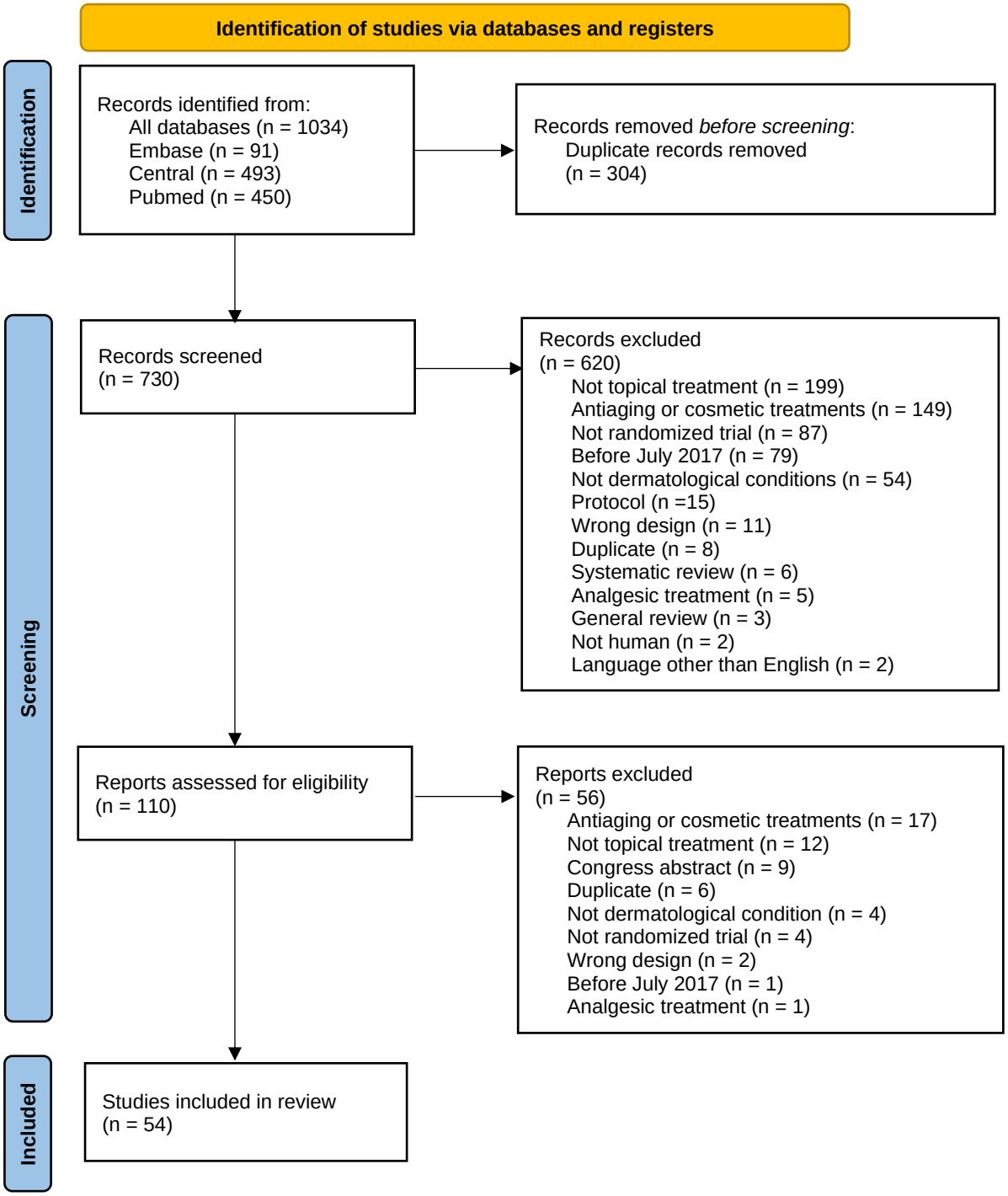
Supplemental file 1. PRISMA checklist

Supplemental file 2. Search strategy

Supplemental file 3. Extraction form of extraction and collection of data

Supplemental file 4. References of included studies

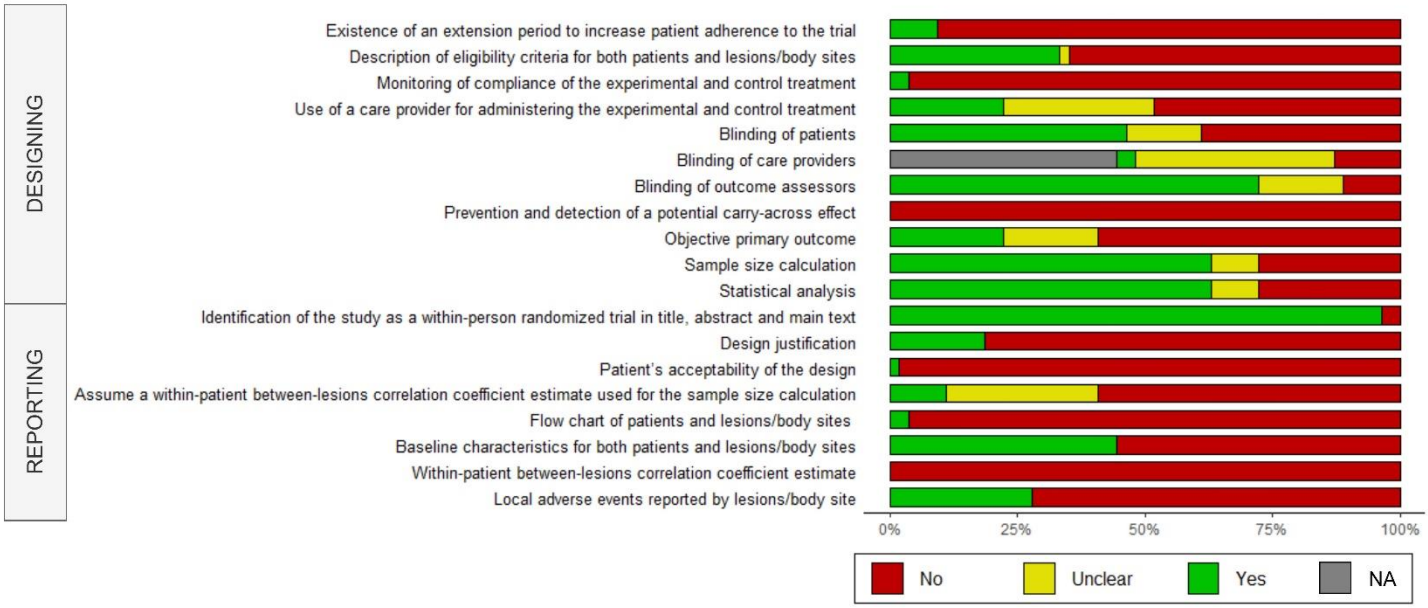
Figure 1



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

Figure 2


DESIGNING
REPORTING
Existence of an extension period to increase patient adherence to the trial
Description of eligibility criteria for both patients and lesions/body sites
Monitoring of compliance of the experimental and control treatment
Use of a care provider for administering the experimental and control treatment
Blinding of patients
Blinding of care providers
Blinding of outcome assessors
Prevention and detection of a potential carry-across effect
Objective primary outcome
Sample size calculation
Statistical analysis
Identification of the study as a within-person randomized trial in title, abstract and main text
Design justification
Patient's 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 site
0%
25%
50%
75%
100%
No
Unclear
Yes
NA

Supplemental file 1.

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4-5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	12-14
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	13, Suppl file 2
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Suppl file 2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	13
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	13-14
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	13-14
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	13-14
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	NA
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	NA
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	14
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	NA
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	NA
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	NA
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	NA

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	5-6
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	NA
Study characteristics	17	Cite each included study and present its characteristics.	6
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	NANA
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	5-9
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	NA
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	NA
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	9-10
	23b	Discuss any limitations of the evidence included in the review.	12
	23c	Discuss any limitations of the review processes used.	12
	23d	Discuss implications of the results for practice, policy, and future research.	12, Box 1
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	12
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	12
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	NA
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	2
Competing interests	26	Declare any competing interests of review authors.	15
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	15

Supplemental file 2.

Full search strategy

MEDLINE via Pubmed

#1 All Dermatology journals

((("Acta dermato-venereologica"[Journal]) OR ("Advances in skin wound care"[Journal]) OR ("Acta dermatovenerologica Croatica : ADC"[Journal]) OR ("Advances in wound care"[Journal]) OR ("Adv Wound Care (New Rochelle)"[Journal]) OR ("American journal of clinical dermatology"[Journal]) OR ("The American Journal of dermatopathology"[Journal]) OR ("Anais brasileiros de dermatologia"[Journal]) OR ("Ann Dermatol"[Journal]) OR ("Annales de dermatologie et de vénéréologie"[Journal]) OR ("Archives of dermatology"[Journal]) OR ("Arch Dermatol Res"[Journal]) OR ("The Australasian journal of dermatology"[Journal]) OR ("The British journal of dermatology"[Journal]) OR ("Burns : journal of the International Society for Burn Injuries"[Journal]) OR ("Burns Trauma"[Journal]) OR ("Clinical, cosmetic and investigational dermatology"[Journal]) OR ("Clinics in dermatology"[Journal]) OR ("Clinical and experimental dermatology"[Journal]) OR ("Contact dermatitis"[Journal]) OR ("Cutis"[Journal]) OR ("Dermatitis : contact, atopic, occupational, drug"[Journal]) OR ("Dermatologic clinics"[Journal]) OR (Dermatol surg [Journal]) OR ("Dermatologic therapy"[Journal]) OR ("Dermatol Ther (Heidelb)"[Journal]) OR ("European journal of dermatology : EJD"[Journal]) OR ("Experimental dermatology"[Journal]) OR ("Giornale italiano di dermatologia e venereologia : organo ufficiale, Società italiana di dermatologia e sifilografia"[Journal]) OR ("Der Hautarzt; Zeitschrift für Dermatologie, Venerologie, und verwandte Gebiete"[Journal]) OR ("Indian journal of dermatology, venereology and leprology"[Journal]) OR ("Indian journal of dermatology"[Journal]) OR ("International journal of cosmetic science"[Journal]) OR ("International journal of dermatology"[Journal]) OR ("International wound journal"[Journal]) OR ("Int J Low Extrem Wounds"[Journal]) OR ("Journal of the American Academy of Dermatology"[Journal]) OR ("JAMA dermatology"[Journal]) OR ("Journal of burn care research : official publication of the American Burn Association"[Journal]) OR ("Journal of cosmetic dermatology"[Journal]) OR ("Journal of cosmetic and laser therapy : official publication of the European Society for Laser Dermatology"[Journal]) OR ("Journal of cosmetic science"[Journal]) OR ("Journal of cutaneous medicine and surgery"[Journal]) OR ("Journal of cutaneous pathology"[Journal]) OR ("J Dermatolog Treat"[Journal]) OR ("The Journal of dermatology"[Journal]) OR ("J Dermatol Sci"[Journal]) OR ("Journal of drugs in dermatology : JDD"[Journal]) OR ("Journal der Deutschen Dermatologischen Gesellschaft Journal of the German Society of Dermatology : JDDG"[Journal]) OR ("Journal of the European Academy of Dermatology and Venereology : JEADV"[Journal]) OR ("The Journal of investigative dermatology"[Journal]) OR ("J Investig Dermatol Symp Proc"[Journal]) OR ("Journal of tissue viability"[Journal]) OR ("Journal of wound care"[Journal]) OR ("Lasers in

surgery and medicine"[Journal]) OR ("Leprosy review"[Journal]) OR ("Melanoma research"[Journal]) OR ("Minerva dermatologica"[Journal]) OR ("Mycoses"[Journal]) OR ("Ostomy wound management"[Journal]) OR ("Pediatric dermatology"[Journal]) OR ("Photodermatology, photoimmunology photomedicine"[Journal]) OR ("Pigment cell research"[Journal]) OR ("Postępy dermatologii i alergologii"[Journal]) OR ("Seminars in cutaneous medicine and surgery"[Journal]) OR ("Skin pharmacology and physiology"[Journal]) OR ("Skin Pharmacol Appl Skin Physiol"[Journal]) OR (“Skin Res Technol"[Journal]) OR (“Wound Repair Regen"[Journal]) OR ("Wound Manag Prev"[Journal]) OR ("Wounds"[Journal]))

#2 6 highest impact factors general medical journals

("The New England journal of medicine"[Journal]) OR ("Lancet"[Journal]) OR ("JAMA"[Journal]) OR ("JAMA internal medicine"[Journal]) OR ("British medical journal"[Journal]) OR ("Annals of internal medicine"[Journal])

#3 Selecting Within-person trials

split-face OR split-body OR split-design OR intraindividual OR intrasubject OR withinsubject OR intrapatient OR intra-individual OR intra-subject OR within-subject OR intra-patient OR within-patient OR within-person OR bilateral comparison OR within-arm OR half-side comparative OR (left half or right half) OR withinpatient OR withinperson OR withinarm

#4 Publication date later than 2017

"2017/01/07"[Date - Publication] : "2021/07/31"[Date - Publication]

#5 Language restriction

English [Language]

#1 OR #2 AND #3 AND #4 AND #5

450 RESULTS

EMBASE

Category: journal name

"Acta dermato-venereologica" OR "Advances in skin wound care" OR "Acta dermatovenerologica Croatica : ADC" OR "Advances in wound care" OR "Adv Wound Care (New Rochelle)" OR "American journal of clinical dermatology" OR "The American Journal of dermatopathology" OR "Anais brasileiros de dermatologia" OR "Ann Dermatol" OR "Annales de dermatologie et de vénéréologie" OR "Archives of dermatology" OR "Arch Dermatol Res" OR "The Australasian journal of dermatology" OR "The British journal of dermatology" OR "Burns : journal of the International Society for Burn Injuries" OR "Burns Trauma" OR "Clinical, cosmetic and investigational dermatology" OR "Clinics in dermatology" OR "Clinical and experimental dermatology" OR "Contact dermatitis" OR "Cutis" OR "Dermatitis : contact, atopic, occupational, drug" OR "Dermatologic clinics" OR “Dermatol surg” OR “Dermatologic therapy OR Dermatol Ther (Heidelb)” OR “European journal of dermatology : EJD OR Experimental dermatology” OR “Giornale italiano di dermatologia e venereologia : organo ufficiale, Società italiana di dermatologia e sifilografia" OR "Der Hautarzt; Zeitschrift für Dermatologie, Venerologie, und verwandte Gebiete" OR “Indian journal of dermatology, venereology and leprology" OR "Indian journal of dermatology" OR "International journal of cosmetic science" OR "International journal of dermatology"

Category: journal name

"International wound journal" OR "Int J Low Extrem Wounds" OR "Journal of the American Academy of Dermatology" OR "JAMA dermatology" OR "Journal of burn care research : official publication of the American Burn Association" OR "Journal of cosmetic dermatology" OR "Journal of cosmetic and laser therapy : official publication of the European Society for Laser Dermatology" OR "Journal of cosmetic science" OR "Journal of cutaneous medicine and surgery" OR "Journal of cutaneous pathology" OR "J Dermatolog Treat" OR "The Journal of dermatology" OR "J Dermatol Sci" OR "Journal of drugs in dermatology : JDD" OR "Journal der Deutschen Dermatologischen Gesellschaft Journal of the German Society of Dermatology : JDDG" OR "Journal of the European Academy of Dermatology and Venereology : JEADV" OR "The Journal of investigative dermatology" OR "J Investig Dermatol Symp Proc" OR "Journal of tissue viability" OR "Journal of wound care" OR "Lasers in surgery and medicine" OR "Leprosy review" OR "Melanoma research" OR “Minerva dermatologica" OR "Mycoses" OR "Ostomy wound management" OR "Pediatric dermatology" OR "Photodermatology, photoimmunology photomedicine" OR "Pigment cell research"

Category: journal name

"Postępy dermatologii i alergologii" OR "Seminars in cutaneous medicine and surgery" OR "Skin pharmacology and physiology" OR "Skin Pharmacol Appl Skin Physiol" OR "Skin Res Technol" OR "Wound Repair Regen" OR "Wound Manag Prev" OR "Wounds"

Category: journal name

"The New England journal of medicine" OR "Lancet" OR "JAMA" OR "JAMA internal medicine" OR "British medical journal" OR "Annals of internal medicine"

Category: all fields

split-face OR split-body OR split-design OR intraindividual OR intrasubject OR withinsubject OR intrapatient OR intra-individual OR intra-subject OR within-subject OR intra-patient OR within-patient OR within-person OR bilateral comparison OR within-arm OR half-side comparative OR (left half or right half) OR withinpatient OR withinperson OR withinarm

Publication date from 2017 to 2021

Publication data 2017 -- 2021

Language restriction

English [Language]

Final search:

((((((('acta dermato-venereologica':jt OR 'advances in skin wound care':jt OR 'acta dermatovenerologica croatica : adc':jt OR 'advances in wound care':jt OR 'adv wound care':jt) AND 'new rochelle':jt OR 'american journal of clinical dermatology':jt OR 'the american journal of dermatopathology':jt OR 'anais brasileiros de dermatologia':jt OR 'ann dermatol':jt OR 'annales de dermatologie et de vénéréologie':jt OR 'archives of dermatology':jt OR 'arch dermatol res':jt OR 'the australasian journal of dermatology':jt OR 'the british journal of dermatology':jt OR 'burns : journal of the international society for burn injuries':jt OR 'burns trauma':jt OR 'clinical, cosmetic':jt) AND 'investigational dermatology':jt OR 'clinics in dermatology':jt OR clinical:jt) AND 'experimental dermatology':jt OR 'contact dermatitis':jt OR 'cutis':jt OR 'dermatitis : contact, atopic, occupational, drug':jt OR 'dermatologic clinics':jt OR 'dermatol surg':jt OR 'dermatologic therapy':jt OR 'dermatol ther':jt) AND heidelb:jt OR 'european journal of dermatology : ejd':jt OR 'experimental dermatology':jt

OR 'giornale italiano di dermatologia e venereologia : organo ufficiale, società italiana di dermatologia e sifilografia':jt OR 'der hautarzt; zeitschrift für dermatologie, venerologie, und verwandte gebiete':jt OR 'indian journal of dermatology, venereology':jt) AND leprology:jt OR 'indian journal of dermatology':jt OR 'international journal of cosmetic science':jt OR 'international journal of dermatology':jt OR (((((('international wound journal':jt OR 'int j low extrem wounds':jt OR 'journal of the american academy of dermatology':jt OR 'jama dermatology':jt OR 'journal of burn care research : official publication of the american burn association':jt OR 'journal of cosmetic dermatology':jt OR 'journal of cosmetic':jt) AND 'laser therapy : official publication of the european society for laser dermatology':jt OR 'journal of cosmetic science':jt OR 'journal of cutaneous medicine':jt) AND surgery:jt OR 'journal of cutaneous pathology':jt OR 'j dermatolog treat':jt OR 'the journal of dermatology':jt OR 'j dermatol sci':jt OR 'journal of drugs in dermatology : jdd':jt OR 'journal der deutschen dermatologischen gesellschaft journal of the german society of dermatology : jddg':jt OR 'journal of the european academy of dermatology':jt) AND 'venereology : jeadv':jt OR 'the journal of investigative dermatology':jt OR 'j investig dermatol symp proc':jt OR 'journal of tissue viability':jt OR 'journal of wound care':jt OR 'lasers in surgery':jt) AND medicine:jt) OR 'leprosy review':jt OR 'melanoma research':jt OR 'minerva dermatologica':jt OR 'mycoses':jt OR 'ostomy wound management':jt OR 'pediatric dermatology':jt OR 'photodermatology, photoimmunology photomedicine':jt OR 'pigment cell research':jt OR (((('postępy dermatologii i alergologii':jt OR 'seminars in cutaneous medicine':jt) AND surgery:jt OR 'skin pharmacology':jt) AND physiology:jt) OR 'skin pharmacol appl skin physiol':jt OR 'skin res technol':jt OR 'wound repair regen':jt OR 'wound manag prev':jt OR 'wounds':jt OR 'the new england journal of medicine':jt OR 'lancet':jt OR 'jama':jt OR 'jama internal medicine':jt OR 'british medical journal':jt OR 'annals of internal medicine':jt) AND ((('split face' OR 'split body' OR 'split design' OR intraindividual OR intrasubject OR withinsubject OR intrapatient OR 'intra individual' OR 'intra subject' OR 'within subject' OR 'intra patient' OR 'within patient' OR 'within person' OR bilateral) AND comparison OR 'within arm' OR 'half side') AND comparative OR ((left AND half OR right) AND half) OR withinpatient OR withinperson OR withinarm) AND english:la AND [01-07-2017]/sd NOT [01-08-2021]/sd

91 RESULTS

COCHRANE

Category: all text

split-face OR split-body OR split-design OR intraindividual OR intrasubject OR withinsubject OR intrapatient OR intra-individual OR intra-subject OR within-subject OR intra-patient OR within-patient OR within-person OR bilateral comparison OR within-arm OR half-side comparative OR (left half or right half) OR withinpatient OR withinperson OR withinarm

Category: all text

Dermatology

Publication Year from 2017 to 2021

Trials

Date limitation

1203 Trials matching (split-face OR split-body OR split-design OR intraindividual OR intrasubject OR withinsubject OR intrapatient OR intra-individual OR intra-subject OR within-subject OR intra-patient OR within-patient OR within-person OR bilateral comparison OR within-arm OR half-side comparative OR (left half or right half) OR withinpatient OR withinperson OR withinarm) in All Text AND dermatology in All Text - with Publication Year from 2017 to 2021, in Trials (Word variations have been searched)

Date custom range 01/07/2017 to 31/07/2021

493 RESULTS (only trials, 0 systematic review)

Supplemental file 3.

EXTRACTION FORM: Within-person randomized controlled trials evaluating topical treatment in dermatology: a systematic review on methodological issues

Extractor name

A. GENERALITIES

A1. First author *Free text*

A2. Publication year *Free text*

A3. Journal *Free text*

A4. Subcontinent of study recruitment *(several answers possible)*

☐ North America
☐ South America
☐ Europe
☐ Asia
☐ Middle East
☐ North Africa
☐ Sub-Saharan Africa
☐ Oceania
☐ Unclear

A5. Multicenter study ☐Yes ☐No ☐ Unclear
Comment

A6. Identification as a within-person randomized trial ☐Yes ☐No ☐ Unclear
Comment

A7. If A6 = yes, term used by the authors in the title *(several answers possible)*

☐ Within-person
☐ Split-body
☐ Intra-individual
☐ Intrasubject/Intra-subject
☐ Other: *Free text*
☐ None

Comment

A8. If A6 = yes, term used by the authors in the abstract *(several answers possible)*

☐ Within-person
☐ Split-body
☐ Intra-individual
☐ Intrasubject/Intra-subject
☐ Other: *Free text*
☐ None
☐ NA (no abstract)

Comment

A9. If A6 = yes, term used by the authors in the full text *(several answers possible)*

☐ Within-person
☐ Split-body

☐ Intra-individual
☐ Intrasubject
☐ Other: *Free text*
☐ None

Comment

A10. Design justification by the authors ☐Yes ☐No
Please describe: *Free text*
Comment

A11. What is the objective? ☐ Superiority
☐ Non–inferiority/Equivalence
☐ Unclear

Comment

B. DESIGN CHARACTERISTICS

Patient and body sites/lesions

B1. Dermatologic condition *Free text*
Comment

B2. Type of population ☐ Adults
☐ Children
☐ Both
☐ Unclear

Comment

B3. Eligibility criteria are described for ☐ Patients
☐ Body sites/lesions
☐ Both
☐ Unclear

Comment

B4. Required number of units (lesions) per patient ☐ 2
☐ >2
☐ Unclear

Comment

B5. If B4 = 2, ☐ Definition of a large buffer between both areas
☐ Definition of 2 different anatomic areas
☐ Unclear

B6. If B4 = > 2, minimal number of lesions per patient = *Free text*
Comment

B7. Unit of randomization
(several answers possible) ☐ Lesion
☐ Anatomic site

☐ Upper limb
☐ Lower limb
☐ Trunk part
☐ Face/neck
☐ Pelvis area
☐ Hands/feet
☐ Nails
☐ Other: Free text
☐ Unclear

Comment

Intervention

B8. What is the number of treatments compared?
☐ 1
☐ 2
☐ 3
☐ 4

B9. Experimental treatment
(several answers possible)
☐ Corticosteroids
☐ Antibiotics
☐ Immunosuppressive drugs
☐ Anti-inflammatory drugs
☐ Chemotherapy
☐ Beta-blockers
☐ Peeling
☐ Retinoids
☐ Emollient
☐ Herbs/plants
☐ Other: *Free text*
☐ Unclear
☐ Experimental and control treatment are not identified

Comment

B10. Type of experimental
☐ Lotion
☐ Ointment
☐ Cream
☐ Gel
☐ Patch
☐ Other: *Free text*
☐ Unclear

Comment

B11. Duration of application of the treatment (in days) *Free text*
Comment

B12. Number of application of the treatment per day *Free text*
Comment

B13. Add-on design ☐Yes ☐No ☐ Unclear
Comment

B14. If B13=yes, what is the standard treatment? (i.e. standard of care)
- ☐ Topical treatment
- ☐ Peeling
- ☐ Physical treatment
  - ☐ Laser
  - ☐ Photodynamic therapy
  - ☐ Phototherapy
  - ☐ Surgery
- ☐ Physical treatment and topical treatment
  - ☐ Laser
  - ☐ Photodynamic therapy
  - ☐ Phototherapy
  - ☐ Surgery

Comment

Methods to enhance compliance
B15. Application of the topical product described (please detail = *Free text*) ☐Patient ☐Family caregiver ☐ Care provider ☐ Not
Comment

B16. Monitoring that the assigned treatment is applied to the correct site
☐Yes ☐No ☐ Not specified
Comment and detail how the monitoring was performed

Blinding
B17. Is one of these actors blinded (for the primary outcome)?
Select the actors concerned, otherwise check "No" (no blind) or "NA" (not specified or not concerned).

Participants	☐Yes ☐No ☐ Unclear
Care provider	☐Yes ☐No ☐NA ☐ Unclear
Outcome assessor	☐Yes ☐No ☐NA ☐ Unclear

Comment

Control
B18. What is the control group?
- ☐Active drug
- ☐Vehicle
- ☐Emollient cream
- ☐Other: *Free text*
- ☐Unclear

Detection of carry across effect
B19. Methods to detect carry across effect *(for example, plasma dosage of the drug)* ☐Yes ☐No ☐ Unclear

Please, describe: *Free text*
Comment

Outcome

B20. Is the primary outcome clearly identified? ☐Yes ☐No
If B20=No, go to B23.

B21. Type of outcome ☐ Objective outcome
Objective: laboratory measures (including biochemical measurements, serologic tests, and parasitology), birthweight, birth or delivery, live births, preterm birth, clinical pregnancy, death or myocardial infarction (composite), and smoking cessation (with laboratory validation).

☐ Objectively measured but potentially influenced by clinician or patient judgment
Blood transfusion, cesarean section, death or institutionalization (composite outcome), epidural analgesia, failed external cephalic version, failure of extubation, mechanical ventilation, unscheduled anesthetic intervention, induction of labor, manual removal of placenta, assisted delivery, operative delivery, other instances of further treatments administered, hospitalizations, adherence to intervention, grade at school, size for gestational age, number lost to follow-up, and withdrawals and dropouts.

☐ Subjective outcome
Signs and symptoms of disease and improvement thereof, symptom scales and scores, mental health outcomes, imaging and radiologic outcomes, pain, quality of life, adverse events of treatment, other patient-reported outcomes or those relying on a diagnosis by a physician, and cause-specific deaths.

☐ Mixture outcome (objective and subjective)

Comment

B22. Level of the primary outcome ☐At the lesion/body site level
☐At the patient level
☐Unclear

Comment

Statistical considerations

B23. What was the estimated sample size (patients)? *Free text*
☐ Not estimated

Comment

B24. What was the estimated sample size (lesions/body sites)? *Free text*
☐ Not estimated

Comment

B25. Is the within patient correlation taken into account? (focusing on correlation due to the fact that each patient will receive the two treatments)
☐Yes ☐No ☐ Unclear ☐ No sample size estimated

Comment

B26. In case more than 2 lesions per patient, correlation of outcome between 2 lesions in the same group incorporated into sample size

☐Yes ☐No ☐ Unclear

Comment

B27. Statistical methods for analysis

☐ Paired test for 2 lesions
☐ Marginal models/GEE
☐ Conditional models/mixed models
☐ No statistical methods for correlated data
☐ Other *Free text*
☐ Not described

Comment

C. RESULTS

C1. Number of patients included

Free text
☐ Unclear

Comment

C2. Mean number of units per patient

Free text
☐ Unclear

Comment

C3. Participant flow chart with number of participants

☐Yes ☐No ☐ Unclear

Comment

C4. Participant flow chart with number of lesions/body sites

☐Yes ☐No ☐ Unclear

Comment

C5. Baseline characteristics are described for

☐ Patients
☐ Body sites/lesions
☐ Both
☐ None

Comment

C6. The authors reported that the lesions/sites of each participant are similar between the 2 groups

☐Yes ☐No ☐ Unclear ☐ Reported but lesions are not similar at baseline

Comment

C7. Patients loss of follow-up/drop out ☐Yes ☐No ☐ Unclear

Comment

C8. If C7=yes, what is the number of loss of follow-up/drop out? *Free text* ☐ Unclear

Comment

C9. General adverse events/patient level ☐Yes ☐No ☐ Unclear
If C9=yes, number of patients *Free text* ☐ Unclear
Comment

C10. Local adverse events/lesion/body site level ☐Yes ☐No ☐ Unclear
If C10=yes, number of lesions/body sites in experimental group *Free text* ☐ Unclear
If C10=yes, number of lesions/body sites in control group *Free text* ☐ Unclear
Comment

D. ETHICAL ASPECTS

D1. Patient acceptability of the design reported ☐Yes ☐No ☐ Unclear
Comment

D2. Extension period ☐Yes ☐No ☐ Unclear
(experimental treatment for all patients)
Comment

D3. Ethical aspects mentioned by the authors in the article ☐Yes ☐No ☐ Unclear
If yes, please detail *Free text*

E. FUNDING BODY

E1. What was the funding sources of the study?
☐ Private
☐ Public
☐ Both private and public
☐ No specific funding
☐ Not reported
☐ Experimental treatment are given by industry

Comment

Supplemental file 4.

References of included studies

1. Saki N, Hosseinpoor S, Heiran A, et al. Comparing the Efficacy of Triamcinolone Acetonide Iontophoresis versus Topical Calcipotriol/Betamethasone Dipropionate in Treating Nail Psoriasis: A Bilateral Controlled Clinical Trial. Dermatol Res Pract. 2018:2637691.
2. Wangsuwan S, Meephansan J. Comparative Study Of Photodynamic Therapy With Riboflavin-Tryptophan Gel And 13% 5-Aminolevulinic Acid In The Treatment Of Mild To Moderate Acne Vulgaris. Clin Cosmet Investig Dermatol. 2019;12:805-814.
3. Barret JP, Podmelle F, Lipový B, et al. Accelerated re-epithelialization of partial-thickness skin wounds by a topical betulin gel: Results of a randomized phase III clinical trials program. Burns. 2017;43:1284-1294.
4. Belum VR, Marchetti MA, Dusza SW, et al. A prospective, randomized, double-blinded, split-face/chest study of prophylactic topical dapsone 5% gel versus moisturizer for the prevention of cetuximab-induced acneiform rash. J Am Acad Dermatol. 2017;77:577-579.
5. Berardesca E, Bonfigli A, Cribier B, et al. A Split-Face Study Assessing the Clinical Benefit, Tolerability and Subject Satisfaction of a Dermocosmetic in Subjects with Rosacea Associated with Erythema and Sensitive Skin. Clin Cosmet Investig Dermatol. 2020 5;13:751-758.
6. Bissonnette R, Pavel AB, Diaz A, et al. Crisaborole and atopic dermatitis skin biomarkers: An intrapatient randomized trial. J Allergy Clin Immunol. 2019;144:1274-1289.
7. Byth LA, Byth J. Topical simvastatin-cholesterol for disseminated superficial actinic porokeratosis: An open-label, split-body clinical trial. Australas J Dermatol. 2021;62:310-313.
8. Cadmus SD, Sebastian KR, Warren D, et al. Efficacy and patient opinion of wet-wrap dressings using 0.1% triamcinolone acetonide ointment vs cream in the treatment of pediatric atopic dermatitis: A randomized split-body control study. Pediatr Dermatol. 2019;36:437-441.
9. Chayahara N, Mukohara T, Tachihara M, et al. Adapalene Gel 0.1% Versus Placebo as Prophylaxis for Anti-Epidermal Growth Factor Receptor-Induced Acne-Like Rash: A Randomized Left-Right Comparative Evaluation (APPEARANCE). Oncologist. 2019;24:885-e413.

10. Chen PL, Hong JB, Shen LJ, et al. The efficacy and safety of topical rapamycin-calcitriol for facial angiofibromas in patients with tuberous sclerosis complex: a prospective, double-blind, randomized clinical trial. Br J Dermatol. 2020;183:655-663.
11. Churee C, Jiamton S, Udol K, Pratchyapruit W. Bilateral Comparison of Liquid Paraffin and Cream Base on Transepidermal Water Loss among Psoriasis Patients: A Randomized Trial. J Med Assoc Thai 2018;101:1629-33.
12. Coman GC, Holliday AC, Mazloom SE, et al. A randomized, split-face, controlled, double-blind, single-centre clinical study: transient addition of a topical corticosteroid to a topical retinoid in patients with acne to reduce initial irritation. Br J Dermatol. 2017;177:567-569.
13. Cortelazzi C, Odorici G, Castagnetti E, et al. Comparative study of imiquimod 3.75% vs. photodynamic therapy for actinic keratosis of the scalp. Photodermatol Photoimmunol Photomed. 2021;37:404-409.
14. Danilenko M, Stamp E, Stocken DD, et al. Targeting Tropomyosin Receptor Kinase in Cutaneous CYLD Defective Tumors With Pegcantratinib: The TRAC Randomized Clinical Trial. JAMA Dermatol. 2018;154:913-921.
15. Del Duca E, Farnetani F, De Carvalho N, et al. Superiority of a vitamin B_{12}-containing emollient compared to a standard emollient in the maintenance treatment of mild-to-moderate plaque psoriasis. Int J Immunopathol Pharmacol. 2017;30:439-444.
16. Dirschka T, Ekanayake-Bohlig S, Dominicus R, et al. A randomized, intraindividual, non-inferiority, Phase III study comparing daylight photodynamic therapy with BF-200 ALA gel and MAL cream for the treatment of actinic keratosis. J Eur Acad Dermatol Venereol. 2019;33:288-297.
17. Djokic-Gallagher J, Rosher P, Oliveira G, Walker J. A Double-Blind, Randomised Study Comparing the Skin Hydration and Acceptability of Two Emollient Products in Atopic Eczema Patients with Dry Skin. Dermatol Ther (Heidelb). 2017;7:397-406.
18. Dréno B, Bissonnette R, Gagné-Henley A, et al. Long-Term Effectiveness and Safety of Up to 48 Weeks' Treatment with Topical Adapalene 0.3%/Benzoyl Peroxide 2.5% Gel in the Prevention and Reduction of Atrophic Acne Scars in Moderate and Severe Facial Acne. Am J Clin Dermatol. 2019;20:725-732.
19. Frew Q, Rennekampff HO, Dziewulski P, et al. Betulin wound gel accelerated healing of superficial partial thickness burns: Results of a randomized, intra-individually controlled, phase III trial with 12-months follow-up. Burns. 2019;45:876-890.

20. Geusau A, Tzaneva S, Petzelbauer P, Mülleg et al. Peptidase inhibitor 3 and chemokine ligand 27 may serve as biomarkers for actinic keratoses in organ transplant recipients. Eur J Dermatol. 2019;29:259-267.
21. Guertler A, Niesert AC, Wilhelm KP et al. Efficacy and tolerability of a detergent and care component for rosacea patients: A split-face, vehicle-controlled, randomized trial. J Cosmet Dermatol. 2022;21:689-697.
22. Guttman-Yassky E, Ungar B, Malik K, et al. Molecular signatures order the potency of topically applied anti-inflammatory drugs in patients with atopic dermatitis. J Allergy Clin Immunol. 2017;140:1032-1042.e13.
23. How KN, Lim PY, Wan Ahmad Kammal WSL, Shamsudin N. Efficacy and safety of Jessner's solution peel in comparison with salicylic acid 30% peel in the management of patients with acne vulgaris and postacne hyperpigmentation with skin of color: a randomized, double-blinded, split-face, controlled trial. Int J Dermatol. 2020;59:804-812.
24. In Jae J, Dong Ju H, Dong Hyun K, et al. Comparative study of buffered 50% glycolic acid (pH 3.0) + 0.5% salicylic acid solution vs Jessner's solution in patients with acne vulgaris. J Cosmet Dermatol. 2018;17:797-801.
25. Jaturapisanukul K, Udompataikul M, Kanokrungsee S, et al. Efficacy and safety of a novel water-soluble herbal patch for acne vulgaris treatment: A randomized, assessor-blinds controlled, intra-individual split-face comparative study. Dermatol Ther. 2021;34:e14925.
26. Ju HJ, Kim SH, Lee JH, et al. Efficacy and safety of tretinoin 0.05% cream to prevent hyperpigmentation during narrowband UV-B phototherapy in patients with facial vitiligo: a randomized clinical trial. J Dermatolog Treat. 2022;33:1738-1741.
27. Juntongjin P, Sangganjanavanich P. Efficacy of the combined excimer light and topical calcipotriol for acral vitiligo: A randomized double-blind comparative study. Dermatol Ther. 2021;34:e14886.
28. Kantikosum K, Chongpison Y, Chottawornsak N, Asawanonda P. The efficacy of glycolic acid, salicylic acid, gluconolactone, and licochalcone A combined with 0.1% adapalene vs adapalene monotherapy in mild-to-moderate acne vulgaris: a double-blinded within-person comparative study. Clin Cosmet Investig Dermatol. 2019;12:151-161.
29. Kulthanan K, Trakanwittayarak S, Tuchinda P, et al. A Double-Blinded, Randomized, Vehicle-Controlled Study of the Efficacy of Moisturizer Containing Licochalcone A, Decanediol, L-Carnitine, and Salicylic Acid for Prevention of Acne Relapse in Asian Population. Biomed Res Int. 2020;2020:2857812.

30. Leshem YA, Wong A, McClanahan D, Simpson EL. The Effects of Common Over-the-Counter Moisturizers on Skin Barrier Function: A Randomized, Observer-Blind, Within-Patient, Controlled Study. Dermatitis. 2020;31:309-315.
31. Lueangarun S, Sriviriyakul K, Tempark T, et al. Clinical efficacy of 0.5% topical mangosteen extract in nanoparticle loaded gel in treatment of mild-to-moderate acne vulgaris: A 12-week, split-face, double-blinded, randomized, controlled trial. J Cosmet Dermatol. 2019. doi: 10.1111/jocd.12856.
32. Maarouf M, Kromenacker BW, Brucks ES, et al. Reducing unpleasant side effects of topical 5-Fluorouracil treatment for actinic keratosis: a randomized controlled trial. J Dermatolog Treat. 2020;31:175-179.
33. Mazzarello V, Piu G, Ferrari M, Piga G. Efficacy of a Topical Formulation of Sodium Bicarbonate in Mild to Moderate Stable Plaque Psoriasis: a Randomized, Blinded, Intrapatient, Controlled Study. Dermatol Ther (Heidelb). 2019;9:497-503.
34. Miola AC, Ferreira ER, Lima TRR, et al. Effectiveness and safety of 0·5% colchicine cream vs. photodynamic therapy with methyl aminolaevulinate in the treatment of actinic keratosis and skin field cancerization of the forearms: a randomized controlled trial. Br J Dermatol. 2018;179:1081-1087.
35. Nasrollahi SA, Ayatollahi A, Yazdanparast T, et al. Comparison of linoleic acid-containing water-in-oil emulsion with urea-containing water-in-oil emulsion in the treatment of atopic dermatitis: a randomized clinical trial. Clin Cosmet Investig Dermatol. 2018;11:21-28.
36. Nestor MS, Berman B, Patel J, Lawson A. Safety and Efficacy of Aminolevulinic Acid 10% Topical Gel versus Aminolevulinic Acid 20% Topical Solution Followed by Blue-light Photodynamic Therapy for the Treatment of Actinic Keratosis on the Face and Scalp: A Randomized, Double-blind Study. J Clin Aesthet Dermatol. 2019;12:32-38.
37. Nistico SP, Del Duca E, Tamburi F, et al. Superiority of a vitamin B12-barrier cream compared with standard glycerol-petrolatum-based emollient cream in the treatment of atopic dermatitis: A randomized, left-to-right comparative trial. Dermatol Ther. 2017;30.
38. Piaserico S, Piccioni A, Gutiérrez Garcìa-Rodrigo C, et al. Sequential treatment with calcitriol and methyl aminolevulinate-daylight photodynamic therapy for patients with multiple actinic keratoses of the upper extremities. Photodiagnosis Photodyn Ther. 2021;34:102325.
39. Räsänen JE, Neittaanmäki N, Ylitalo L, et al. 5-aminolaevulinic acid nanoemulsion is more effective than methyl-5-aminolaevulinate in daylight photodynamic therapy for actinic

keratosis: a nonsponsored randomized double-blind multicentre trial. Br J Dermatol. 2019;181:265-274.

40. Rossi AB, Bacquey A, Nocera T, Thouvenin MD. Efficacy and Tolerability of a Medical Device Repairing Emollient Cream Associated with a Topical Corticosteroid in Adults with Atopic Dermatitis: An Open-label, Intra-individual Randomized Controlled Study. Dermatol Ther (Heidelb). 2018;8:217-228.
41. Saki N, Ahramiyanpour N, Heiran A, et al. Efficacy of topical dimethyl sulfoxide (DMSO) 50% solution vs tretinoin 0.5% cream in treatment of patients with primary macular amyloidosis: A split-side single-blinded randomized clinical trial. Dermatol Ther. 2020;33:e13305.
42. Samadi A, Sartipi Z, Ahmad Nasrollahi S, et al. Efficacy assessments of tretinoin-loaded nano lipid carriers in acne vulgaris: a double blind, split-face randomized clinical study. Arch Dermatol Res. 2022;314:553-561.
43. Serra-Guillén C, Nagore E, Bancalari E, et al. A randomized intraindividual comparative study of methyl-5-aminolaevulinate vs. 5-aminolaevulinic acid nanoemulsion (BF-200 ALA) in photodynamic therapy for actinic keratosis of the face and scalp. Br J Dermatol. 2018;179:1410-1411.
44. Shatalebi MA, Bokaie Jazi S, Yegdaneh A, et al. Comparative evaluation of Gracilaria algae 3% cream vs Clobetasol 0.05% cream in treatment of plaque type psoriasis: A randomized, split-body, triple-blinded clinical trial. Dermatol Ther. 2020;33:e14317.
45. Suchonwanit P, Chanasumon N, Sriphojanart T. Efficacy and Safety of Bimatoprost 0.01% for the Treatment of Eyebrow Hypotrichosis: A Randomized, Double-Blind, Vehicle-Controlled Study. Dermatol Surg. 2019;45:1549-1556.
46. Togsverd-Bo K, Halldin C, Sandberg C, et al. Photodynamic therapy is more effective than imiquimod for actinic keratosis in organ transplant recipients: a randomized intraindividual controlled trial. Br J Dermatol. 2018;178:903-909.
47. Tsai J, Chien AL, Kim N, et al. Topical timolol 0.5% gel-forming solution for erythema in rosacea: A quantitative, split-face, randomized, and rater-masked pilot clinical trial. J Am Acad Dermatol. 2021;85:1044-1046.
48. Ulrich M, Reinhold U, Dominicus R, et al. Red light photodynamic therapy with BF-200 ALA showed superior efficacy in the treatment of actinic keratosis on the extremities, trunk, and neck in a vehicle-controlled phase III study. J Am Acad Dermatol. 2021;85:1510-1519.

49. Vissing AE, Dierickx C, Karmisholt KE, Haedersdal M. Topical brimonidine reduces IPL-induced erythema without affecting efficacy: A randomized controlled trial in patients with facial telangiectasias. Lasers Surg Med. 2018;50:1002-1009.
50. Wanitphakdeedecha R, Tavechodperathum N, Tantrapornpong P, et al. Acne treatment efficacy of intense pulsed light photodynamic therapy with topical licochalcone A, l-carnitine, and decanediol: A spilt-face, double-blind, randomized controlled trial. J Cosmet Dermatol. 2020;19:78-87.
51. Zhang J, Zhang X, He Y, et al. Photodynamic therapy for severe facial acne vulgaris with 5% 5-aminolevulinic acid vs 10% 5-aminolevulinic acid: A split-face randomized controlled study. J Cosmet Dermatol. 2020;19:368-374.
52. Zhang Y, Zhang H, Zhang L, et al. Modified 5-aminolevulinic acid photodynamic therapy to reduce pain in the treatment of moderate to severe acne vulgaris: A prospective, randomized, split-face study. J Am Acad Dermatol. 2021;84:218-220.
53. Zheng Y, Yin S, Xia Y, et al. Efficacy and safety of 2% supramolecular salicylic acid compared with 5% benzoyl peroxide/0.1% adapalene in the acne treatment: a randomized, split-face, open-label, single-center study. Cutan Ocul Toxicol. 2019;38:48-54.
54. Zorko MS, Štrukelj B, Švajger U, et al. Efficacy of a polyphenolic extract from silver fir (*Abies alba*) bark on psoriasis: a randomised, double-blind, placebo-controlled trial. Pharmazie. 2018;73:56-60.

3. Comparaison des méthodes statistiques pour l'analyse des essais randomisés en comparaison intra-individuelle évaluant un traitement topique avec un critère de jugement binaire : étude de simulation

3.1.Présentation du travail

Dans ce 3ème travail, nous nous sommes intéressés aux méthodes d'analyse disponibles pour les essais en « within-person ». Deux scénarios sont à considérer : i) deux lésions/sites anatomiques sont inclus ; ii) plus de 2 lésions/sites anatomiques par patient sont inclus, permettant donc d'augmenter le nombre d'observations au sein de l'essai. Dans le 1er scénario, des tests pour séries appariées (par exemple, le test de Student pour données appariées en cas de données quantitatives ou le test de Mc Nemar en cas de données qualitatives) sont utilisés. Dans le 2ème scénario, les tests pour séries appariées ne pourront pas être utilisés : la structure de corrélation entre les données est en effet plus complexe. Il existe en réalité deux types de corrélation. D'une part la corrélation entre deux lésions d'un même patient recevant le même traitement (qu'il soit expérimental ou contrôle). On appellera cette corrélation la corrélation intraclasse et on la notera ρ. On fera aussi l'hypothèse que cette corrélation intraclasse sera la même quel que soit le traitement. D'autre part, il existe une corrélation entre deux lésions d'un même patient lorsque l'une des lésions reçoit le traitement expérimental quand l'autre reçoit le traitement contrôle. Cette corrélation est définie comme la corrélation intra-patient inter-traitements et est notée η. Intuitivement, on s'attend à ce que cette seconde corrélation soit moindre que la première puisque dans ce second cas les lésions reçoivent des traitements différents, contrairement au premier cas. Le « within-person » design admet donc des similitudes avec le « pair-matched cluster randomized design »cluster en. Dans ce dernier design on apparie des clusters, et on les alloue l'un au groupe expérimental, l'autre au groupe contrôle. Dans un « within-person » design, en randomisant les lésions, on peut considérer que chaque patient a un « cluster » de lésions qui reçoivent le traitement expérimental quand un second « cluster » de lésions reçoivent le traitement contrôle. La structure des données recueillies est donc la même dans les deux designs. Les méthodes d'analyse utilisées dans les essais en cluster en « pair-matched » peuvent donc être utilisées pour l'analyse d'un « within-person trial ».

Cependant, les conditions sont différentes : les corrélations (ρ et η) sont très certainement plus élevées dans les essais en « within-person » (car il s'agit de la corrélation entre lésions d'un même patient, et non pas la corrélation entre des participants d'un même cluster), le nombre d'observations par cluster (patient) est plus faible et le nombre de patients plus faible. Nous avons donc décidé de mener une étude de simulation pour étudier les propriétés des méthodes d'analyse utilisées pour les paired-matched cluster trials lorsqu'elles sont appliquées aux essais en « within-person ». Nous avons fait le choix d'un critère de jugement binaire. Pour calibrer notre étude de simulation, nous avons utilisé les données d'un essai randomisé sur le traitement du vitiligo utilisant un schéma d'étude contrôlé en groupes parallèles avec « clustering ». Cet essai nous a permis d'estimer le nombre de lésions par patient et d'estimer un coefficient de corrélation intraclasse. Plusieurs scénarios ont donc été considérés et définis à l'aide de cette base de données. 2000 jeux de données ont été simulés et analysés pour chaque scénario.
Pour les méthodes d'analyse, nous avons retenu 2 approches : l'approche conditionnelle d'une part, avec les modèles mixtes comprenant deux effets aléatoires (patient/cluster et interaction patient/cluster-lésion), pour l'estimation d'un odds-ratio, risque relatif et différence de proportion ; et l'approche marginale d'autre part avec les *generalized estimating equations*.
Dans notre étude de simulation, il a été mis en évidence que l'approche conditionnelle avec l'estimation d'une différence de proportion (lien d'identité) et l'approche marginale permettant d'estimer un odds-ratio ou une différence de proportion ont des performances correctes.
La maîtrise et l'implémentation de ces méthodes statistiques demeurent cependant non triviale, ce qui peut expliquer que nombre d'essais en « within-person » ne retiennent que 2 lésions/sites anatomiques par patient, ce qui permet l'utilisation de tests appariés, simples d'utilisation et connus des cliniciens. En cas de nécessité d'augmentation de la puissance de l'essai ou si un ajustement de l'analyse est envisagé, un schéma d'étude avec plus de 2 lésions/sites anatomiques par patient pourra être retenu. Dans ce cas-là, il faudra privilégier une approche conditionnelle (modèle mixte avec deux effets aléatoires [patient/cluster et interaction patient/cluster-lésion]) avec lien d'identité ou une approche marginale.

3.2.Article 3

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Comparison of statistical methods to analyze a within-person randomized trial evaluating a topical drug with a binary outcome: a simulation study

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Abstract

In a dermatological within-person randomized clinical trial (WP-RCT), lesions rather than patients are randomized. Within each patient, we may then have two clusters of lesions: lesions treated with an experimental treatment and lesions treated with a control. The WP-RCT is then similar to a pair-matched cluster randomized trial (PM-CRT). However, cluster sizes are expected to be lower and number of clusters (participants) higher. Correlations between observations (lesions) are expected to be higher in WP-RCTs than PM-CRTs. Using a simulation study, we investigated the statistical properties of several methods used in PM-CRTs when applied in the context of a WP-RCT aimed at evaluating topical treatments. We considered mixed effects models using a logit, log or identity link function. Each time, three correlation structures were considered: a common, distinct or null within-patient intragroup correlation. We also assessed a marginal approach using generalized estimating equations with a relative and absolute treatment effect estimate. Variance estimators were model-based considering an exchangeable correlation structure. The marginal approach for any link and conditional approach with an identity link showed good statistical properties, whereas other approaches had convergence problems and/or inflated Type I error rates and/or bias.

1. Introduction

Some skin diseases such as vitiligo, plantar warts, and chronic plaque psoriasis are characterized by multiple, countable well-limited lesions. Topical drugs such as pharmacological drugs (topical corticosteroids, antibiotics, antifungals etc.), topical medical devices (bandages) or emollients are often used as first-line treatments, to avoid systemic effects. When assessing a topical drug in dermatology, three main designs can be used: (1) a classical individually randomized parallel design, in which patients are randomized and only one lesion per patient is considered; (2) an individually randomized parallel design with clustering: patients are randomized, but several lesions per patient are considered; the data structure of such a design is the same as that obtained in a cluster randomized trial (CRT), with patients corresponding to clusters and lesions to participants; and (3) designs allowing for a within-individual comparison, 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 (within patients) are randomized and concomitantly treated and assessed.[1]

The within-person design has been used for dermatological conditions involving several countable lesions that can be individualized (e.g., vitiligo, psoriasis).[2,3] One requirement for using this design is the absence or negligible systemic dissemination of the experimental treatment to avoid a carry across effect (defined as the potential leakage of the treatment effect from one site to another), which would correspond to an intergroup contamination.

One may distinguish two distinct types of within-person randomized clinical trials (WP-RCTs). First, a fixed and common number of two lesions per patient corresponds to a pair-matched individual design, and classical pair-matched tests can be used. Second, if the number of lesions per patient is two or more and varies among patients, by randomizing lesions to treatment groups, the design is close to a pair-matched CRT (PM-CRT).[4] Indeed, by randomly allocating lesions to treatment groups, for each patient, a cluster of lesions can be treated with the

experimental treatment and a second cluster of lesions with the control. The two so-defined clusters of lesions are pair-matched and are embedded within patients **(Figure 1**). Obviously, these "clusters" are, in some way, artificial because they do not correspond to any social unit, body site, or whatever. Nevertheless, the data structure is the same as that corresponding to a PM-CRT. Therefore, statistical methods (mixed effects models and generalized estimating equations) used to analyze PM-CRTs are potentially suitable for the analysis of a WP-RCT.

However, these methods have not been formally evaluated for the analysis of a WP-RCT. There may be two major differences between PM-CRTs and WP-RCTs. First, cluster sizes are expected to be much lower in a WP-RCT than a PM-CRT. Second, correlations are expected to be much higher because they reflect the resemblance in outcomes between lesions of a common patient, rather than resemblance among distinct individuals within social clusters. Moreover, convergence problems could be a particular challenge for this design owing to the small number of lesions per patient. This study was designed to assess the properties of common statistical methods used to analyze a PM-CRT in the specific context of the WP-RCT.

WP-RCTs are common in ophthalmology, orthopedics or dentistry. If there are only two units per participant, such as in ophthalmology (in which units are eyes) or orthopedics (in which units are knees, for instance), paired tests are used for the analysis of contralateral units, and the statistical analysis remains simple.[5] In situations with two or more units per individual, such as split-mouth trials, which are common in dentistry, cluster level analyses (e.g., adjusted chi-squared test, ratio estimation approach are common.[6,7] However, individual-level analyses would be of interest, notably because they allow for performing covariate-adjusted analyses in a unique step and they allow for estimating intervention-effect point estimates and their associated confidence intervals. Moreover, trials in dentistry, ophthalmology and orthopedics differ greatly from the within-person design used in dermatology, mainly because of the number of units per patient. Indeed, in dentistry trials, the number of units could be defined by the

number of teeth, which is larger than the number of lesions per patient expected in dermatology trials. In ophthalmology and orthopedic trials, only two eyes or two limbs are usually considered. Conversely, in dermatology, depending on the disease, the mean number of lesions per patient can reasonably be expected to be between 2 and 8 or 10.

Therefore, we conducted a simulation study to evaluate individual/lesion-level methods of analysis in the framework of a within-person design aimed at evaluating topical treatments. In section 2, we report a motivating example. Section 3 is devoted to the presentation of the statistical methods. In section 4, we present the simulation plan and report the results in section 5. We conclude with a short discussion in section 6.

2. Motivating example

Cavalié *et al* reported the results of a randomized double-blind placebo-controlled trial that assessed the effect of a maintenance therapy of a twice-weekly application of 0.1% tacrolimus ointment for adult vitiligo.[8] In this study, patients were randomized and lesions were the observational units. Therefore, the design used was an individually randomized parallel design with clustering.[1] The primary outcome was binary, corresponding to the level of depigmentation, with 0 indicating no depigmentation and 1 at least some depigmentation. Thirty-five patients were randomized (16 in the placebo group and 19 in the tacrolimus group), for a total of 72 lesions (31 in the placebo group and 41 in tacrolimus group). The mean number of lesions per patient was 2.06 (SD 0.954). Outcomes were missing for five patients and were imputed as failures. In all, 30 (73.2%) lesions showed no depigmentation in the tacrolimus group and 16 (51.6%) in the placebo group. Within-patient intragroup correlations were estimated at 0.89 [95% CI 0.76-0.96] and 0.51 [95% CI 0.0-0.80] in the tacrolimus and placebo groups, respectively (intention-to-treat population) or 0.68 [95% CI 0.33-0.88] and 0.37 [95% CI 0.0-0.76], respectively (per-protocol population). Obviously, no within-patient inter-group

correlation was estimated because of the design. Although the Cavalié *et al.* study is not a WP-RCT, it provides helpful parameter estimates that can be used for planning a future trial with a WP-RCT design. These parameter estimates are also useful to calibrate the simulation study reported in the present manuscript.

3. Methods

3.1. Notation

We define y_{ijs} as the observation associated with lesion *i* in patient *j* exposed to intervention *s*, where $s \in \{0, 1\}$ with *s* = 0 referring to the control group and *s* = 1 to the treatment group. y_{ijs} is a binary outcome with $y_{ijs} = 1$ corresponding to success and $y_{ijs} = 0$ to failure.

Within each patient *j* (who may be considered as a stratum), half of the lesions are randomly allocated to the treatment group (*s* = 1) and the others to the control group (*s* = 0), which leads to defining two clusters of lesions, with lesions exchangeable within each cluster (**Figure 1**).

3.2. Conditional approach: mixed effects models

Let us consider the following model:

$$y_{ijs} \sim Bin\left(1, E\left(y_{ijs}\right)\right)$$

Three link functions are considered: a logit, a log and an identity link, thus leading to estimating an odds ratio, a relative risk and a risk difference, respectively.

Logit link

We assume:

$$logit E\left(y_{ijs}\right) =$$

$$\mu^{C;\,Logit} + x_{ijs}\theta^{C;\,Logit} + \gamma_j^{C;\,Logit} + x_{ijs}\gamma^{C;\,Logit}(T)_j + \left(1 - x_{ijs}\right)\gamma^{C;Logit}(C)_j \qquad (1)$$

where

the *C; Logit* superscript refers to the conditional approach with a logit link

$\mu^{C;\,Logit}$ is the overall mean

x_{ijs} is the treatment indicator, with $x_{ij0} = 0$ for the control group and $x_{ij1} = 1$ for the treatment group

$\theta^{C;\,Logit}$ is the fixed treatment effect

${\gamma_j}^{C;\,Logit}$ $\gamma^{C;\,Logit}(C)_j$ and $\gamma^{C;\,Logit}(T)_j$ are the random patient effect and the random cluster effect for control (C) and treatment (T) conditions, respectively, with

$$\begin{pmatrix} {\gamma_j}^{C;\,Logit} \\ \gamma^{C;\,Logit}(C)_j \\ \gamma^{C;\,Logit}(T)_j \end{pmatrix} \sim N\left[\begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \tau^2_{\gamma^{C;\,Logit}} & 0 & 0 \\ 0 & \tau^2_{\gamma^{C;\,Logit}(C)} & 0 \\ 0 & 0 & \tau^2_{\gamma^{C;\,Logit}(T)} \end{pmatrix} \right]$$

From model (1), the treatment effect estimate $exp\left(\hat{\theta}^{C;Logit}\right)$ is expressed on a relative scale by an odds ratio.

Log link

We assume:

$$logE(y_{ijs}) =$$

$$\mu^{C;\,Log} + x_{ijs}\theta^{C;\,Log} + \gamma_j^{C;\,Log} + x_{ijs}\gamma^{C;\,Log}(T)_j + (1 - x_{ijs})\gamma^{C;Log}(C)_j \qquad (2)$$

where the *C; Log* superscript refers to the conditional approach with a log link, and parameters, both fixed and random, are defined as in model (1). The treatment effect estimate $exp\left(\hat{\theta}^{C;Log}\right)$ is expressed on a relative scale by a relative risk.

Identity link

We assume:

$$E(y_{ijs}) = \mu^{C;\,Id} + x_{ijs}\theta^{C;\,Id} + \gamma_j^{C;\,Id} + x_{ijs}\gamma^{C;\,Id}(T)_j + (1 - x_{ijs})\gamma^{C;\,Id}(C)_j \qquad (3)$$

where the *C; Id* superscript refers to the conditional approach with an identity link, and parameters, both fixed and random, are defined as in model (1). The treatment effect estimate $\hat{\theta}^{C;\,Id}$ is expressed as an absolute risk difference.

Random effect variances

For each model (1) to (3), we consider the following three correlation structures (CSs):

1) $\tau^2_{\gamma^{C;\,Link}(C)} = \tau^2_{\gamma^{C;\,Link}(T)}$ (CS 1)

2) $\tau^2_{\gamma^{C;\,Link}(C)} \neq \tau^2_{\gamma^{C;\,Link}(T)}$ (CS 2)

3) $\tau^2_{\gamma^{C;\,Link}(C)} = \tau^2_{\gamma^{C;\,Link}(T)} = 0$ (CS 3)

Where the *C; Link* superscript refers to a conditional model (C) with a *logit*, *log* or *identity* link function.

In the special case of an identity link function, one can easily derive the following results in terms of the CS (**Figure 1**):

1) In CS 1, the two groups share a common non-null within-patient intragroup correlation:

   $\forall s, \forall j \;\; corr\left(y_{i_1 js};\, y_{i_2 js}\right) = \rho \;\; (i_1 \neq i_2).$

   The within-patient intergroup correlation is defined as:

   $\forall j \;\; corr\left(y_{i_1 j0};\, y_{i_2 j1}\right) = \eta \;\; (i_1 \neq i_2)$

2) In CS 2, the two groups have distinct within-patient intragroup correlations:

   $\forall j \;\; corr\left(y_{i_1 js};\, y_{i_2 js}\right) = \rho_s \;\; (i_1 \neq i_2)$

   with $(\rho_0 \neq \rho_1)$.

   The within-patient intergroup correlation is defined as:

$$\forall j \ corr\left(y_{i_1 j0};\ y_{i_2 j1}\right) = \eta \ \ (i_1 \neq i_2)$$

3) In CS 3, the within-patient correlation between two lesions is the same, whether the two lesions are treated in the same way or not:

$$\forall j \ \forall s_1 \ \forall s_2 corr\left(y_{i_1 j s_1};\ y_{i_2 j s_2}\right) = \eta \ \ (i_1 \neq i_2)$$

3.3. Marginal approach

We use the approach proposed by Liang *et al.* in the context of a matched case–control/family sampling design.[9] In this latter design, cases and matched controls are recruited. Then family members of both cases and controls are recruited. In the end, for each case–control pair, we have two matched families, which may be considered two matched clusters. As a consequence, the data structure is the same as that obtained in a WP-RCT. Liang *et al.* proposed to use a generalized estimating equation (GEE) approach to analyse such data.[9] For that, they consider "pseudo-observations" by considering all possible differences $\left(y_{i_1 j1} - y_{i_2 j0}\right)$ and then applying a GEE method.

Relative treatment effect estimate

Because data are binary, pseudo-observations $\left(y_{i_1 j1} - y_{i_2 j0}\right)$ can take only three values: -1, 0 and +1. A 0 value corresponds to a "concordant" pair and a -1 or +1 value corresponds to a "discordant" pair, for which we have $\left(y_{i_1 j1} + y_{i_2 j0} = 1\right)$. As in a conventional individually matched design, only "discordant" pairs are of interest.

In patient *j*, the number N_j of "discordant" pseudo-observations is defined by:

$$N_j = y_{+j1}\left(n_{j0} - y_{+j0}\right) + y_{+j0}\left(n_{j1} - y_{+j1}\right)$$

where n_{j0} and n_{j1} are the number of lesions in patient *j* in the control and treatment conditions, respectively, and y_{+j0} and y_{+j1} are the number of lesions with a success outcome in patient *j* in the control and treatment conditions, respectively.

For the statistical analysis, we only consider the "discordant" pairs; that is, we will consider only N_j pseudo-observations in patient *j*. For each of these pseudo-observations, we consider y_{ij1} and use a GEE approach to model its expectation. The associated model is:

$$logit\left(E\left(y_{i_1 j1}/y_{i_1 j1} + y_{i_2 j0} = 1\right)\right) = \theta^{M;\,Logit} \quad (4)$$

where the *M; Logit* superscript refers to the marginal approach with a logit link and $exp\left(\hat{\theta}^{M}\right)$ corresponds to the treatment effect estimate expressed on a relative scale by an odds ratio.

Absolute treatment effect estimate

To estimate a risk difference, we take into account all pseudo-observations, whether discordant or not. Thus, we have $\left(n_{j0} + n_{j1}\right)$ observations for subject *j*. We then consider the following model:

$$E\left(y_{i_1 j1} - y_{i_2 j0}\right) = \theta^{M;Id'} \quad (5)$$

where the *M; Id* superscript refers to the marginal approach with an identity link and $\hat{\theta}^{M;\,Id}$ the treatment effect estimate expressed on an absolute scale as a risk difference.

4. Simulation study

4.1. Data-generating mechanism

The following steps are followed:

(1) The number of lesions per patient (i.e., stratum) is generated by using a Poisson distribution with parameter m. The distribution is truncated to have a minimum number of two lesions and a maximum number of 10, 12 and 18 lesions for m equal to 4, 6 and 10, respectively.

(2) Outcomes are generated considering multivariate correlated binary data with marginal probabilities of $(p_0, p_0, \ldots, p_0, p_1, p_1, \ldots, p_1)$, with p_0 and p_1 the success rates in the two groups and correlation matrix $\sum$ defined as:

$$\sum = \begin{pmatrix} 1 & \cdots & \rho_0 & \eta & \cdots & \eta \\ \vdots & 1 & \vdots & \vdots & \eta & \vdots \\ \rho_0 & \cdots & 1 & \eta & \cdots & \eta \\ \eta & \ldots & \eta & 1 & \cdots & \rho_1 \\ \vdots & \eta & \vdots & \vdots & 1 & \vdots \\ \eta & \cdots & \eta & \rho_1 & \cdots & 1 \end{pmatrix}$$

with ρ_0 the within-patient intragroup correlation in the control group, ρ_1 the within-patient intragroup correlation in the experimental group and η the within-patient inter-group correlation.

Data were generated by using the Emrich and Piedmonte method.[10] Such an approach requires having a paired number of observations. As a consequence, if the number of lesions generated in the previous step was an odd number, we generated one more outcome and then randomly discarded one of these outcomes.

4.2. Simulation parameters

If there is no treatment effect, simulation parameters are specified as follows:

- Mean number of lesions per cluster (m): m = (2, 3 and 5)
- Success rates in the control and intervention groups: (p_0, p_1) = (0.1, 0.1), (0.3, 0.3) and (0.5 and 0.5)
- Within-patient intragroup correlation (common to both treatment groups): ρ = (0.2, 0.37 and 0.6). The 0.37 value was the value observed in the motivating example.
- Within-patient intergroup correlation: η = (0.3ρ, 0.5ρ and 0.8ρ)
- Number of patients: 100

If there is a treatment effect, simulation parameters are specified as follows:

- Mean number of lesions per cluster: m = (2, 3 and 5)

- Success rates in the control and intervention groups: $(p_{0,}\, p_1)$ = (0.1, 0.2), (0.3, 0.4) and (0.3 and 0.5)
- Within-patient intragroup correlation:
    - ρ_0 = (0.2, 0.37 and 0.6)
    - $\rho_1 = (\rho_0)^{0.9}$ when $(p_{0,}\, p_1)$ = (0.1, 0.2), (0.3, 0.4)
    - $\rho_1 = (\rho_0)^{0.8}$ when $(p_{0,}\, p_1)$ = (0.3, 0.5)

  Indeed, intra-group correlation is expected to differ between the two groups because the intraclass correlation coefficient (ICC) is known to depend on the prevalence.[11,12]
- Within-patient intergroup correlation: η = ($0.3\rho_0$, $0.5\rho_0$ and $0.8\rho_0$)
- Number of patients: to our knowledge, there is currently no available sample size formula to calculate the required number of patients for a binary outcome in the context of a PM-CRT. Therefore, we approached the required sample size by using the formula derived in the framework of a cross-over cluster randomized design with a continuous outcome, thus abusively considering p_0 and p_1 as means rather than proportions, which led us to consider $\rho_0 = \rho_1 = \rho$.[13]

4.3. Estimands

Estimands of interest are the odds ratio, the risk ratio and the risk difference, depending on the link function.

4.4. Methods of analysis

Generalized linear mixed-effects models (1), (2) and (3) and marginal models (4) and (5) are fitted (**Table 1**).

4.5. Performance measures

The statistical methods performance is evaluated based on the following:

- Convergence rate defined as the proportion of simulated datasets with a convergence problem. We considered that there was a convergence problem when specified by the software but also when a fit singular problem occurred and finally when the estimated odds ratio was > 10, which we considered an outlier value. No outlier value was observed for the risk difference and relative risk.
- Type I error rate defined as the proportion of simulated datasets with a significant intervention effect when the effect size is fixed at 0.
- Bias of the treatment effect estimate: $\frac{1}{n_{sim}} \sum_{i=1}^{n_{sim}} \hat{\theta}_i - \theta$, where θ corresponds to the odds ratio, risk ratio or the success-rate difference and n_{sim} the number of simulated datasets.
- Power is calculated as the proportion of datasets with a significant intervention effect ($p<0.05$).
- Coverage rates defined as the proportion of 95% confidence intervals (CIs) containing the true parameter value.

4.6. Implementation

For each scenario, we simulated 2000 datasets by using R 4.1.1 (R Foundation for Statistical Computing, Vienna, Austria). The input seed was specified as “123” for each scenario. The MultiOrd package (generate.binary function) was used to generate binary correlated data. Generalized linear mixed-effects models were estimated by using the lme4 package and the glmmTMB package. Marginal models were estimated by using the geepack package. The code is available at https://github.com/sleducq/Simulation-study-with-R-software.git .

5. Results

Results are presented in three steps (**Table 2**). Indeed, some methods were gradually withdrawn depending on the results obtained for type I error rate, convergence and bias.

5.1. First step: type I error rate (**Figure 2**)

Figure 2A displays the results associated with CS 1 (i.e., when a common within-patient intragroup correlation is hypothesized, no model misspecification), and **Figure 2B and 2C** display the results associated with CS 2 (i.e., when a distinct within-patient intragroup correlation is hypothesized, model over-specification) and CS 3 (i.e., when a null within-patient intragroup correlation is hypothesized, model misspecification), respectively. Results associated with the marginal approach are also displayed in **Figure 2A**. In CS 1, the Type I error is close to the 5% nominal value when using an identity link in a conditional approach and when using a marginal approach (whatever the link function). When using a logit or a log link and a conditional approach, depending on ρ and η, the type I error is close to the nominal value or higher or lower. In CS 2, when using an identity link, the Type I error rates are quite close to the 5% nominal value. Otherwise, they are sometimes much higher or much lower, depending on the link function and the ICC. In CS 3, Type I error is much higher than the 5% nominal value when using a logit or an identity link. This is all the more true as the ICC increases. When using a log link, the type I error rate is higher than the 5% nominal level in some circumstances and lower in others. A major limitation of methods corresponding to CS 3 is that they do not respect the correlation structure of the simulated data, and this translates to poor Type I error rates. Therefore, CS 3 has been ruled out for the next step.

5.2. Second step: convergence rate and bias (**Figures 3 and 4**)

Figure 3A displays the results for convergence rate associated with CS 1 (i.e., when a common within-patient intragroup correlation is hypothesized, no model misspecification), whereas **Figure 3B** displays the results for convergence rate associated with CS 2 (i.e., when a distinct within-patient intragroup correlation is hypothesized, model over-specification). Convergence rates associated with marginal approaches are also displayed in **Figure 3A**. In CS 1, the convergence rate is close to 100% when using a marginal approach. When using a logit link and a conditional approach, the convergence rate is much lower than 100% in some circumstances. When using a log link and a conditional approach, the convergence rate is close to 0% in some circumstances and increases as the ICC increases. When using an identity link and a conditional approach, depending on ρ and η, the convergence rate is close to 100%, or lower. In CS 2, when using a log or identity link, the convergence rate is close to 100%. When using a logit link, the convergence rate decreases as the ICC increases.

Figure 4A displays the results for bias rate associated with the conditional approach considering a logit link associated with CSs 1 and 2 and the marginal approach with a relative treatment effect estimate. **Figure 4B** displays the results for bias rate associated with a conditional approach considering a log link associated with CSs 1 and 2 and a marginal approach with an absolute treatment effect estimate. **Figure 4C** displays the results for bias rate associated with a conditional approach considering an identity link associated with CSs 1 and 2. A conditional approach with a logit or log link considering both a common non-null and a distinct within-patient intragroup correlation show some bias especially when the ICC increases. The conditional approach with an identity link considering both a common non-null and a distinct within-patient intragroup and marginal approach with an absolute treatment effect estimate showed nearly no bias. The marginal approach with a relative treatment effect estimate showed some bias, notably as the ICC increases, but much less smaller than when using a conditional approach.

Therefore, the conditional approach considering a logit and log link (i.e., with the convergence rate low and/or the bias high) has been ruled out for the third step.

5.3. Third step: power and coverage rate (**Figures 5 and 6**)

Figures 5 and 6 show the results for power and convergence rate, respectively, associated with the conditional approach involving an identity link and the marginal approach. When using an identity link and a conditional approach, the empirical power is close to the nominal power 80%. When using a marginal approach, depending on ρ and η, the empirical power is close to the nominal value or lower for some circumstances. When using an identity link and a conditional approach, the coverage rate is close to the nominal value of 95%. When using a marginal approach, depending on ρ and η, the coverage rate is close to the nominal value or lower in some circumstances.

6. Discussion

In this paper, we evaluated different methods of analysis for WP-RCTs assessing a topical treatment in dermatology. Conditional models with an identity link function as well as marginal models (both for estimating an odds ratio or a risk difference) performed well overall, and we recommend their use for analysing WP-RCTs. The correlation structure should be correctly specified considering a distinct between-group correlation than within-group correlations. Specifying a common within-patient intragroup correlation or two distinct within-patient intragroup correlations is of limited influence. One limitation of this simulation study was the choice of parameters for simulation. Indeed, simulation parameters were calibrated by using an individually randomized parallel design with clustering rather than a WP-RCT.

To conclude, for a WP-RCT, we propose the following. If possible, prefer a design with two units per patient. In doing so, classical paired tests will be used: processes will be easy and

better understood by clinicians. Otherwise, to increase power, especially for rare skin diseases, or if adjusting the analysis is considered, a WP-RCT can be used. Then data should be analysed using a conditional approach with an identity link function (with a common or distinct within-patient intragroup correlation) or a marginal approach with an absolute or relative treatment effect estimate.

Abbreviations

CS: Correlation structure

PM-CRT: pair-matched cluster randomized trial

WP-RCT: within-person randomized clinical trial

Declaration of conflicting interests: The authors declare no conflict of interest.

References

1. Leducq S, Caille A, Le Cleach L, et al. Research Techniques Made Simple: Randomized Controlled Trials for Topical Drugs in Dermatology: When and How Should We Use a Within-Person Design? *J Invest Dermatol* 2020; 140: 931-938.e1
2. Lepé V, Moncada B, Castanedo-Cazares JP, et al. A double-blind randomized trial of 0.1% tacrolimus vs 0.05% clobetasol for the treatment of childhood vitiligo. *Arch Dermatol* 2003; 139: 581-5.
3. Tzaneva S, Hönigsmann H, Tanew A. Observer-blind, randomized, intrapatient comparison of a novel 1% coal tar preparation (Exorex) and calcipotriol cream in the treatment of plaque type psoriasis. *Br J Dermatol* 2003; 149: 350-3.
4. Donner A. Some aspects of the design and analysis of cluster randomization trials. *Appl Statist* 1998; 47: 95-113
5. Lee CF, Cheng AC, Fong DY. Eyes or subjects: are ophthalmic randomized controlled trials properly designed and analyzed? *Ophthalmology* 2012: 119: 869-72.
6. Donner A, Klar N, Zou G. Methods for the statistical analysis of binary data in split-cluster designs. *Biometrics* 2004; 60: 919-25.
7. Pandis N, Walsh T, Polychronopoulou A, et al. Split-mouth designs in orthodontics: an overview with applications to orthodontic clinical trials. *Eur J Orthod* 2013; 35: 783-9.
8. Cavalié M, Ezzedine K, Fontas E, et al. Maintenance therapy of adult vitiligo with 0.1% tacrolimus ointment: a randomized, double blind, placebo-controlled study. *J Invest Dermatol* 2015; 135: 970-974.
9. Liang KY, Pulver AE. Analysis of case-control/family sampling design. *Genet Epidemiol* 1996; 13: 253-70.
10. Emrich LJ, Piedmonte MR. A method for generating high-dimensional multivariate binary variates. *Am Stat* 1991; 45: 302-4.

11. Gulliford MC, Adams G, Ukoumunne OC, Latinovic R, Chinn S, Campbell MJ. Intraclass correlation coefficient and outcome prevalence are associated in clustered binary data. *J Clin Epidemiol* 2005; 58: 246-51.
12. Mbekwe Yepnang AM, Caille A, Eldridge SM, Giraudeau B. Association of intracluster correlation measures with outcome prevalence for binary outcomes in cluster randomised trials. *Stat Methods Med Res* 2021; 30: 1988-2003.
13. Giraudeau B, Ravaud P, Donner A. Sample size calculation for cluster randomized cross-over trials. *Stat Med* 2008; 27: 5578-85.

Figure legends

Figure 1. Definition of strata, clusters, observations and correlations for a within-person design

Figure 2. Type I error simulation results. Horizontal reference line is added to the figure at 5%. The following parameters are used: mean number of lesions per cluster (*m*): *m* = (2, 3 and 5); success rates in the control and intervention groups: (p_0, p_1) = (0.1, 0.1), (0.3, 0.3) and (0.5 and 0.5); within-intragroup correlation (ICC): ρ = (0.2, 0.37 and 0.6) and within inter-group intra-patient correlation: η = (0.3ρ, 0.5ρ and 0.8ρ). We performed 2000 simulations for each parameter combination. (A) Simulation results associated with conditional models and correlation structure 1 (CS 1) (i.e., when a common within-patient intragroup correlation is hypothesized) and marginal models. For the conditional approach using a log link, some values are missing because analyses failed to converge; (B) simulation results associated with conditional models and CS 2 (i.e. when a distinct within-patient intragroup correlation is hypothesized) and (C) simulation results associated with conditional models and CS 3 (i.e. when a null within-patient intragroup correlation is hypothesized).

Figure 3. Convergence rate simulation results. Horizontal reference line is added to the figure at 100%. The following parameters are used: mean number of lesions per cluster (*m*): *m* = (2, 3 and 5); success rates in the control and intervention groups: (p_0, p_1) = (0.1, 0.2), (0.3, 0.5) and (0.3 and 0.4); within-intragroup correlation (ICC): ρ_0 = (0.2, 0.37 and 0.6), $\rho_1 = (\rho_0)^{0.9}$ when (p_0, p_1) = (0.1, 0.2), (0.3, 0.4) and $\rho_1 = (\rho_0)^{0.8}$ when (p_0, p_1) = (0.3, 0.5) (only values of ρ_0 are represented on the figures) and within intergroup intra-patient correlation: η = (0.3ρ, 0.5ρ and 0.8ρ). We performed 2000 simulations for each parameter combination. (A) Simulation results associated with conditional models and correlation structure 1 (i.e., when a common within-patient intragroup correlation is hypothesized) and marginal models; and (B) simulation results associated with conditional models and CS 2 (i.e. when a distinct within-patient intragroup correlation is hypothesized).

Figure 4. Bias rate simulation results. Horizontal reference line is added to the figure at 0%. The following parameters are used: mean number of lesions per cluster (m): m = (2, 3 and 5); success rates in the control and intervention groups: (p_0, p_1) = (0.1, 0.2), (0.3, 0.5) and (0.3 and 0.4); within-intragroup correlation (ICC): ρ_0 = (0.2, 0.37 and 0.6), $\rho_1 = (\rho_0)^{0.9}$ when (p_0, p_1) = (0.1, 0.2), (0.3, 0.4) and $\rho_1 = (\rho_0)^{0.8}$ when (p_0, p_1) = (0.3, 0.5) (only values of ρ_0 are represented on the figures) and within intergroup intra-patient correlation: η = (0.3ρ, 0.5ρ and 0.8ρ). We performed 2000 simulations for each parameter combination. (A)* Simulation results for conditional approach based on mixed models considering a logit link associated with CS 1 (i.e., when a common within-patient intragroup correlation is hypothesized) and marginal approach with a relative treatment effect estimate; (B)* simulation results for conditional approach considering a log link associated with CS 1 (i.e., when a common within-patient intragroup correlation is hypothesized) and 2 (i.e. when a distinct within-patient intragroup correlation is hypothesized), and marginal approach with an absolute treatment effect estimate; and (C)* simulation results for conditional approach considering an identity link associated with CSs 1 and 2. *The scale is different between these three figures.

Figure 5. Power simulation results for the conditional approach using an identity link with a common non-null and a distinct within-patient intragroup and for the marginal approach with an absolute and relative treatment effect estimate. Horizontal reference line is added to the figure at 80%. The following parameters are used: mean number of lesions per cluster (m): m = (2, 3 and 5); success rates in the control and intervention groups: (p_0, p_1) = (0.1, 0.2), (0.3, 0.5) and (0.3 and 0.4); within-intragroup correlation (ICC): ρ_0 = (0.2, 0.37 and 0.6), $\rho_1 = (\rho_0)^{0.9}$ when (p_0, p_1) = (0.1, 0.2), (0.3, 0.4) and $\rho_1 = (\rho_0)^{0.8}$ when (p_0, p_1) = (0.3, 0.5) (only values of ρ_0 are represented on the figures) and within intergroup intra-patient correlation: η = (0.3ρ, 0.5ρ and 0.8ρ). We performed 2000 simulations for each parameter combination.

Figure 6. Coverage rate simulation results for the conditional approach using an identity link with a common non-null and a distinct within-patient intragroup and for the marginal approach with an absolute and relative treatment effect estimate. Horizontal reference line is added to the figure at 95%. The following parameters are used: mean number of lesions per cluster (m): m = (2, 3 and 5); success rates in the control and intervention groups: (p_0, p_1) = (0.1, 0.2), (0.3, 0.5) and (0.3 and 0.4); within-intragroup correlation (ICC): ρ_0 = (0.2, 0.37 and 0.6), $\rho_1 = (\rho_0)^{0.9}$ when (p_0, p_1) = (0.1, 0.2), (0.3, 0.4) and $\rho_1 = (\rho_0)^{0.8}$ when (p_0, p_1) = (0.3, 0.5) (only values of ρ_0 are represented in the figures) and within intergroup intra-patient correlation: η = (0.3ρ, 0.5ρ and 0.8ρ). We performed 2000 simulations for each parameter combination.

Tables

Table 1. Summary of methods of analysis used

	Model	**Correlation structure**
Conditional approach based on mixed models		
Logit link: estimation of odds ratio	(1)	Correlations structures 1, 2, 3
Log link: estimation of relative-risk	(2)	Correlations structures 1, 2, 3
Identity link: estimation of risk difference	(3)	Correlations structures 1, 2, 3
Marginal approach using generalized estimating equations		
Relative treatment effect estimate	(4)	-
Absolute treatment effect estimate	(5)	-

Table 2. Summary of methods used for analysing of each simulated dataset

	Included in first step (type I error rate)	**Included in second step (bias and convergence rate)**	**Included in third step (power and coverage rate)**
Conditional approach based on mixed models			
Logit link: estimation of odds ratio			
• Correlation structure 1 (no model misspecification)	**X**	**X**	
• Correlation structure 2 (model over-specification)	**X**	**X**	
• Correlation structure 3 (model misspecification)	**X**		
Log link: estimation of relative-risk			
• Correlation structure 1 (no model misspecification)	**X**	**X**	
• Correlation structure 2 (model over-specification)	**X**	**X**	
• Correlation structure 3 (model misspecification)	**X**		
Identity link: estimation of risk difference			
• Correlation structure 1 (no model misspecification)	**X**	**X**	**X**
• Correlation structure 2 (model over-specification)	**X**	**X**	**X**
• Correlation structure 3 (model misspecification)	**X**		
Marginal approach using generalized estimating equations			

Relative treatment effect estimate	**X**	**X**	**X**
Absolute treatment effect estimate	**X**	**X**	**X**

Correlation structure 1: common non-null within-patient intragroup correlation, correlation structure 2: distinct within-patient intragroup correlation, correlation structure 3: same within-patient correlation between 2 lesions regardless of the treatment received

Figures

Figure 1

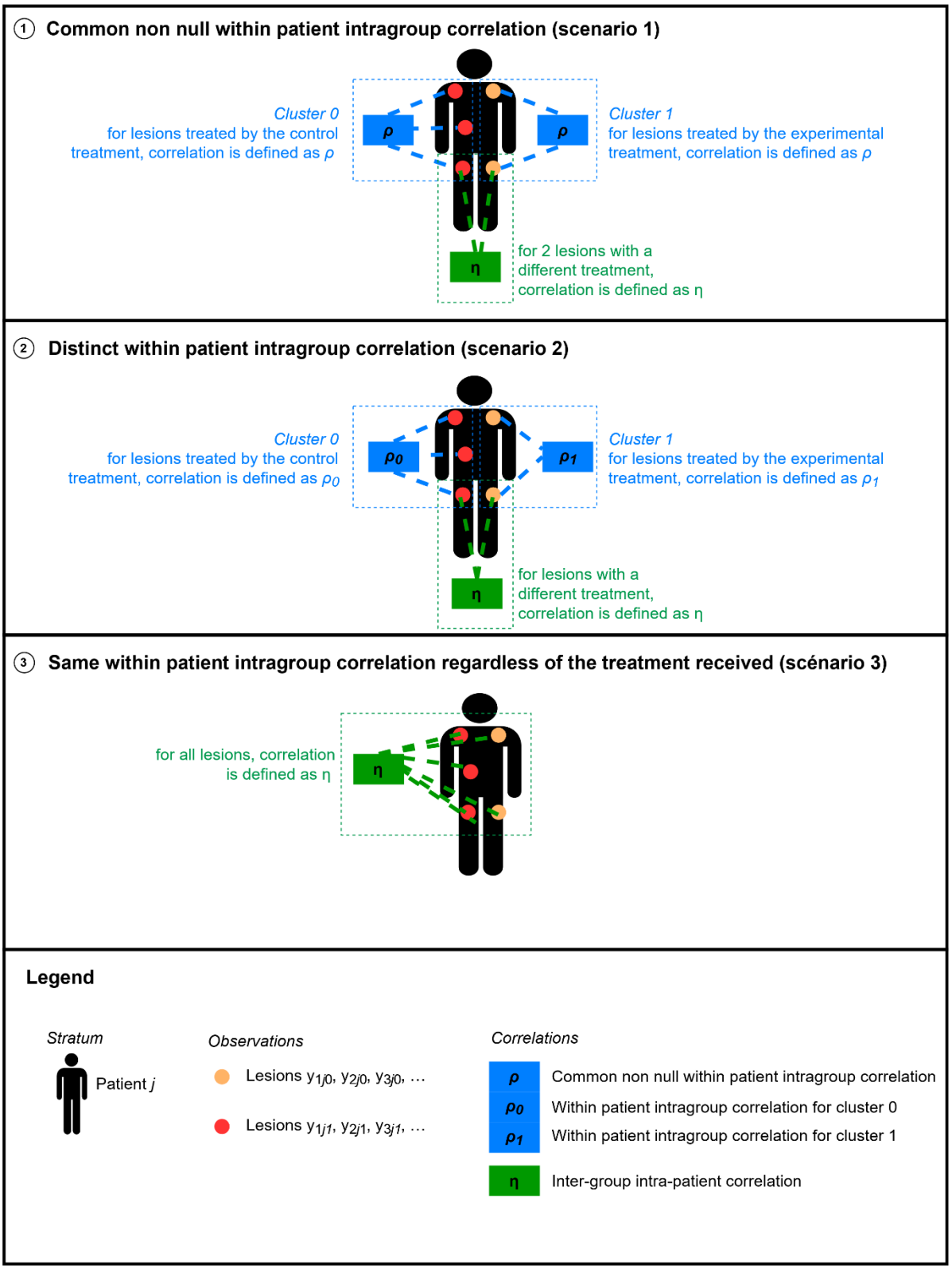


Figure 2A

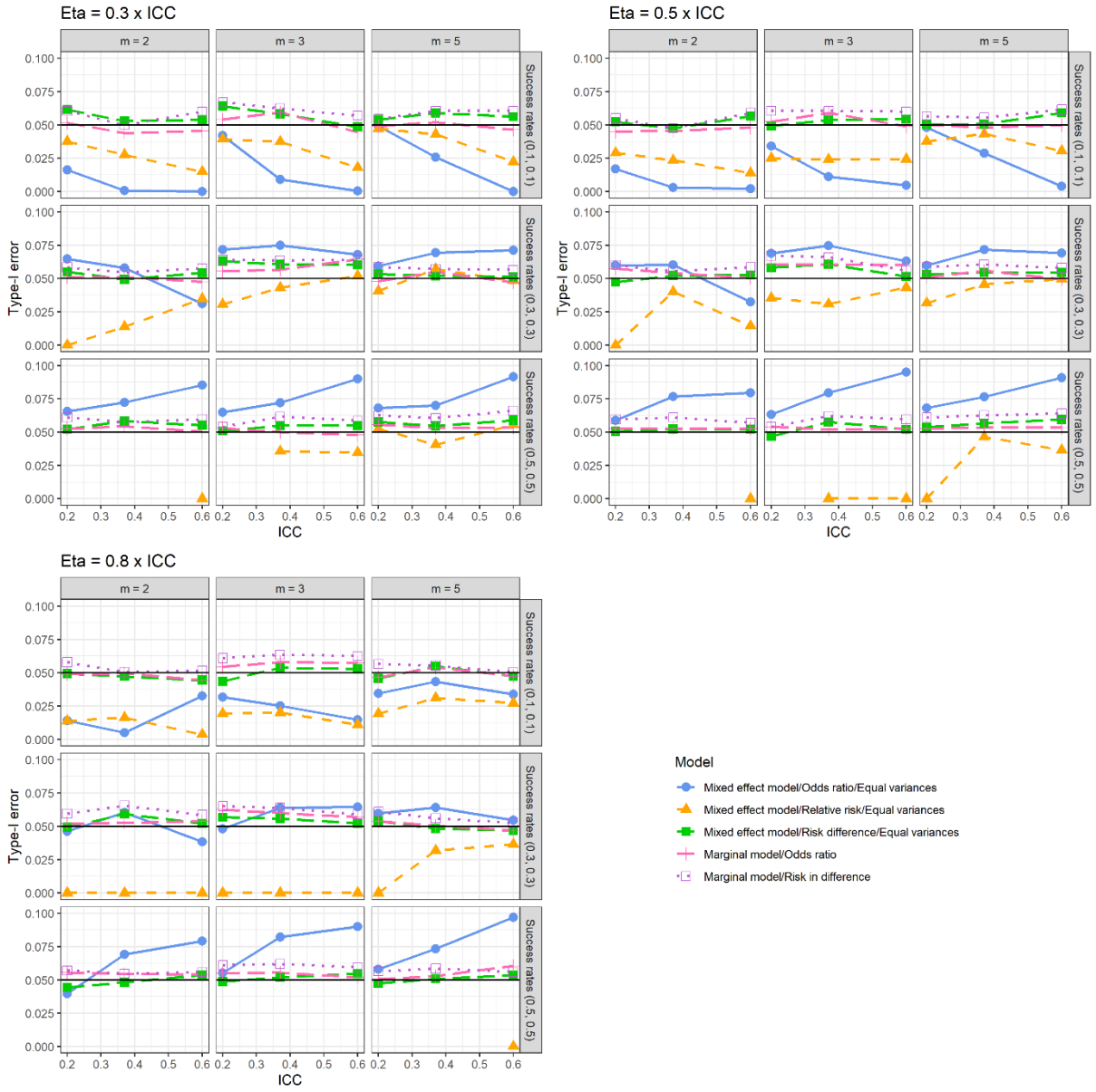

Eta = 0.3 x ICC
Eta = 0.5 x ICC
Eta = 0.8 x ICC
m = 2
m = 3
m = 5
Success rates (0.1, 0.1)
Success rates (0.3, 0.3)
Success rates (0.5, 0.5)
Type-I error
ICC
Model
Mixed effect model/Odds ratio/Equal variances
Mixed effect model/Relative risk/Equal variances
Mixed effect model/Risk difference/Equal variances
Marginal model/Odds ratio
Marginal model/Risk in difference

Figure 2B

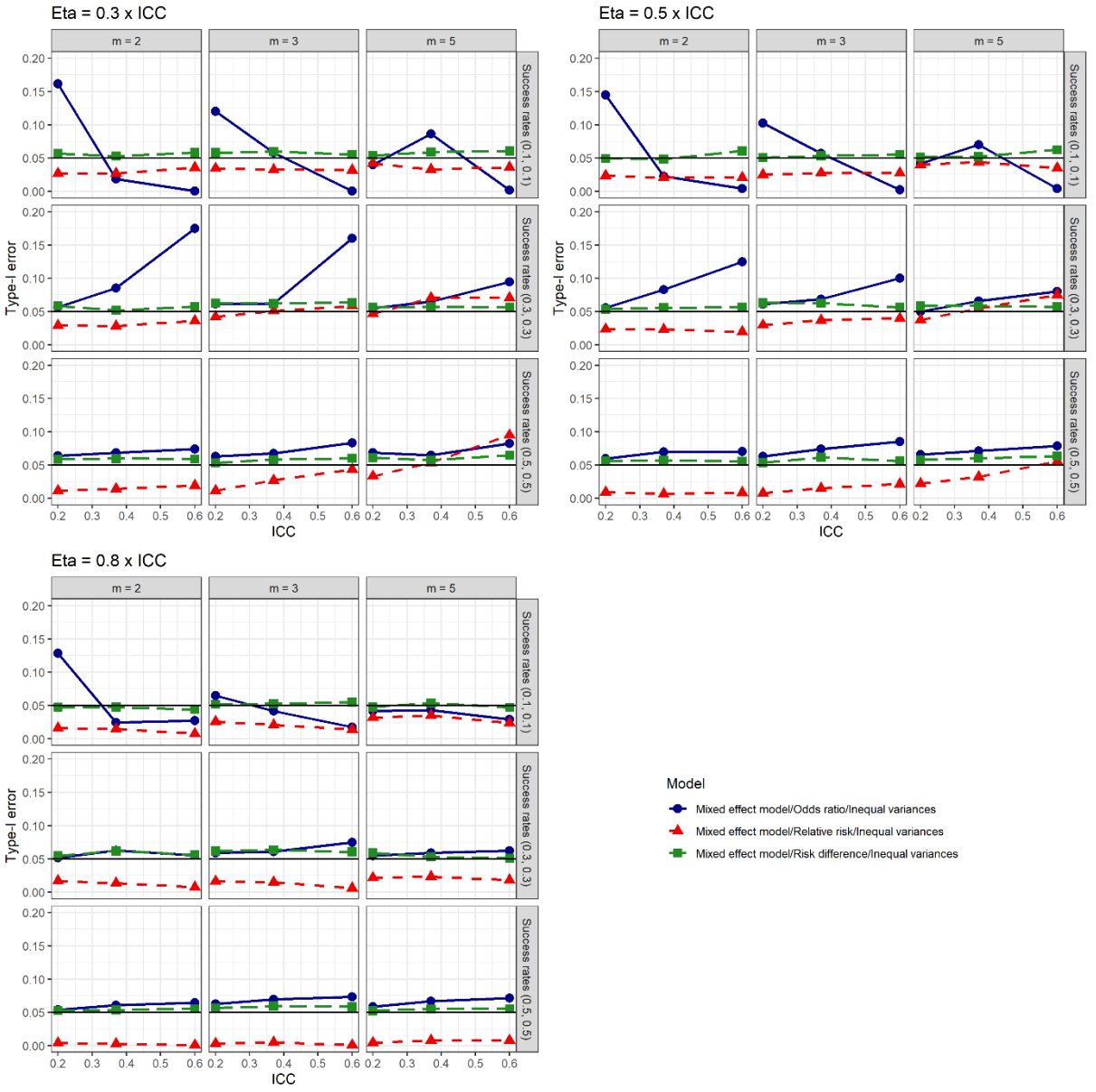

Eta = 0.3 x ICC
Eta = 0.5 x ICC
Eta = 0.8 x ICC
m = 2
m = 3
m = 5
Success rates (0.1, 0.1)
Success rates (0.3, 0.3)
Success rates (0.5, 0.5)
Type-I error
ICC
Model
Mixed effect model/Odds ratio/Inequal variances
Mixed effect model/Relative risk/Inequal variances
Mixed effect model/Risk difference/Inequal variances

Figure 2C

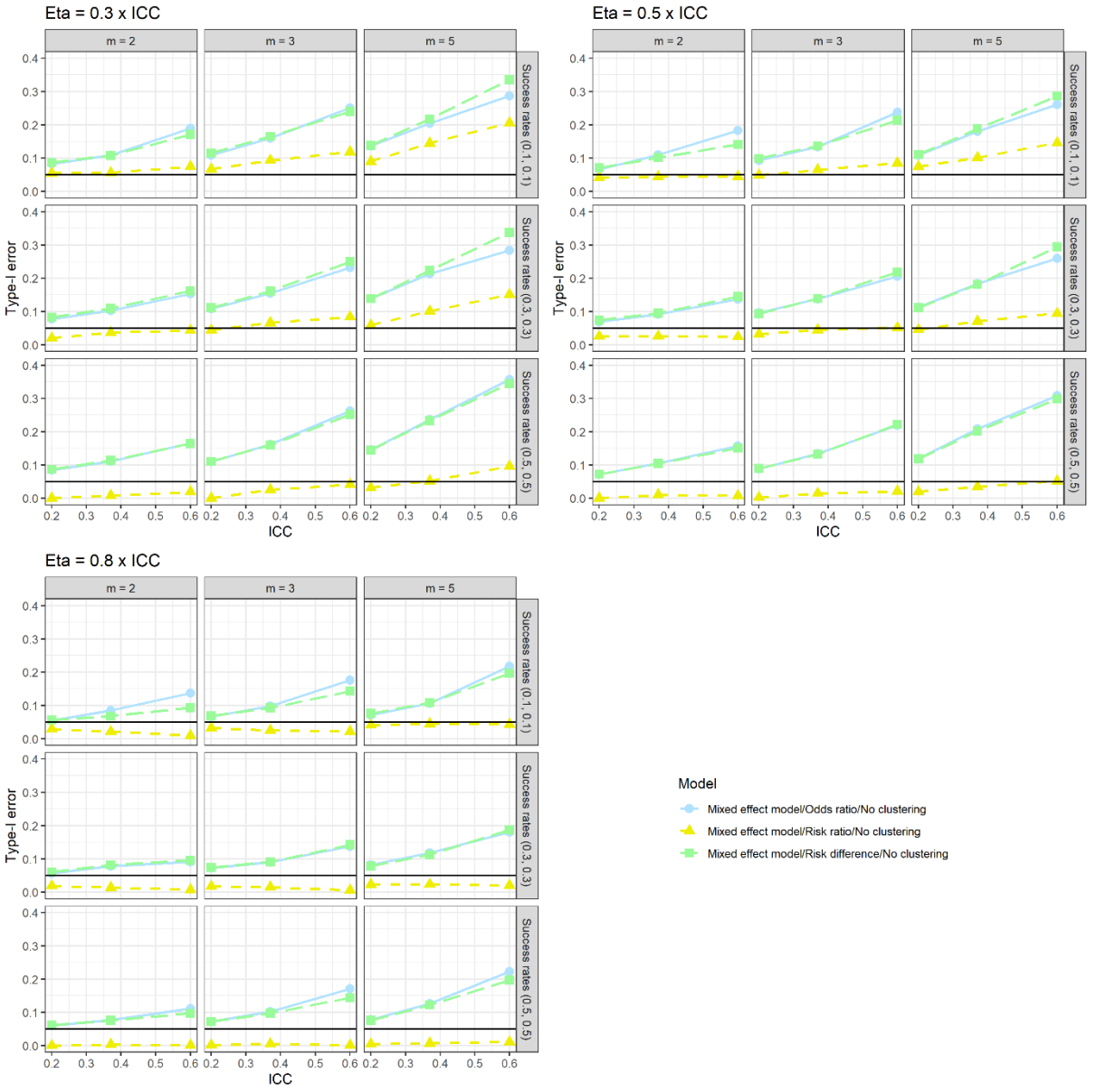

Eta = 0.3 x ICC
Eta = 0.5 x ICC
Eta = 0.8 x ICC
m = 2
m = 3
m = 5
Success rates (0.1, 0.1)
Success rates (0.3, 0.3)
Success rates (0.5, 0.5)
Type-I error
ICC
Model
Mixed effect model/Odds ratio/No clustering
Mixed effect model/Risk ratio/No clustering
Mixed effect model/Risk difference/No clustering

Figure 3A

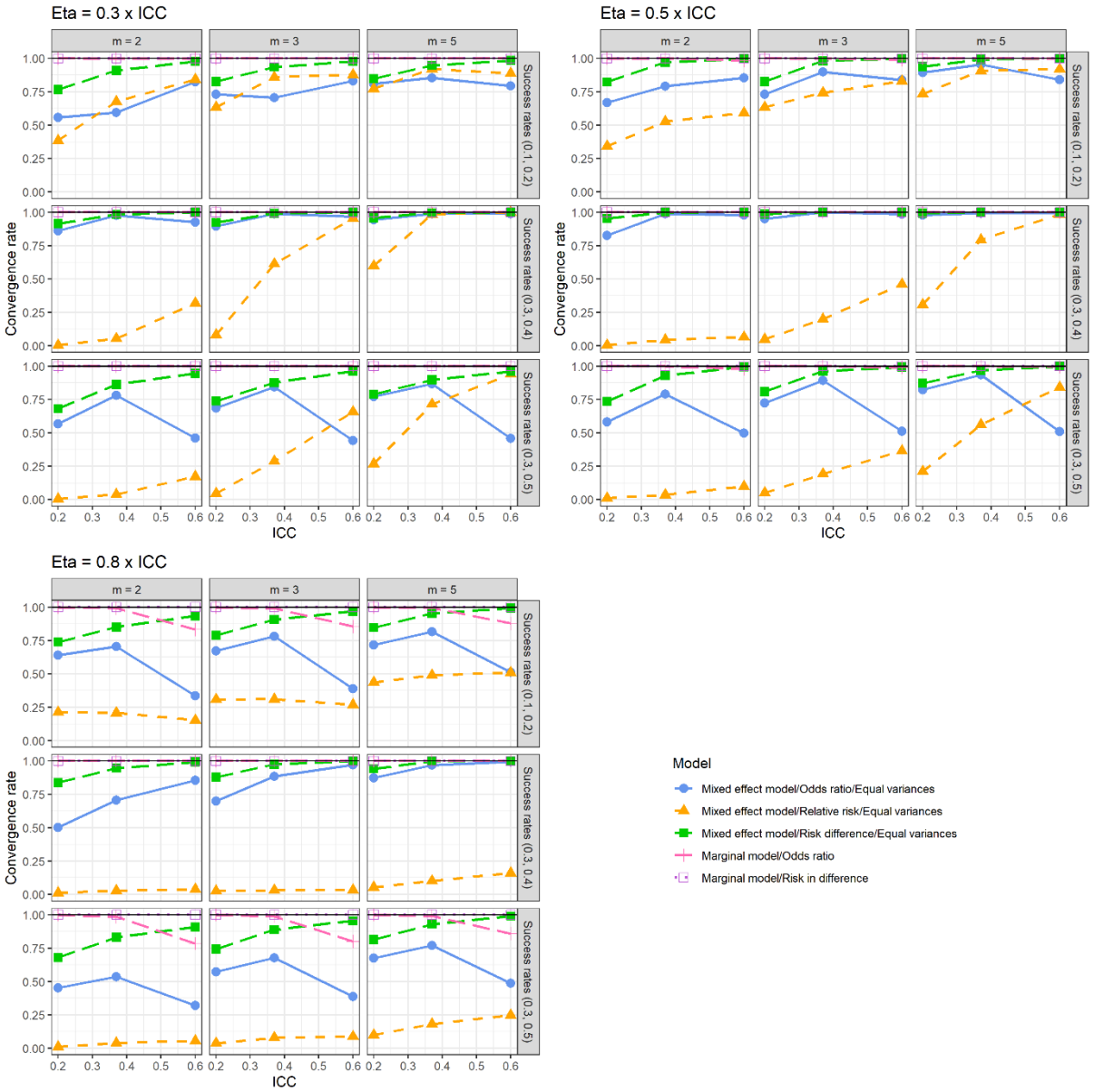

Eta = 0.3 x ICC
Eta = 0.5 x ICC
Eta = 0.8 x ICC
m = 2
m = 3
m = 5
Success rates (0.1, 0.2)
Success rates (0.3, 0.4)
Success rates (0.3, 0.5)
Convergence rate
ICC
Model
Mixed effect model/Odds ratio/Equal variances
Mixed effect model/Relative risk/Equal variances
Mixed effect model/Risk difference/Equal variances
Marginal model/Odds ratio
Marginal model/Risk in difference

Figure 3B

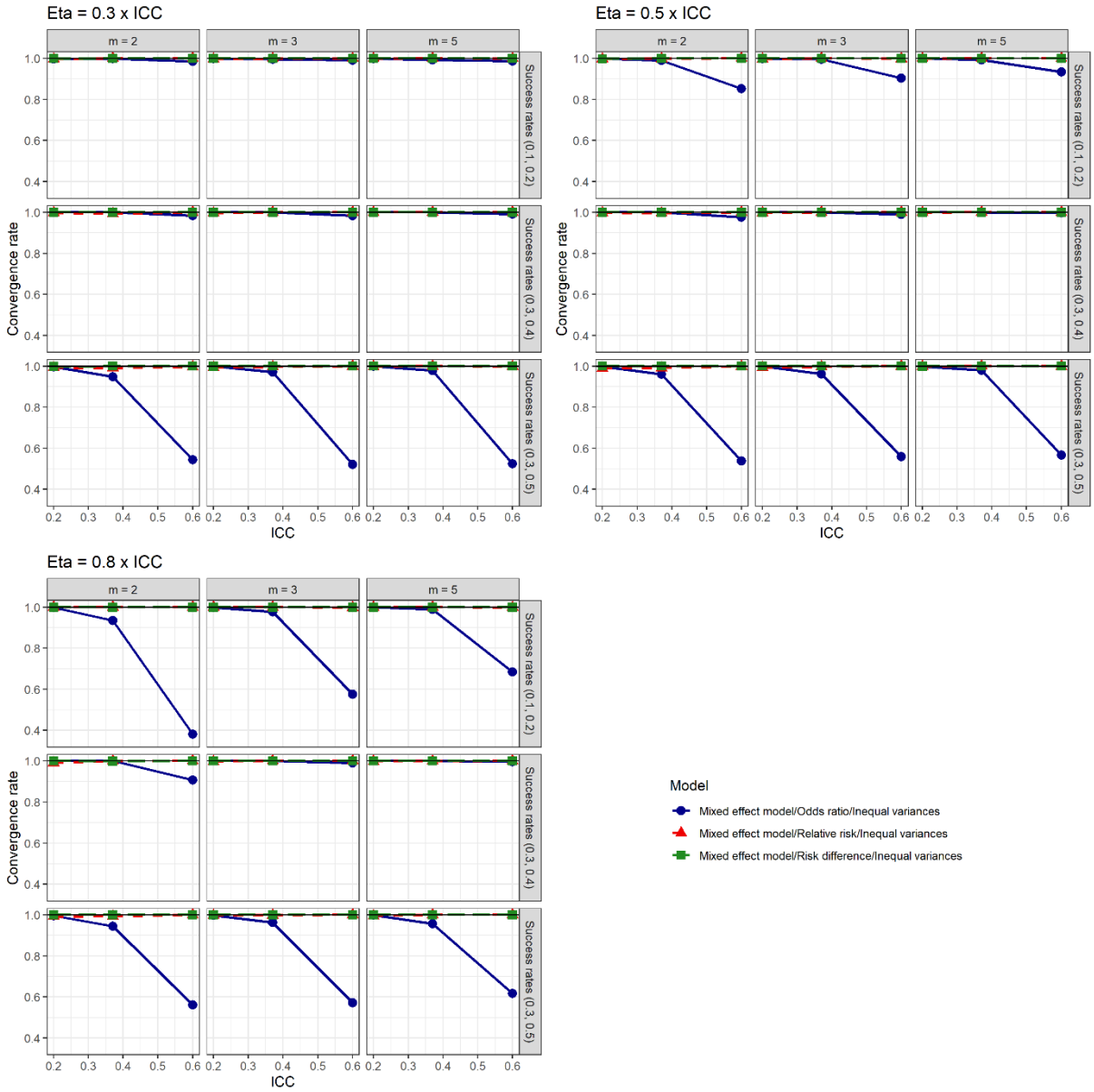

Eta = 0.3 x ICC
Eta = 0.5 x ICC
Eta = 0.8 x ICC
m = 2
m = 3
m = 5
Success rates (0.1, 0.2)
Success rates (0.3, 0.4)
Success rates (0.3, 0.5)
Convergence rate
ICC
Model
Mixed effect model/Odds ratio/Inequal variances
Mixed effect model/Relative risk/Inequal variances
Mixed effect model/Risk difference/Inequal variances

Figure 4A

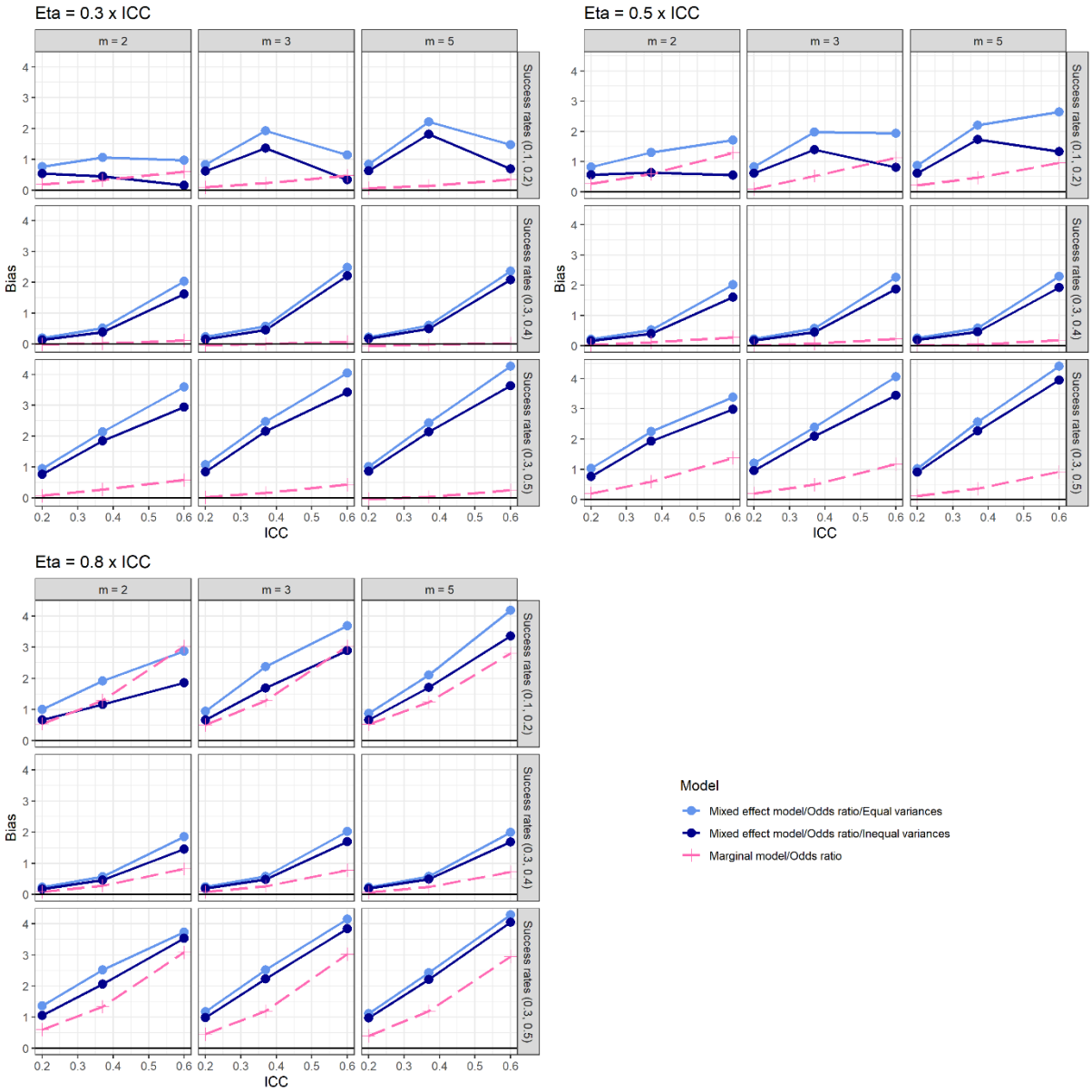

Eta = 0.3 x ICC
Eta = 0.5 x ICC
Eta = 0.8 x ICC
m = 2
m = 3
m = 5
Success rates (0.1, 0.2)
Success rates (0.3, 0.4)
Success rates (0.3, 0.5)
Bias
ICC
Model
Mixed effect model/Odds ratio/Equal variances
Mixed effect model/Odds ratio/Inequal variances
Marginal model/Odds ratio

Figure 4B

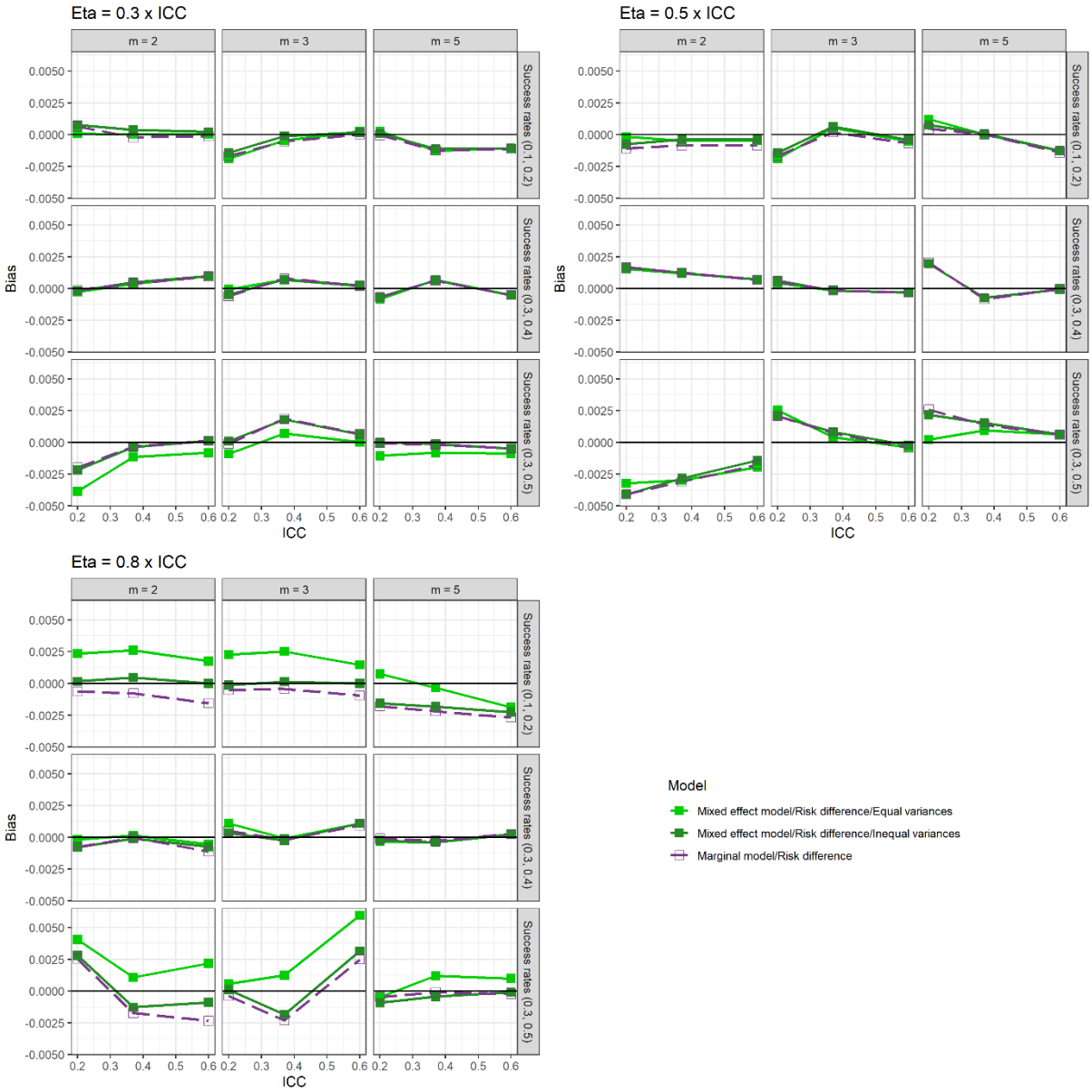

Eta = 0.3 x ICC
Eta = 0.5 x ICC
Eta = 0.8 x ICC
m = 2
m = 3
m = 5
Success rates (0.1, 0.2)
Success rates (0.3, 0.4)
Success rates (0.3, 0.5)
Bias
ICC
Model
Mixed effect model/Risk difference/Equal variances
Mixed effect model/Risk difference/Inequal variances
Marginal model/Risk difference

Figure 4C

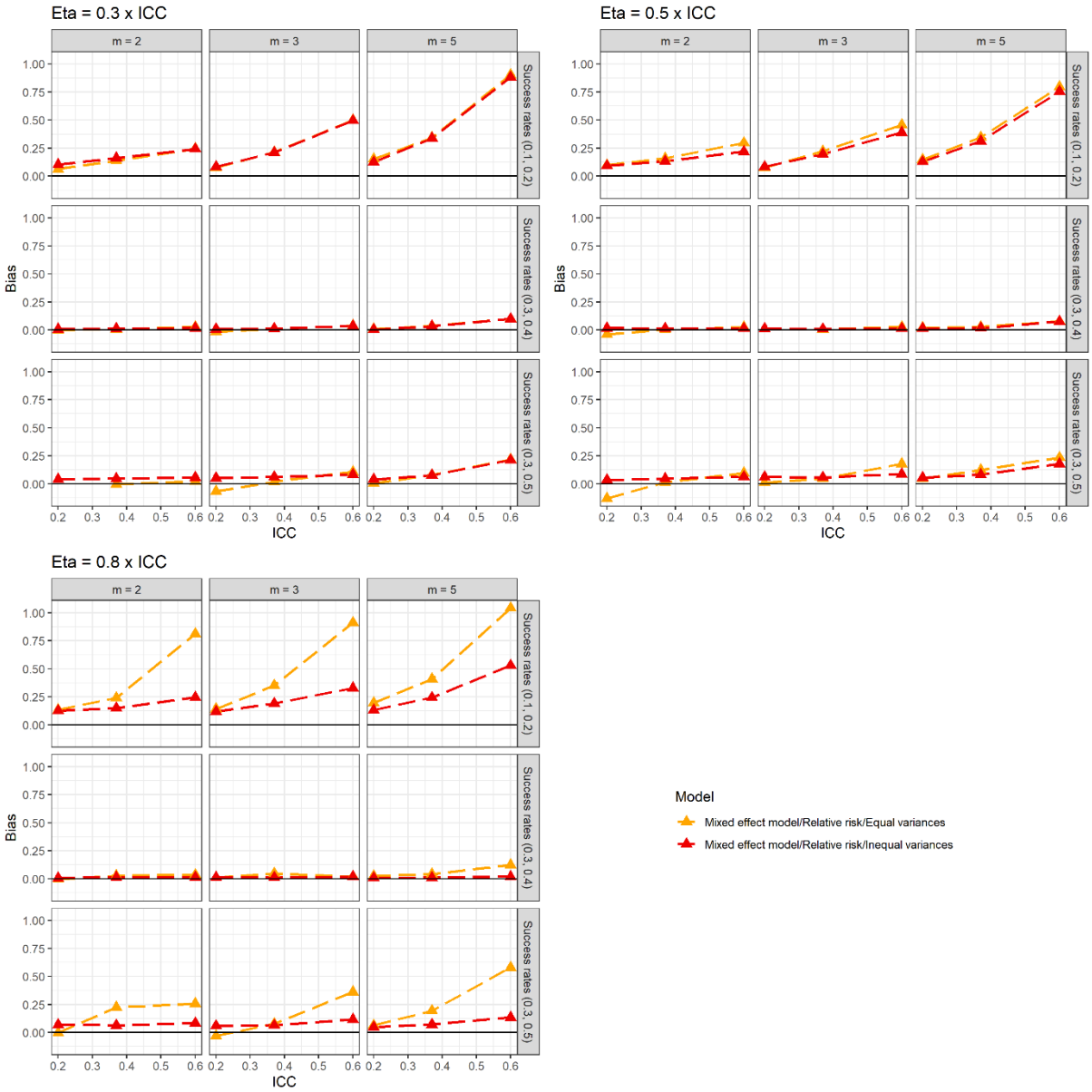

Eta = 0.3 x ICC
Eta = 0.5 x ICC
Eta = 0.8 x ICC
m = 2
m = 3
m = 5
Success rates (0.1, 0.2)
Success rates (0.3, 0.4)
Success rates (0.3, 0.5)
Bias
ICC
Model
Mixed effect model/Relative risk/Equal variances
Mixed effect model/Relative risk/Inequal variances

Figure 5

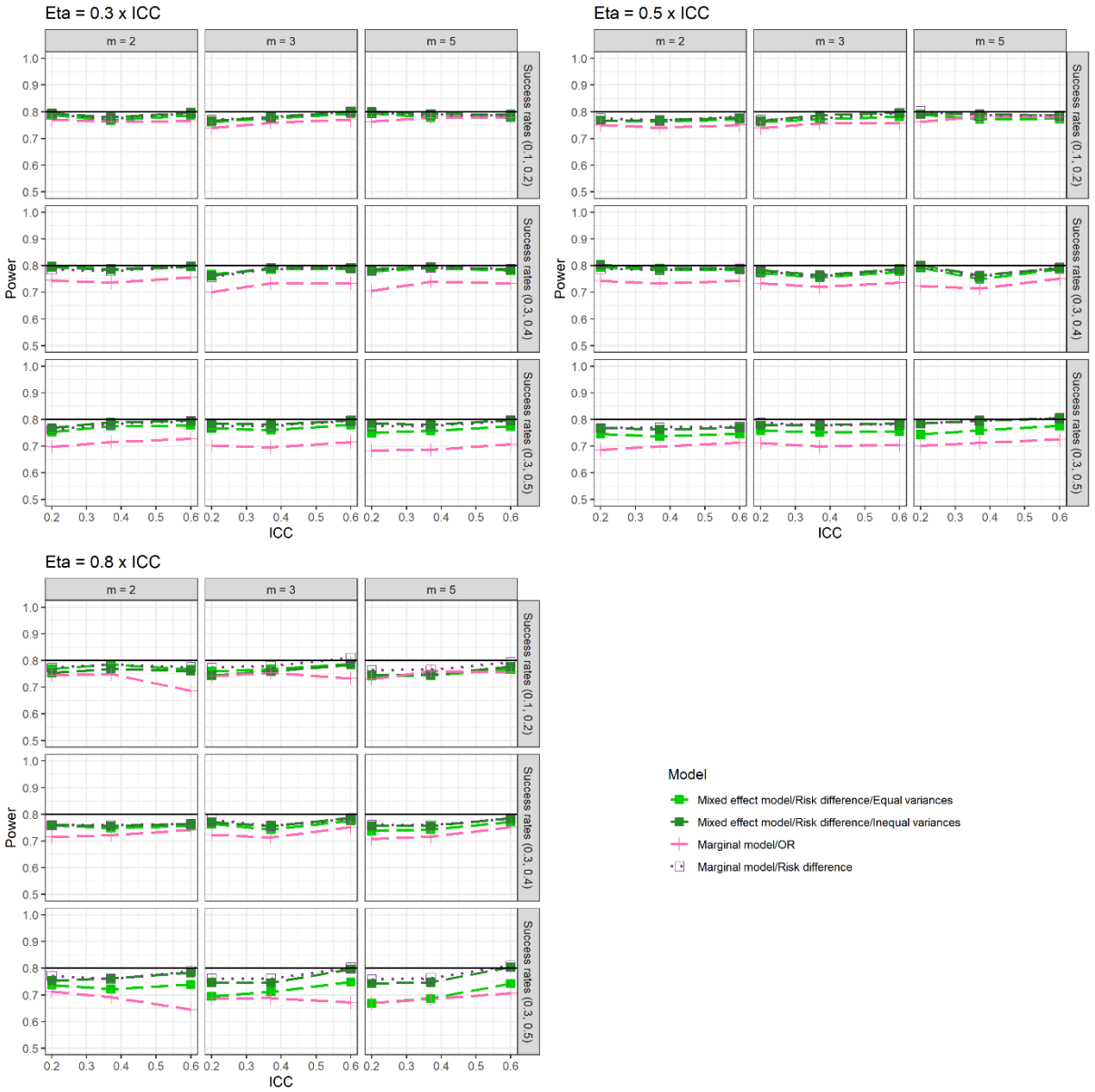
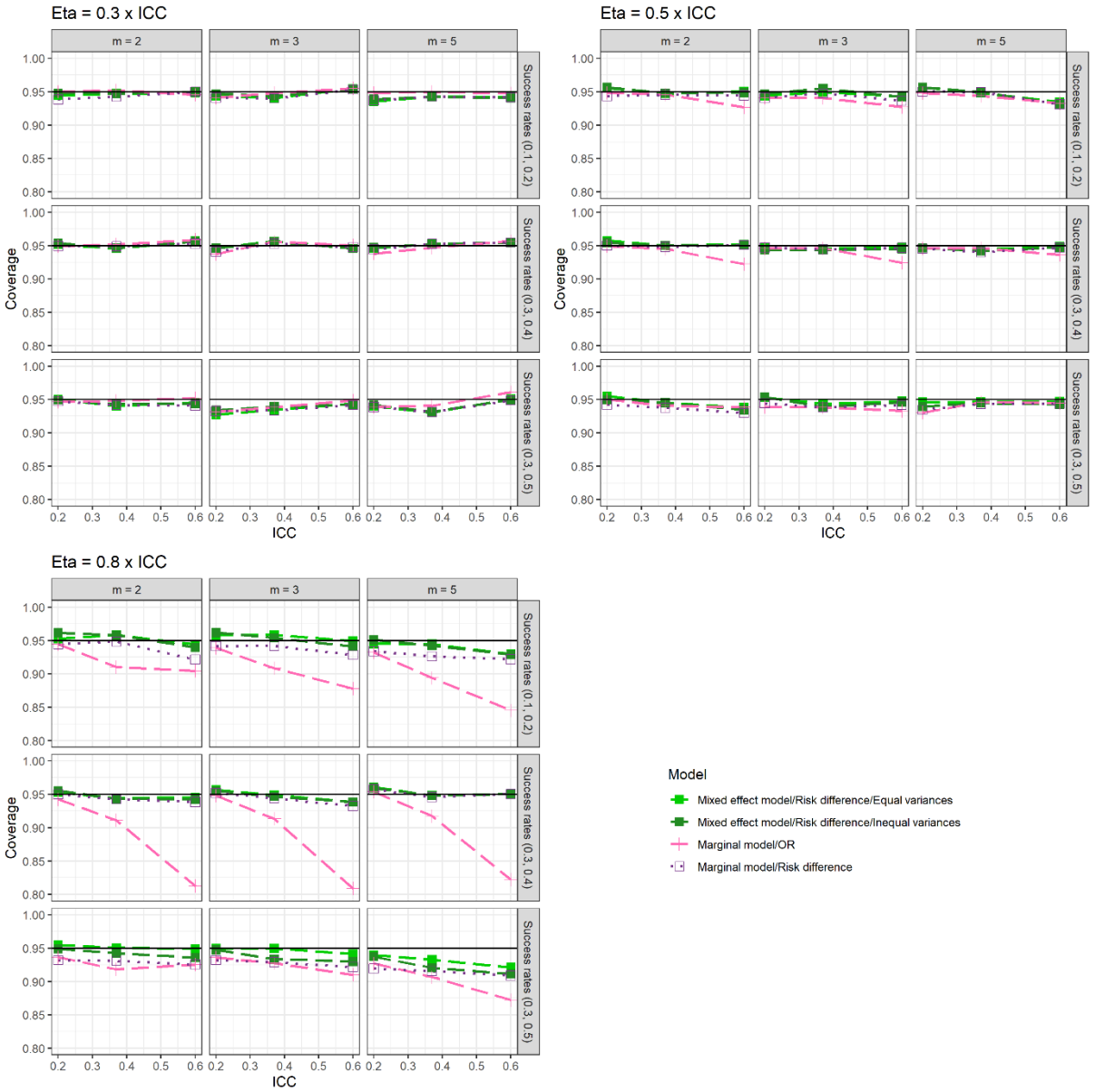

Eta = 0.3 x ICC
Eta = 0.5 x ICC
Eta = 0.8 x ICC
m = 2
m = 3
m = 5
Success rates (0.1, 0.2)
Success rates (0.3, 0.4)
Success rates (0.3, 0.5)
Power
ICC
Model
Mixed effect model/Risk difference/Equal variances
Mixed effect model/Risk difference/Inequal variances
Marginal model/OR
Marginal model/Risk difference

Figure 6


Eta = 0.3 x ICC
Eta = 0.5 x ICC
Eta = 0.8 x ICC
m = 2
m = 3
m = 5
Success rates (0.1, 0.2)
Success rates (0.3, 0.4)
Success rates (0.3, 0.5)
Coverage
ICC
Model
Mixed effect model/Risk difference/Equal variances
Mixed effect model/Risk difference/Inequal variances
Marginal model/OR
Marginal model/Risk difference

4. Protocole de recherche utilisant un schéma d'étude en « within-person ». 'Traitement des malformations cutanées lymphatiques microkystiques par sirolimus topique 0,1% : protocole pour un essai thérapeutique de phase II, randomisé, en double aveugle, en comparaison intraindividuelle (« within-person ») versus véhicule'

4.1.Présentation du travail

Dans cette dernière partie, à titre d'illustration, nous rapportons ici un protocole de recherche utilisant un schéma d'étude en « within-person ».

Ce protocole a été rédigé en 2018 et est actuellement en cours de recrutement. Il a été rédigé dans le cadre du centre de référence des malformations vasculaires (centre MAGEC, site constitutif Tours). Ce projet de recherche est financé par le Programme Hospitalier de Recherche Clinique National (PHRC) du Ministère de la Santé (appel d'offre obtenu en 2017).

Les malformations lymphatiques sont des maladies rares de l'enfant et de l'adulte (prévalence estimée à moins de 0,1%) (Smith, 2004). Il s'agit de malformations vasculaires congénitales bénignes rares constituées de dilatations kystiques. Deux formes cliniques sont distinguées : les malformations lymphatiques macrokystiques se manifestant par des volumineux kystes et les malformations cutanées lymphatiques microkystiques (MCLM) se manifestant par des petits kystes responsables de saignements, douleurs et suintements. Des formes mixtes peuvent également être observées. Un suintement lymphatique et/ou des saignements peuvent survenir, pouvant induire macération, douleurs, surinfections bactériennes, préjudice esthétique et altération de la qualité de vie. La prise en charge des malformations lymphatiques microkystiques n'est pas codifiée et fait appel à une approche multidisciplinaire (Hawkins, 2019). Des traitements par laser ou chirurgie peuvent être proposés mais sont douloureux avec un taux de récidive élevé.

Le sirolimus topique est un inhibiteur de mTOR (*mammalian target of rapamycin*) et inhibe l'angiogenèse et lymphangiogenèse (Luo, 2012). Dans plusieurs publications traitant des malformations vasculaires le sirolimus par voie orale a été rapporté comme ayant une bonne efficacité dans les malformations comportant une composante lymphatique (Maruani, 2021 ; Hammer, 2018 ; Adams, 2016). Cependant, dans les MCLM sans atteinte profonde, l'utilisation du sirolimus par voie orale semble une option thérapeutique trop invasive. Plusieurs cas cliniques et séries de cas ont rapporté l'utilisation du sirolimus topique dans les malformations lymphatiques microkystiques avec une bonne efficacité et une bonne tolérance (Garcia-Montero, 2019 ; Badia, 2020 ; Dodds, 2020).

L'objectif de cet essai, en « within-person », randomisé, contrôlé, multicentrique, en double aveugle, est d'évaluer l'efficacité à 12 semaines du sirolimus topique 0,1% dans les MCLM, chez les enfants et adultes, versus crème placebo. Le critère de jugement principal repose sur le score PGA, évalué à 12 semaines par le médecin investigateur (en aveugle). Le score PGA va de 0 (aucune manifestation) à 5 (lésions sévères), et est utilisé couramment en dermatologie dans différentes pathologies. La MCLM sera divisée par l'investigateur en 2 zones égales de sévérité équivalente, qui seront randomisées pour recevoir le sirolimus topique 0,1%, ou le placebo. Les 2 traitements topiques seront appliqués par une infirmière à domicile, dans le but d'éviter une contamination inter-groupes, pour une durée de 12 semaines. À la fin des 12 semaines, l'ensemble de la MCLM sera traitée par le sirolimus topique 0,1% par le patient/parent sur les lésions restantes, pour 8 semaines supplémentaires. Pour chaque patient, le PGA de la zone traitée par le traitement à l'étude (sirolimus topique 0,1%) sera comparé avec le PGA de la zone traitée

Le schéma d'étude en « within-person » a été choisi pour réduire le nombre de sujets à inclure, et ainsi en assurer la faisabilité, les MCLM étant des maladies rares. Pour améliorer l'observance des patients au protocole, il a été prévu que l'application du traitement expérimental et contrôle soit réalisé par une infirmière au domicile. Enfin, pour améliorer l'adhérence des patients (et parents), une période d'extension après 12 semaines au cours de laquelle l'ensemble de la malformation sera traitée par le sirolimus tropique pendant 8 semaines a été prévue.

4.2.Article 4

Ce travail a fait l'objet d'une publication dans le journal *Trials* :

Leducq S, Caille A, Barbarot S, Bénéton N, Bessis D, Boccara O, Bursztejn AC, Chiaverini C, Dompmartin A, Droitcourt C, Gissot V, Goga D, Guibaud L, Herbreteau D, Le Touze A, Léauté-Labrèze C, Lorette G, Mallet S, Martin L, Mazereeuw-Hautier J, Phan A, Plantin P, Quéré I, Vabres P, Bourgoin H, Giraudeau B, Maruani A; Groupe de Recherche de la Société Française de Dermatologie Pédiatrique. Topical sirolimus 0.1% for treating cutaneous microcystic lymphatic malformations in children and adults (TOPICAL): protocol for a multicenter phase 2, within-person, randomized, double-blind, vehicle-controlled clinical trial. *Trials*. 2019;20:739.

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Trials

STUDY PROTOCOL Open Access

Topical sirolimus 0.1% for treating cutaneous microcystic lymphatic malformations in children and adults (TOPICAL): protocol for a multicenter phase 2, within-person, randomized, double-blind, vehicle-controlled clinical trial

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Abstract

Background: Cutaneous microcystic lymphatic malformations (CMLMs) are rare conditions in children and adults. They present as clusters of vesicles full of lymph and blood to various extents, inducing maceration, esthetic impairment, pain, and impaired quality of life. The treatment is challenging. Sirolimus is an inhibitor of mammalian target of rapamycin (mTOR) involved in angio-lymphangiogenesis. Topical sirolimus has recently been reported as effective in a few reports of patients with CMLMs. The objective is to compare the efficacy and safety of a 12-week application of 0.1% topical sirolimus versus topical vehicle in CMLMs in children and adults.

Methods: This French blinded multicenter within-person randomized controlled phase 2 trial aims to include 55 patients aged ≥ 6 years who have a primary CMLM. The CMLM will be divided into two equal areas that will be randomly allocated to 0.1% topical sirolimus or topical vehicle applied for 12 weeks. At the end of the 12-week period, the patient/parent will treat the whole area of CMLM with 0.1% topical sirolimus on remaining lesions, for eight more weeks. Patients will be seen at week 20 (treatment will be stopped) and at month 12 to evaluate long-term efficacy. The primary outcome will be improvement of the CMLM in the area treated with topical sirolimus compared to the area treated with topical vehicle by the investigator physician (blinded to the treatment) with the Physician Global Assessment score at week 12. Secondary outcomes will include: assessment of efficacy by independent experts on the basis of standardized photographs; impact on quality of life; efficacy for oozing, bleeding, erythema, and thickness evaluated by the investigators; and global efficacy as well as efficacy for functional and aesthetic impairment evaluated by the patient. Systemic passage of sirolimus will be measured at weeks 6, 12, and 20, and at week 16 for CMLMs ≥ 900 cm^2.

(Continued on next page)

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(Continued from previous page)
Discussion: For patients with CMLMs, topical sirolimus could be a non-invasive and well-tolerated therapeutic option. If the trial demonstrates efficacy and safety of this treatment, this result will lead to a real change in the management of this condition, and 0.1% sirolimus cream would become the first-line treatment.

Trial registration: ClinicalTrials.gov, NCT03972592. Registered on 3 June 2019. EU Clinical Trials Register EudraCT, 2018–001359-11.

Keywords: Cutaneous microcystic lymphatic malformation, Lymphangiectasia, Sirolimus, Rapamycin, Topical rapamycin, Mammalian target of rapamycin inhibitor, Vascular malformation

Background

Background and rationale

Vascular malformations (VMs) are congenital anomalies that can involve four types of vessels (capillary, lymphatic, venous, and arterial vessels) according to their classification as low- or high-flow VMs. The International Society for the Study of Vascular Anomalies updated their classification in 2014 [1]. Among VMs, cystic lymphatic malformations are rare conditions in children and adults (estimated prevalence < 0.1%) [2, 3] consisting of low-flow congenital VMs resulting from abnormal embryologic development of lymphatic vessels [4]. They might be macrocystic, microcystic, or combined and can affect viscera, soft tissues, and/or skin.

Cutaneous microcystic lymphatic malformations (CMLMs), also called lymphangiectasia, present as clusters of vesicles full of lymph and blood to various extents, usually located in a segmental area (head/neck, lower limbs, gluteal area) [5]. They ooze and bleed, inducing maceration, esthetic impairment, scars, pain, bacterial infections, impaired quality of life, and sometimes anemia. The natural history is progressive worsening during life (increase in lesions and complications). There are no guidelines for managing CMLMs, but therapeutic options are sclerotherapy (an efficient treatment for macrocystic lymphatic malformations but disappointing in CMLMs), physical treatments (pulsed-dye laser, CO_2 laser, radiofrequency, etc.) [6, 7], and surgery [8, 9], but these options are painful and induce inflammation and scars, and their efficacy is usually incomplete and transitory, with the rate of recurrence being very high [10]. Management requires multidisciplinary care. The "wait-and-see" attitude is frequently chosen.

Sirolimus belongs to mammalian target of rapamycin (mTOR) inhibitors. mTOR is a serine/threonine kinase, regulated by phosphoinositide-3-kinase, that acts as a master switch in cell proliferation, apoptosis, metabolism, and angio/lymphangiogenesis. Sirolimus directly inhibits the mTOR pathway, which thereby inhibits cell proliferation, angiogenesis, and lymphangiogenesis [11, 12]. Oral sirolimus is commonly used to prevent rejection of kidney transplants (U.S. Food and Drug Administration [FDA]-approved in this indication) [13]. It was recently reported as an efficient drug to reduce the volume and limit complications in VMs, especially with lymphatic components, in children of all ages [14]. Two randomized controlled trials (RCTs) of oral sirolimus in VMs are ongoing in France and in the United States (ClinicalTrials.gov NCT02509468 and NCT02110069). For CMLMs without underlying painful involvement, many physicians consider oral sirolimus as a too-aggressive option, despite the high level of impairment linked to the condition.

Topical sirolimus is known to be efficient and well tolerated in cutaneous angiofibromas linked to tuberous sclerosis complex: several RCTs have been performed and the drug is currently used in general practice [15, 16]. Recently, topical sirolimus was reported as effective in CMLMs, decreasing the number of vesicles, bleeding, oozing, and pain, in one retrospective study involving 11 patients and in three case reports [17–20]. In the reported cases of CMLMs and angiofibromas, only local side effects were reported, mostly irritative. Systemic passage of sirolimus was not, or almost not, detectable, but the concentration of sirolimus in the preparations and the surface areas that received topical sirolimus were heterogeneous.

Objectives

We aim to perform a clinical trial (TOPical sIrolimus in CutAneous Lymphatic malformation; TOPICAL) to assess the efficacy and safety of a 12-week application of 0.1% topical sirolimus versus topical vehicle for CMLMs in children and adults.

Trial design

TOPICAL is a within-person randomized, vehicle-controlled, investigator- and patient-blinded, multicenter, superiority study comparing 0.1% topical sirolimus and topical vehicle treatment for CMLMs. For each patient, the investigator will divide the CMLM area into two equal areas of homogeneous severity separated by a 2-cm–wide strip (Fig. 1). Each area will be randomly allocated to receive 0.1% topical sirolimus or topical vehicle, applied by a nurse, once daily for 12 weeks.

At the end of the 12-week period, the patient/parent will treat the whole area of CMLM with 0.1% topical sirolimus on the remaining lesions, for eight more weeks (Fig. 2). The purpose of this extension phase is to strengthen

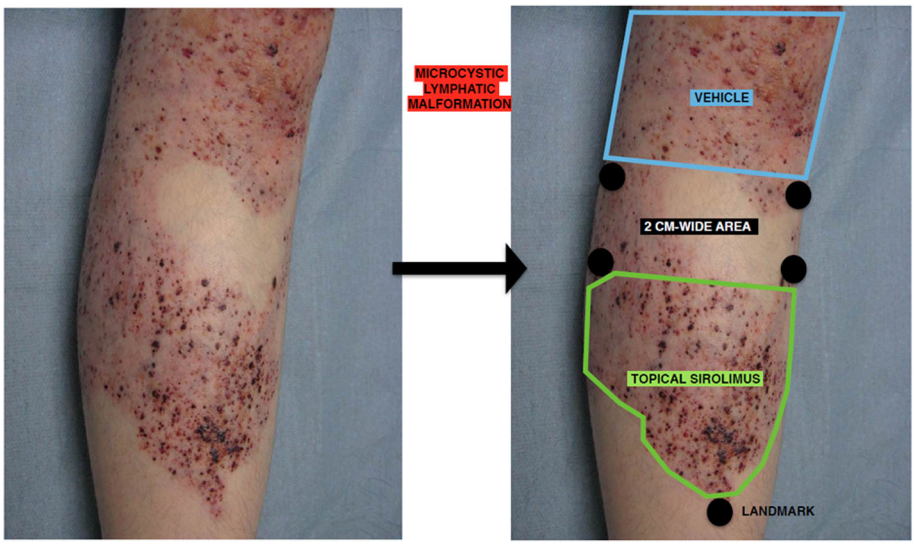


Fig. 1 Example of a CMLM of the leg: the investigator will define two areas of similar size and severity by using a ruler, with a separation area of at least 2 cm between both areas (5 points will be drawn on the patient to define the two areas to apply the product in a reproducible way by the nurse and to avoid inter-area contamination). CMLM cutaneous microcystic lymphatic malformation

patients' adherence to the protocol. Indeed, due to the design, each patient will be his/her own control. Patients may observe an improvement in one of the two areas during the 12-week period and may therefore be attempted to apply the treatment allocated to this area to the whole CMLM, which would introduce group contamination. Therefore, we planned to have nurses apply the treatments; also, patients will be allowed to treat the whole CMLM area with the active drug at the end of the 12-week period. In doing so, we expect patients to be compliant with the protocol and not stop the study.

After week 20 (W20), treatments will be left to the discretion of the investigator.

The within-person design allows for reducing the number of patients to be included; indeed, the population is too rare for a parallel-group trial. Furthermore, the location and severity of CMLMs are heterogeneous among patients and a within-person design has the advantage of reducing inter-observation variability because each patient is his/her own control. Finally, all patients will receive the experimental treatment, which would not be the case with a parallel-group trial.

Methods: participants, interventions, and outcomes

Study setting

The study will involve 16 French tertiary-care hospital centers, all involved in managing vascular anomalies.

Eligibility criteria

Inclusion criteria Eligible patients will be aged ≥ 6 years (for a minimal size) and have a diagnosis of primary CMLM

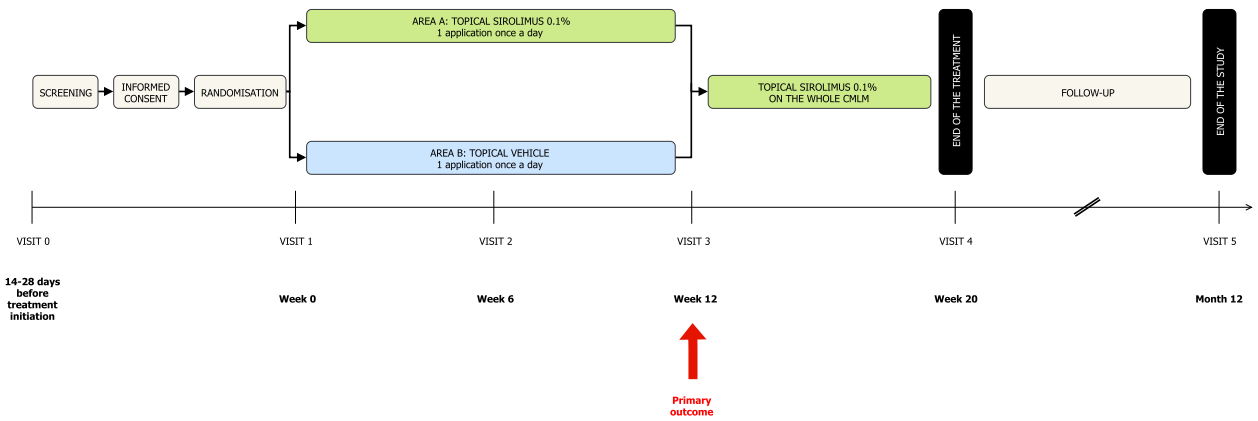


Fig. 2 *Flow chart* of the study procedure. CMLM cutaneous microcystic lymphatic malformation

confirmed by histopathological or desmoscopic examination [21, 22], with or without an underlying malformation or a syndromic malformation (e.g. Proteus syndrome) responsible for impairment (oozing, bleeding, and/or pain).

We chose to include adults and children aged ≥ 6 years because CMLMs can be seen in both children and adults; however, because the natural history of these malformations is a progressive worsening, impairments of CMLMs are usually not yet major in very young children. Moreover, we need a CMLM area large enough to apply both preparations, with a 2-cm central area in-between, and consider that the required minimum area is 20 cm^2, which is usually not possible in children aged < 6 years. A 2-cm–wide space will delimit the two areas of the CMLM to avoid contamination between these two areas.

Exclusion criteria Patients with a lymphatic malformation requiring continued background therapy (involving deep organs) will be excluded, as will patients with secondary lymphatic malformations (lymphangiectasia post-radiotherapy, etc.); immunosuppression; ongoing neoplasia; active chronic infectious disease such as chronic viral hepatitis, tuberculosis or HIV infection; and pregnant women and women of childbearing age not using birth control.

We will exclude patients who previously received systemic or topical mTOR inhibitors within 12 months before inclusion or oral or topical steroids within 10 days before inclusion. Finally, we will exclude patients with contraindications to topical sirolimus, such as skin necrosis, local fungal infections, viral infections (e.g. herpes), or bacterial infection (impetigo, etc.) on the site of the CMLM and known allergy to one of the components of the topical sirolimus preparations or the control.

Intervention

For each patient, the investigator will divide the CMLM area into two equal areas separated by a 2-cm–wide area. Severity of CMLM is usually quite homogeneous; the two areas chosen by the investigator will need to be of similar severity. In case of horizontal malformation, area A will correspond to the area on the left-hand side of the malformation and area B on the right-hand side. In case of vertical malformation, area A will correspond to the area on the upper part of the malformation and area B on the lower part. Each area will be randomly allocated to receive 0.1% topical sirolimus or topical vehicle, applied once daily for 12 weeks (Fig. 1). The 0.1% topical sirolimus application will be prepared and packaged by the pharmacy of the Hospital University Center (CHU) Angers. The formulation of topical sirolimus was developed by the pharmacy team of CHU Angers. Its stability and conservation have been tested and published [23]. Sirolimus cream will be prepared by first solubilizing rapamycin in Transcutol®. Then, the mixture will be progressively added to Excipial® hydrocream. The formulation is 0.03 g rapamycin, 1.5 g Transcutol®, and QS 30 g Excipial® hydrocream, corresponding to a 0.1% concentration. The cream will be packaged in 30-mL aluminum tubes. The stability of this formulation was studied by high-performance liquid chromatography: the rapamycin concentration remained > 95% of the initial concentration for at least 85 days. The odor, appearance, and color of the preparation remained unchanged during storage.

During the double-blind 12-week period, a nurse, trained to the protocol, will apply both topical treatments to avoid inter-group contamination and for better compliance. In addition, treatments will be kept by the nurses.

A research nurse of CHRU Tours will coordinate and support the nurses at home (two nurses will be trained for each patient). A nursing notebook with a guide (explanation for application) and material will be provided to the nurses.

Each of the two products will be applied using a different glove and massaged until complete penetration of thin thickness. The amount to be applied will be defined by using the fingertip unit (FTU), which is widely used in dermatology [24]. One FTU is equivalent to 20–25 mm of cream squeezed onto the fingertip. One FTU is 0.5 g cream and is sufficient to treat an area of skin twice the size of an adult's hand (including palm and fingers). Thus, the amount of cream to be applied will be adjusted by using the FTU depending on the size of the area. The maximal amount of products to be applied will be 2 g per application for each area (during W0–W12) and 4 g per application for the whole malformation (during W12–W20). Indeed, the maximal size of the malformation expected is 2500 cm^2 (50 × 50 cm).

Regarding concomitant treatments, bandages in case of oozing and bleeding and topical or systemic antibiotics in case of local bacterial infection will be authorized. Topical steroids, topical immunosuppressive drugs, sclerotherapy, lasers, and surgery on the area will be prohibited. Systemic steroids for a > 3 days, systemic immunosuppressive drugs, and oral mTOR inhibitors will also be prohibited.

A participant may stop study treatment at any time if the participant, investigator, or sponsor feels that it is not in the participant's best interest to continue. If a participant is withdrawn from treatment because of an adverse effect, the participant will be followed and treated by the investigator until the abnormal parameter or symptom has resolved or stabilized. If a woman becomes pregnant during the clinical trial, treatment will be stopped but all assessments planned in the study will be performed. The investigator must follow the patient until the end of the pregnancy or until its interruption. In case of skin necrosis, which would be unexpected, temporary

discontinuation of the treatment is recommended until the next visit. The investigator will check that the skin necrosis is healed.

Outcomes

Primary outcome

The primary outcome will be evaluation of the CMLM in the area treated with the intervention (0.1% topical sirolimus) compared to the area treated with topical vehicle (inactive comparator) by the investigator physician (blinded to treatment) by using the 6-point Physician Global Assessment (PGA) score at W12.

There are no specific scores for VMs. We chose the 6-point PGA score because it is relevant for this condition and is easy to understand. The PGA score ranges from 0 (clear) to 5 (severe) and is often used in trials investigating dermatological conditions such as psoriasis [25, 26]. We consider that a 1-point improvement in PGA score is clinically relevant for CMLM.

Secondary outcomes

Secondary outcomes are clinical assessments of the efficacy of sirolimus as well as safety. Clinical efficacy will be assessed by different endpoints (Table 1).

- Two blinded independent experts will qualitatively assess digital photographs. Experts will be provided photographs for each patient at baseline and at W12; they will be asked to identify, at the end of the study, which area among the two areas received the active treatment;
- Assessment by the physician of the global efficacy of topical sirolimus in the whole CMLM by using the PGA score at baseline, W6, W20, and month 12 (M12);
- Quality of life will be self-assessed by the patient, at baseline, W20, and M12 in comparison to baseline by using the validated Dermatology Life Quality Index (DLQI) or Child-DLQI for children;
- Pain linked to the CMLM will be self-assessed by the patient (and parents for children aged < 16 years) with a visual analog scale (VAS; 0–10) at baseline, W20, and M12;
- Improvement in terms of oozing, bleeding, erythema, and thickness will be assessed by the investigator with blinding to treatment on a VAS scale of 0–10 (0 = no improvement, 10 = recovery) at baseline (on both areas), W12 (on both areas), W20 (on the whole area), and M12 (on the whole area);
- Global improvement in CMLM will be self-assessed by the patient on a VAS scale of 0–10 (and parents for children aged < 16 years) at W12 (in both areas), W20 (on the whole area), and M12 (on the whole area);
- Functional and aesthetic impairment will be self-assessed by the patient (and parents for children aged < 16 years) on a VAS scale of 0–10 at baseline, W20, and M12.

Safety

Local adverse events (AEs) in both areas treated with topical sirolimus and topical vehicle before W12 and the whole CMLM at W20 will be recorded. The expected local AEs are mostly irritative (erythema, burning, dryness, itching, pruritus). Systemic passage of sirolimus will be assessed at W6, W12, and W20 (dosage of serum level of sirolimus) and at W16 with CMLM $\geq 30 \times 30$ cm or ≥ 900 cm^2. Evaluation of biological safety will be assessed at W12 and W20 in comparison to baseline (we will use biological measurements that are required for assessing safety of oral sirolimus: blood cell count; liver and renal functions; ionography; lipids [cholesterol and triglycerides]; and glycemia).

Classical AEs of oral sirolimus are clinical (mostly mucositis, gastrointestinal effects, fatigue, headaches, hypertension) and biological (thrombocytopenia, leucopenia, anemia, hyperlipidemia, hyperglycemia, hypokalemia, and increased levels of liver enzymes). However, no general AE has ever been reported with topical sirolimus, but several local AEs were reported. Indeed, the risk of a systemic adverse reaction seems low with topical sirolimus, because systemic absorption is very low or hardly detectable. This risk will be assessed with blood samples to assess the safety of the treatment and systemic passage. If a level of sirolimus is detectable, the study treatment will not be stopped. With a level of sirolimus ≥ 15 ng/mL [27], the treatment will be stopped.

Safety evaluation parameters will be performed at each visit by asking the patients/parents to report clinical AEs.

At the screening visit, the inclusion visit, W12, W20, and once a month, a urinary pregnancy test will be performed for women and girls of childbearing potential. With a detectable level of sirolimus, a monthly urinary pregnancy test will be performed for an additional three months.

Participant timeline

Duration of participation will be 12 months for each patient. The time schedule of enrolment and visits is shown in Table 1.

Sample size

The study is planned as a within-person design, which means that data from the two areas on a patient will be matched. In addition, the PGA score is an ordered score

Table 1 Schedule of enrolment, interventions, and assessments

	Study period					
	Screening	Inclusion	Follow-up			
	V0	D1 (V1)	W6 (V2)	W12 (V3)	W20 (V4)	M12 (V5)
Timepoint	14–28 days before treatment initiation	–	±3 days	±3 days	±3 days	±5 days
Drug administration		Once daily				
Enrollment						
Eligibility screening	X					
Informed consent	X					
Control of inclusion/exclusion criteria	X					
Randomization		X				
Physical examination		X	X	X	X	X
Height and weight measurement		X				
Vital signs (cardiac frequency, arterial pressure)		X	X	X	X	X
Photographs		X		X		
Location and measure of the CMLM	X					
Definition of the two areas		X				
Urinary pregnancy test for women[a]	X	X	Once a month until S20		X	
Blood sample for tolerance[b]		X		X	X	
Serum level of sirolimus[c]			X	X	X	
Cutaneous effects			X	X	X	
Adverse events			X	X	X	
Delivery of nursing notebook		X	X	X		
Interventions[d]						
Delivery of topical sirolimus		X	X	X		
Delivery control		X	X			
Treatment returns			X	X	X	
Assessments						
PGA score		X	X	X	X	X
Dermatological quality of life scale – DLQI		X			X	X
VAS for self-assessment of pain		X			X	X
VAS for assessment of efficacy by the investigator on oozing, bleeding, erythema, thickness		X		X	X	X
VAS for self-assessment of global efficacy				X	X	X
VAS for self-assessment of functional and esthetic impairments		X			X	X

CMLM cutaneous microcystic lymphatic malformation, *PGA* Physician Global Assessment, *VAS* visual analog scale

[a] If detectable sirolimus level: monthly pregnancy test for three additional months

[b] Blood count, ionogram, liver function (ASAT, ALAT, gamma-GT), renal function (creatinine), lipids (cholesterol, triglycerides), glycemia. Local analysis

[c] With CMLM $\geq 30 \times 30$ cm and/or ≥ 900 cm^2, a blood sample for evaluation of systemic passage of sirolimus (residual serum level of sirolimus) will be performed at W16

[d] Application of both topical preparations (intervention or inactive comparator) by a nurse

ranging from 0 (clear) to 5 (severe). Therefore, to estimate the sample size, we used an approach based on continuous data and a paired sample *t* test, assuming that the PGA score difference (between the two areas) follows a normal distribution. Hypothesizing a 1-point difference and a 2.5-point standard deviation would lead to a 0.4 effect size. Assuming a power of 80%, a two-sided type I error rate of 5%, we will need to recruit 52 patients. We plan to recruit 55 patients.

Recruitment

The recruitment of children with these malformations is facilitated by the fact that all co-investigators belong to tertiary-care centers for vascular anomalies and

participate in multidisciplinary consultations on lymphatic malformations. Most co-investigators are already involved in the French trial on oral sirolimus PERFORMUS (NCT02509468) for which recruitment ended in March 2018. Some belong to the French network for research on pediatric dermatology (Groupe de Recherche de la Société Française de Dermatologie Pédiatrique).

Methods: assignment of interventions

Allocation

Sequence generation and allocation concealment mechanism In this within-person trial, areas of the CMLM (area A and area B) will be randomly assigned to the control or experimental group with a 1:1 ratio allocation as per a computer (SAS-based)–generated randomization schedule. Participants will be randomized by using Ennov Clinical©, an online central randomization procedure via the electronic case report form (e-CRF). To ensure allocation concealment, the randomization procedure will not be possible until the participant has been recruited into the trial; in particular, the consent and all eligibility criteria must be collected and met.

Implementation The allocation sequence will be generated by a statistician not involved in the recruitment or follow-up of participants.

Blinding

Patients, parents, nurses, and investigators will be blinded to the treatment allocated to each area of the CMLM during the first step of the study (until W12, when the primary endpoint will be assessed). To ensure double-blinding, both areas will be randomized and the topical treatments (sirolimus and control) to be applied will have similar packaging. The appearance of the drugs is similar; thus, the active drug (topical sirolimus) and the control cannot be distinguished at drug allocation. In addition, the consistency of the creams is similar.

Topical sirolimus might induce burning or pruritus. However, we do not consider that this side effect would compromise the blinding by allowing the patient to know which area is being treated with the active cream and the control because: (1) identifying precisely which area is itching or burning on a CMLM is difficult; (2) itching and burning might be linked to the CMLM itself; and (3) usually, no inflammation is objectively detectable. The allocation table will be kept in an envelope and will be stored in a secure place. Unblinding will be requested for any reason considered essential by the investigating physician following the procedure determined in advance.

Methods: data collection, management, and analysis

Data collection methods

Table 1 shows data collection according to inclusion and follow-up visits. An individual may be discontinued from study treatment at any time if the individual, the investigator, or the sponsor feels that it is not in the participant's best interest to continue. If a participant is withdrawn from treatment due to an adverse effect, the participant will be followed and treated by the investigator until the abnormal parameter or symptom has resolved or stabilized. All individuals who discontinue study treatment should be encouraged to complete all remaining scheduled visits and procedures. Once a participant is randomized in the study, every reasonable effort will be made to follow the participant for the entire study period even if there is a deviation from the intervention protocol, an early discontinuation of study treatment, or one missed follow-up visit. If an individual is lost to follow-up, every possible effort must be made by the study center to contact the individual and determine the reason. The measures taken to follow-up must be documented. Primary and secondary outcomes, as well as safety, will be collected for all participants even for participants who discontinue or deviate from intervention protocol.

Data management

An e-CRF will be developed by using Ennov Clinical© software. The e-CRF will be managed in agreement with INSERM CIC 1415 Standardized Operating Procedures (SOPs). Data from investigating centers will be entered using a secure website monitored by clinical research associates, and queries will be edited by data managers, in agreement with an *a priori*-specified data-management plan. A blinded review will be performed before locking the database. The database will be locked in agreement with INSERM CIC 1415 SOPs and data will be extracted in a SAS format or another format, according to statistical requirements. Raw data will be stored in an XML format.

Statistical methods

The statistical analysis will be conducted according to the intention-to-treat (ITT) principle: areas will be analyzed within the groups to which they were initially randomized even if the patient do not adhere to the intervention. We will use multiple imputation to account for missing variables. Considering the primary outcome, the study is planned as a within-person trial with the specificity that in these types of studies, each patient serves as his/her own control. In this way, we will have a paired sample. For the primary analysis, the PGA score at W12 will be compared between the two areas by paired Student's t test. For secondary outcomes, PGA score, physician assessment of efficacy, and patient self-

assessment will be analyzed by the same approach (i.e. paired Student's t test). Considering efficacy seen on digital photographs (i.e. correct identification of intervention/control-treated area), interpretation by dermatologic experts will be considered correct or false, and the proportion of correct interpretation will be estimated and provided with 95% confidence intervals. The proportion of correct interpretation will be compared to the theoretical 50% value, corresponding to a random assessment. At W20 and M12, PGA score, physician assessment of efficacy, and patient self-assessment will be reported using descriptive statistics. Change in quality of life and in pain between baseline and M12 will be analyzed by using a linear mixed effects model with a random intercept to account for repeated measures for the same patient. Regarding AEs and systemic passage of sirolimus, descriptive statistics (numbers and percentages) will be calculated. No subgroup analyses or adjusted analyses are planned.

Methods: monitoring

Data monitoring

A clinical research assistant will be responsible for coordinating the study: the assistant will be responsible for the logistics and monitoring the study, producing reports concerning its state of progress, verifying that the e-CRFs are updated (request for additional information, corrections, etc.), and transmitting information on severe AEs to the sponsor. The assistant will follow the SOPs. A data safety monitoring board (DSMB) will be composed of three medical doctors specialized in pharmacodermatology and dermatology. The DSMB will be systematically contacted: (1) at any time by the sponsor for each case of expected serious adverse reaction or for a suspected unexpected serious adverse drug reaction (SUSAR); (2) before each development safety update report is sent to the French Agency for the Safety of Health Products (ANSM); and (3) if data may change the benefit/risk ratio during the clinical trial. The study may be stopped definitely or temporarily at any time by the sponsor on the basis of information provided by the DSMB. The DSMB will meet in case of a SUSAR, new fact, new safety information that could lead to re-evaluation of the benefit/risk ratio of the participant, and new scientific information challenging study continuation.

The sponsor reserves the right to interrupt definitively the study at any time if it appears that the inclusion objectives have not been met.

There is no prespecified interim analysis and no statistical stopping rules.

Harms

All AEs will be monitored until they are completely resolved. The investigator will immediately notify the sponsor of any serious AE. The sponsor will report all SUSARs to the Eudravigilance (European pharmacovigilance database), French health authorities (ANSM), and the investigators within the regulatory time periods for reporting.

Auditing

An audit may be performed at any time by sponsor-appointed individuals who are independent of those responsible for the study. The investigators agree to comply with the requirements of the sponsor and the relevant authority for an audit or inspection of the study. The audit can apply at all stages of the study, from development of the protocol to publication of results.

Ethics and dissemination

Research ethics approval

The sponsor and the investigators undertake to conduct this study in compliance with French law no. 2004–806 of 9 August 2004 and following Good Clinical Practice and the Helsinki Declaration (Ethical Principles for Medical Research involving Human Subjects, Tokyo 2004). The study will be conducted in accordance with this protocol. With the exclusion of emergency situations requiring specific therapeutic actions, the investigators will observe the protocol in all respects, particularly in obtaining consent and the notification and follow-up of serious AEs.

The protocol was approved by the French institutional review board (18.07.19.74306) and received authorization from ANSM.

Protocol amendments

Important protocol modifications will be submitted for approval to the institutional review board of the University Hospital of Tours and will be communicated to coinvestigators.

Consent and assent

Participants will be orally informed of the study and will receive written information; their informed sign consent will be obtained (Additional file 1). For children aged < 18 years, parents will give their informed signed consent after their child has consented (if able). Children aged ≥ 16 years must also consent to use of their data according to article 89 (Regulation [EU] 2016/679 - RGPD). No biological specimens for genetic or molecular analysis will be collected.

Confidentiality

During this biomedical research study or when it is completed, the information collected for participants and forwarded to the sponsor by the investigators (or any other specialized staff member involved) will be made anonymous. Under no circumstances will the uncoded names or addresses of the participants concerned appear in any data.

Access to data

The sponsor is responsible for obtaining agreement from all parties involved in the study in order to guarantee direct access (in all sites where the study is being conducted) to source data, source documents, and reports, to control their quality, and to audit them.

The investigators will make available to people with right of access according to the legislative and regulatory provisions in force (articles L.1121–3 and R.5121–13 of the French Public Health Act) the documents and individual data strictly necessary for monitoring, performing quality control, and auditing the biomedical research.

Ancillary and post-trial care

The current trial is not planned to include patient ancillary care or post-trial care. On completion of the trial, topical sirolimus could be continued and will be on the investigator's initiative.

Dissemination policy

INSERM CIC 1415 Tours will analyze the data provided by the study centers. Results will be displayed in a written report that will be submitted to the sponsor. At the end of the analysis, results will be published at ClinicalTrials.gov. The international rules for writing and publication (Vancouver Agreement, February 2006) will be followed. The study results will be presented at scientific conferences and in peer-reviewed publication. We do not intend to use a professional writer. All study investigators will be eligible for authorship depending on contributions to the trial, analysis, and manuscript preparation.

Patients will be informed, at their request, about the overall results of the study.

SPIRIT

This protocol has been written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines. The SPIRIT checklist is in Additional file 2.

Discussion

This within-person, blinded RCT aims to compare 0.1% topical sirolimus with topical vehicle in CMLMs in children aged > 6 years and adults. Several case reports have suggested efficacy of this treatment, linked to the antilymphangiogenic properties of sirolimus, but this needs to be demonstrated. CMLMs are very rare diseases and this design allows for reducing the number of patients to be included; indeed, the population is too rare for a parallel-group trial. Furthermore, the location and severity of CMLMs are heterogeneous among patients; a within-person design, also called a split-body design, has the advantage of reducing individual inter-variability. Finally, all patients will receive the experimental treatment, which would not be the case with a parallel-group trial.

The hypothesis of this protocol study is that 0.1% topical sirolimus applied once daily during 12 weeks on CMLM is more efficient than a placebo cream (control), by reducing the thickness of CMLM, oozing, bleeding, impairments, and pain. In the literature, modalities of use of topical sirolimus are highly heterogeneous: the product has been used as a cream or solution, with concentrations in the range of 0.015%–8%. Creams were better tolerated than solutions; the most frequently used was sirolimus cream 0.1%, all conditions included [28]. This heterogeneity is linked to the fact that topical sirolimus is not marketed and therefore different formulations are used. Sirolimus has high molecular weight, 914.17 Da [29], which allows for diffusion limited to the skin. Thus, rapamycin was solubilized in a solvent (Transcutol®), which is an excellent permeation agent that enhances drug diffusion through the skin [30].

We expect no general side effects and no severe local adverse effects: for topical sirolimus, adverse effects previously described are local and of mild intensity (irritation, burning sensation, pruritus), reported in one-third of cases. We also expect a non-significant blood passage of the drug. Indeed, in previous reports, systemic passage of sirolimus with different concentrations of topical sirolimus in different skin conditions was not, or almost not, detectable and depended on the quantity of active principle administered and the surface to be treated [28]. In the present study, if systemic passage of sirolimus is evidenced, the consequence would be a reduced difference between the two areas; this would be unfavorable to our expected results.

Current treatments in CMLM are often disappointing and painful (lasers, surgery, sclerotherapy), so we expect an individual benefit with sirolimus. If the trial demonstrates the efficacy and safety of the treatment in patients with CMLMs, this will lead to a real change in the management of this rare condition and 0.1% sirolimus cream would become the first-line treatment.

Trial status

The current version of the protocol is V1.3, dated 21 December 2018.

This study was due to start recruitment in June 2019 and have a total period of recruitment of 24 months (June 2021).

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s13063-019-3767-8.

Additional file 1. Informed consent.

Additional file 2. SPIRIT checklist.

Abbreviations
AEs: Adverse events; ANSM: Agence Nationale de Sécurité du Médicament et des produits de santé; CMLM: Cutaneous microcystic lymphatic malformation; DLQI: Dermatology Life Quality Index; DSMB: Data Safety Monitoring Board; e-CRF: Electronic case report form; FTU: Fingertip unit; mTOR: Mammalian target of rapamycin; PGA: Physician Global Assessment; RCT: Randomized controlled trial; SOP: Standardized Operating Procedures; SUSAR: Suspected unexpected serious adverse reaction; VAS: Visual analog scale; VM: Vascular malformation

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Authors' contributions
SL, AM, GL, DG, DH, ALT, VG, HB, AC, and BG conceived the study. OB, DB, LG, PV, IQ, JMH, NB, AD, ACB, CLL, AP, PP, HB, CC, SB, CD, SM, LM, SL, and AM participated in its design and coordination. AC and BG perform the statistical calculations. SL, AM, BG, and AC will write the manuscript. All authors will read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
Central ethics approval was confirmed from the French institutional review board (ref approval no. 18.07.19.74306), but approval from local ethics boards of the other centers in the trial was not required according to the French law. The protocol received authorization from ANSM. Written and oral informed consent was obtained from all participants before enrolment.

Consent for publication
We will obtain informed consent for publication of the dataset from patients on enrollment in the trial. All patient details will be fully anonymous.

Competing interests
The authors declare that they have no competing interests.

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References
1. Wassef M, Blei F, Adams D, Alomari A, Baselga E, Berenstein A, et al. Vascular anomalies classification: recommendations from the International Society for the Study of Vascular Anomalies. Pediatrics. 2015;136:e203–14.
2. Kennedy TL, Whitaker M, Pellitteri P, Wood WE. Cystic hygroma/lymphangioma: a rational approach to management. Laryngoscope. 2001;111:1929–37.
3. Smith RJH. Lymphatic malformations. Lymphat Res Biol. 2004;2:25–31.
4. Schulte-Merker S, Sabine A, Petrova TV. Lymphatic vascular morphogenesis in development, physiology, and disease. J Cell Biol. 2011;193:607–18.
5. Eliasson JJ, Weiss I, Høgevold HE, Oliver N, Andersen R, Try K, et al. An 8-year population description from a national treatment centre on lymphatic malformations. J Plast Surg Hand Surg. 2017;51:280–5.
6. Acord M, Srinivasan AS, Cahill AM. Percutaneous treatment of lymphatic malformations. Tech Vasc Interv Radiol. 2016;19:305–11.
7. Erikçi V, Hoşgör M, Yıldız M, Örnek Y, Aksoy N, Okur Ö, et al. Intralesional bleomycin sclerotherapy in childhood lymphangioma. Turk J Pediatr. 2013;55:396–400.
8. Defnet AM, Bagrodia N, Hernandez SL, Gwilliam N, Kandel JJ. Pediatric lymphatic malformations: evolving understanding and therapeutic options. Pediatr Surg Int. 2016;32:425–33.
9. Bagrodia N, Defnet AM, Kandel JJ. Management of lymphatic malformations in children. Curr Opin Pediatr. 2015;27:356–63.
10. Lerat J, Mounayer C, Scomparin A, Orsel S, Bessede J-P, Aubry K. Head and neck lymphatic malformation and treatment: Clinical study of 23 cases. Eur Ann Otorhinolaryngol Head Neck Dis. 2016;133:393–6.
11. Xue Q, Nagy JA, Manseau EJ, Phung TL, Dvorak HF, Benjamin LE. Rapamycin inhibition of the Akt/mTOR pathway blocks select stages of VEGF-A164 driven angiogenesis, in part by blocking S6Kinase. Arterioscler Thromb Vasc Biol. 2009;29:1172–8.
12. Desai N, Heenan S, Mortimer PS. Sirolimus-associated lymphoedema: eight new cases and a proposed mechanism. Br J Dermatol. 2009;160:1322–6.
13. Kasap B. Sirolimus in pediatric renal transplantation. Pediatr Transplant. 2011;15:673–85.
14. Strychowsky JE, Rahbar R, O'Hare MJ, Irace AL, Padua H, Trenor CC. Sirolimus as treatment for 19 patients with refractory cervicofacial lymphatic malformation. Laryngoscope. 2018;128:269–76.
15. Wataya-Kaneda M, Nakamura A, Tanaka M, Hayashi M, Matsumoto S, Yamamoto K, et al. Efficacy and safety of topical sirolimus therapy for facial angiofibromas in the tuberous sclerosis complex : a randomized clinical trial. JAMA Dermatol. 2017;153:39–48.
16. Koenig MK, Bell CS, Hebert AA, Roberson J, Samuels JA, Slopis JM, et al. Efficacy and safety of topical rapamycin in patients with facial angiofibromas secondary to tuberous sclerosis complex: the TREATMENT randomized clinical trial. JAMA Dermatol. 2018;154:773–80.
17. Çalışkan E, Altunel CT, Özkan CK, Tunca M. A case of microcystic lymphatic malformation successfully treated with topical sirolimus. Dermatol Ther. 2018;31:e12673.
18. Ivars M, Redondo P. Efficacy of topical sirolimus (rapamycin) for the treatment of microcystic lymphatic malformations. JAMA Dermatol. 2017;153:103–5.
19. García-Montero P, del Boz J, Baselga-Torres E, Azaña-Defez JM, Alcaraz-Vera M, Tercedor-Sánchez J, et al. Use of topical rapamycin in the treatment of superficial lymphatic malformations. J Am Acad Dermatol. 2019;80:508–15.

20. Leducq S, Vrignaud S, Lorette G, Herbreteau D, Dubée V, Martin L, et al. Topical rapamycin (sirolimus) for treatment of cutaneous microcystic lymphatic malformation of the gluteal area. Eur J Dermatol. 2019;29:82–3.
21. Zaballos P, del Pozo LJ, Argenziano G, Karaarslan IK, Landi C, Vera A, et al. Dermoscopy of lymphangioma circumscriptum: A morphological study of 45 cases. Australas J Dermatol. 2018;59:e189–93.
22. Jha AK, Lallas A, Sonthalia S. Dermoscopy of cutaneous lymphangioma circumscriptum. Dermatol Pract Concept. 2017;7:37–8.
23. Bouguéon G, Lagarce F, Martin L, Pailhories H, Bastiat G, Vrignaud S. Formulation and characterization of a 0.1% rapamycin cream for the treatment of Tuberous Sclerosis Complex-related angiofibromas. Int J Pharm. 2016;509:279–84.
24. Long CC, Finlay AY. The finger-tip unit--a new practical measure. Clin Exp Dermatol. 1991;16:444–7.
25. Breuer K, Braeutigam M, Kapp A, Werfel T. Influence of pimecrolimus cream 1% on different morphological signs of eczema in infants with atopic dermatitis. Dermatology (Basel). 2004;209:314–20.
26. Garduno J, Bhosle MJ, Balkrishnan R, Feldman SR. Measures used in specifying psoriasis lesion(s), global disease and quality of life: a systematic review. J Dermatolog Treat. 2007;18:223–42.
27. Nadal M, Giraudeau B, Tavernier E, Jonville-Bera A-P, Lorette G, Maruani A. Efficacy and safety of mammalian target of rapamycin inhibitors in vascular anomalies: a systematic review. Acta Derm Venereol. 2016;96:448–52.
28. Leducq S, Giraudeau B, Tavernier E, Maruani A. Topical use of mammalian target of rapamycin inhibitors in dermatology: a systematic review with meta-analysis. J Am Acad Dermatol. 2019;80:735–42.
29. Tanaka M, Wataya-Kaneda M, Nakamura A, Matsumoto S, Katayama I. First left-right comparative study of topical rapamycin vs. vehicle for facial angiofibromas in patients with tuberous sclerosis complex. Br J Dermatol. 2013;169:1314–8.
30. Mura P, Faucci MT, Bramanti G, Corti P. Evaluation of transcutol as a clonazepam transdermal permeation enhancer from hydrophilic gel formulations. Eur J Pharm. 2000;9:365–72.

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Supplemental file 1. Informed consent

Formulaire de consentement de participation à une Recherche interventionnelle sur la personne humaine : Mineurs participant à l'étude

Parent (1) : Je soussigné(e),
Nom : ..... *Prénom :* .....
Adresse : .....
.....

Parent (2) : Je soussigné(e),
Nom : ..... *Prénom :* .....
Adresse (à compléter si différente de (1)) : .....
.....

Merci de cocher seulement si applicable : ☐ Certifie être le seul titulaire de l'exercice de l'autorité parentale

De l'enfant *Nom :* ..... *Prénom :* ..... **Né(e) le :** ___ / ___ / _____

Déclarent avoir pris connaissance des informations orales et écrites (*lettres d'information v1-2-PARENTS du 21/12/2018*) qui nous ont été transmises pour une **participation de notre enfant à l'étude clinique TOPICAL** « *Évaluation de l'efficacité et de la tolérance du sirolimus topique 0.1% dans les malformations cutanées lymphatiques microkystiques : essai thérapeutique de phase II, randomisé, en double aveugle, en comparaison intra individuelle versus véhicule* » organisée par le CHRU de Tours qui en est le Promoteur, autorisée par l'ANSM (n° MEDAECNAT-2018-12-00055) et le CPP Nord-Ouest 1 (n° 18.07.19.74306).

Nous avons reçu du médecin investigateur qui suit notre enfant, toutes les informations nécessaires concernant l'objectif de cette recherche, son déroulement ainsi que les conditions de participation de notre enfant, nos droits, les bénéfices attendus, les contraintes et les risques prévisibles. Nous avons pu poser toutes les questions que nous voulions et nous avons reçu les réponses adaptées. Nous avons bénéficié d'un temps de réflexion suffisant entre ces informations et le présent consentement. Nous avons également compris que nous pouvions refuser que notre enfant participe à cette étude sans que cela ne porte préjudice à la suite de sa prise en charge.

Compte tenu des informations qui nous ont été transmises,

- **Nous acceptons librement et volontairement que notre enfant participe à cette étude,**

- **Nous acceptons que les données enregistrées à l'occasion de cette étude puissent faire l'objet d'un traitement informatisé par le promoteur ou pour son compte dans les conditions prévues par la Loi Informatique et Libertés, de la loi n° 2018-493 du 20 juin 2018 relative à la protection des données personnelles et du Règlement (UE) 2016/679 du Parlement européen et du Conseil du 27 avril 2016. Nous avons été informés de tous nos droits, ainsi que des droits de notre enfant, concernant ces données personnelles selon les modalités décrites dans la lettre d'information en vigueur.** Nous avons été informés que notre enfant doit également donner son consentement pour le traitement informatisé de ses données, et qu'il peut y consentir seul à compter de l'âge de quinze ans. Si notre enfant a quinze ans, ou plus, il a également le droit de s'opposer à ce que nous ayons accès ou soyons informés du traitement de ses données au cours de la recherche.

- **Nous certifions être bénéficiaires d'un régime de sécurité sociale.**

Pour les jeunes filles réglées : une contraception efficace devra être utilisée jusqu'à la fin de l'étude.

Conformément à la loi, le CHRU de Tours, promoteur de l'étude, a souscrit une assurance de responsabilité auprès de la compagnie SHAM afin de couvrir tout préjudice corporel ou toute incapacité que pourrait entraîner cette étude.

Partie à remplir par les parents (ou titulaire de l'exercice de l'autorité parentale)	
Date : __ / __ / ____ Signature :	Date : __ / __ / ____ Signature :

Partie à remplir par le participant mineur

J'ai bien été informé(e) de l'étude et j'ai reçu une lettre d'information. J'accepte le traitement informatisé de mes données.

Nom, Prénom : ..... Date : __ / __ / ____ Signature :

Partie à remplir par le médecin investigateur

Nom, Prénom : ..... Date : __ / __ / ____ Signature :

Merci de cocher seulement si applicable : ☐ Enfant dans l'incapacité de donner son consentement ci-dessus.

En trois exemplaires : original pour le médecin investigateur, un exemplaire pour les parents, et un exemplaire pour le promoteur

Formulaire de consentement de participation à une Recherche interventionnelle sur la personne humaine : **Participants devenus majeurs en cours d'étude**

Je soussigné(e) *Nom :* ..... ***Prénom :*** .....

Adresse : .....

.....

Déclare avoir pris connaissance des informations orales et écrites (*lettre d'information v1-MAJEUR du 21/12/2018*) qui m'ont été transmises afin de confirmer ma **participation à l'étude clinique TOPICAL** « *Évaluation de l'efficacité et de la tolérance du sirolimus topique 0.1% dans les malformations cutanées lymphatiques microkystiques : essai thérapeutique de phase II, randomisé, en double aveugle, en comparaison intra individuelle versus véhicule* » organisée par le CHRU de Tours qui en est le Promoteur, autorisée par l'ANSM (n° MEDAECNAT-2018-12-00055) et le CPP Nord-Ouest 1 (n° 18.07.19.74306).

Je confirme voir reçu du médecin investigateur, toutes les informations nécessaires concernant l'objectif de cette recherche, son déroulement ainsi que mes conditions de participation, mes droits, les bénéfices attendus, les contraintes et les risques prévisibles. J'ai pu poser toutes les questions que je voulais et j'ai reçu les réponses adaptées. J'ai bénéficié d'un temps de réflexion suffisant entre ces informations et le présent consentement. J'ai également compris que je pouvais refuser de continuer de participer à cette étude sans que cela ne porte préjudice à la suite de ma prise en charge. Compte tenu des informations qui m'ont été transmises,

- J'accepte librement et volontairement de continuer de participer à cette étude,

- J'accepte que les données enregistrées à l'occasion de cette étude puissent faire l'objet d'un traitement informatisé par le promoteur ou pour son compte dans les conditions prévues par la Loi Informatique et Libertés, de la loi n° 2018-493 du 20 juin 2018 relative à la protection des données personnelles et du Règlement (UE) 2016/679 du Parlement européen et du Conseil du 27 avril 2016. J'ai été informé(e) de tous mes droits concernant mes données personnelles selon les modalités décrites dans la lettre d'information en vigueur,

- Je certifie être bénéficiaire d'un régime de sécurité sociale.

- Si je suis une jeune femme, je m'engage à utiliser une méthode de contraception efficace jusqu'à la fin de l'étude.

Conformément à la loi, le CHRU de Tours, promoteur de cette étude, a souscrit une assurance de responsabilité auprès de la compagnie SHAM afin de couvrir tout préjudice corporel ou toute incapacité que pourrait entraîner cette étude.

Partie à remplir par le participant à l'étude	***Partie à remplir par le médecin investigateur***
Nom et prénom : _____	Nom et prénom : _____
Date : ____ / ____ / _____ Signature :	Date : ____ / ____ / _____ Signature :

En trois exemplaires : original pour le médecin investigateur, un exemplaire pour le participant, et un exemplaire pour le promoteur

Formulaire de consentement de participation à une Recherche interventionnelle sur la personne humaine : **Adultes participant à l'étude**

Je soussigné(e) *Nom :* ..... ***Prénom :*** .....

Adresse : .....

.....

Déclare avoir pris connaissance des informations orales et écrites (*lettre d'information v1-ADULTE du 21/12/2018*) qui m'ont été transmises pour une **participation à l'étude clinique TOPICAL** « *Évaluation de l'efficacité et de la tolérance du sirolimus topique 0.1% dans les malformations cutanées lymphatiques microkystiques : essai thérapeutique de phase II, randomisé, en double aveugle, en comparaison intra individuelle versus véhicule* » organisée par le CHRU de Tours qui en est le Promoteur, autorisée par l'ANSM (n° MEDAECNAT-2018-12-00055) et le CPP Nord-Ouest 1 (n° 18.07.19.74306).

J'ai reçu du médecin investigateur, toutes les informations nécessaires concernant l'objectif de cette recherche, son déroulement ainsi que mes conditions de participation, mes droits, les bénéfices attendus, les contraintes et les risques prévisibles. J'ai pu poser toutes les questions que je voulais et j'ai reçu les réponses adaptées. J'ai bénéficié d'un temps de réflexion suffisant entre ces informations et le présent consentement. J'ai également compris que je pouvais refuser de participer à cette étude sans que cela ne porte préjudice à la suite de ma prise en charge. Compte tenu des informations qui m'ont été transmises,

- **J'accepte librement et volontairement de participer à cette étude,**

- **J'accepte que les données enregistrées à l'occasion de cette étude puissent faire l'objet d'un traitement informatisé par le promoteur ou pour son compte dans les conditions prévues par la Loi Informatique et Libertés, de la loi n° 2018-493 du 20 juin 2018 relative à la protection des données personnelles et du Règlement (UE) 2016/679 du Parlement européen et du Conseil du 27 avril 2016. J'ai été informé(e) de tous mes droits concernant mes données personnelles selon les modalités décrites dans la lettre d'information en vigueur,**

- **Je certifie être bénéficiaire d'un régime de sécurité sociale.**

- **Si je suis une femme en âge de procréer, je m'engage à utiliser une méthode de contraception efficace jusqu'à la fin de l'étude.**

Conformément à la loi, le CHRU de Tours, promoteur de cette étude, a souscrit une assurance de responsabilité auprès de la compagnie SHAM afin de couvrir tout préjudice corporel ou toute incapacité que pourrait entraîner cette étude.

Partie à remplir par le participant à l'étude	***Partie à remplir par le médecin investigateur***
Nom et prénom : _____	Nom et prénom : _____
Date : ____ / ____ / _____ Signature :	Date : ____ / ____ / _____ Signature :

En trois exemplaires : original pour le médecin investigateur, un exemplaire pour le participant, et un exemplaire pour le promoteur

Supplemental file 2. SPIRIT checklist



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page Number on which item is reported
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	5
	2b	All items from the World Health Organization Trial Registration Data Set	1, 3, 5 -14, 23 - 24
Protocol version	3	Date and version identifier	23
Funding	4	Sources and types of financial, material, and other support	24
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1-3
	5b	Name and contact information for the trial sponsor	24
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	24
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	24
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-7

	6b	Explanation for choice of comparators	6-7
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7-8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	10-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10-11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11-13
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	14, Table 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	14-15
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	15
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	15
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	15
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	15-16
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	15-16
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	16
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	16-17
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18-19
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	19
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	18-19
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	18-19
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	19
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	19
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	19-20
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	20
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	20, Additional file 1
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	20

Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	24
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	20
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	20-21
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21
	31b	Authorship eligibility guidelines and any intended use of professional writers	21
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	24
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Additional file 1
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	20

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

III- Conclusion générale et perspectives

1. Synthèse des principaux résultats

Ce travail de thèse a permis de mieux préciser et appréhender les aspects méthodologiques et statistiques pour la planification et le « reporting » d'essais en « within-person » dans l'évaluation d'un traitement topique en dermatologie.

Tout d'abord, le choix entre les différents schémas d'étude doit être réalisé en fonction de la prévalence de la maladie, du critère de jugement principal (au niveau du patient, par exemple l'évaluation de la qualité de vie ; ou au niveau de la lésion), du risque de contamination inter-groupes et du nombre de lésions par patient. L'utilisation d'un essai en « within-person » est à privilégier en cas de maladie rare pour augmenter la puissance de l'essai.

Au travers de notre revue systématique, nous avons mis en évidence que l'essai en « within-person » est finalement un schéma d'étude peu utilisé et peu connu en dermatologie avec une méthodologie comportant de nombreuses limites dans les essais utilisant ce schéma d'étude, malgré la publication de l'extension du CONSORT Statement pour l'essai en « within-person », en 2017.

L'étude de simulation a permis de mieux appréhender les méthodes d'analyse à utiliser en cas d'essais en « within-person » incluant plus de 2 lésions par patient. Les méthodes d'analyse retenues sont des méthodes d'analyse complexes faisant appel à des modèles mixtes pour l'estimation d'une différence de proportion et des *generalized estimating equations.*

2. Recommandations pour l'évaluation d'un traitement topique à l'aide d'un schéma d'étude en « within-person » en dermatologie

2.1.Privilégier les essais en « within-person » incluant 2 lésions par patient

Les essais en « within-person » utilisant 2 lésions par patient sont le plus utilisés et sont les plus simples à planifier. Leur analyse statistique est également la plus simple car elle fait appel à des tests simples pour séries appariées (par exemple, le test de Student pour données appariées en cas de données quantitatives ou le test de Mc Nemar en cas de données qualitatives). Cependant,

afin de gagner en puissance, un schéma d'étude en « within-person » avec plus de 2 lésions par patient peut être envisagé. Leur analyse statistique est cependant plus complexe avec l'utilisation de modèles mixtes avec estimation d'une différence de proportion (approche conditionnelle) ou l'utilisation de *generalized estimating equations* (approche marginale).

2.2.Planification de l'essai

Il est important de bien prendre en compte certains points lors de la planification d'un essai en « within-person ». Les critères d'éligibilité doivent être définis (et rapportés) tant pour les patients que pour les lésions. La mise en place d'un « care provider », bien que majorant le coût de l'étude, permet d'améliorer l'observance des traitements à l'étude et de limiter la contamination inter-groupes. Ce risque de contamination est réel et il est donc nécessaire, plus encore que dans un essai classique dans lequel on randomise les patients, de mesurer l'observance aux traitements. L'aveugle est implémenté si possible et le sera au niveau du patient, de l'évaluateur mais également du « care provider ».

Le risque de « carry-across effect » doit être discuté par les auteurs et mesuré si possible. Une période d'extension, après la période d'étude, peut être proposée pour favoriser l'adhérence des patients au protocole. En effet, la particularité du « within-person design » c'est que chaque patient voit ses lésions traitées de façon distincte. Si l'un des traitements s'avère plus efficace que l'autre, offrir au patient la possibilité d'avoir accès aux traitements dans le cadre d'une période d'extension peut aider à accepter de participer à l'essai et être observant. Un critère de jugement objectif doit être retenu autant que possible, puisqu'il y a un risque de biais d'évaluation plus important que dans un essai classique du fait, encore une fois, que le patient reçoit les 2 traitements de façon concomitante.

2.3.« Reporting » de l'essai

Il est important qu'il soit clairement identifié dans le titre de l'article, le résumé et le corps de texte, que l'essai est un « within-person design ». Une justification de l'utilisation de ce schéma d'étude doit être apportée par les auteurs. De même, l'acceptabilité du patient est à discuter. Un coefficient de corrélation intra-classe est utilisé pour lors du calcul d'effectif et il doit être estimé lors de l'analyse statistique. Enfin, un diagramme de flux et une description des caractéristiques à l'inclusion à la fois des patients et lésions doivent être inclus.

3. Enjeux du schéma d'étude en « within-person »

Ce schéma d'étude, peu connu et peu utilisé, présente comme avantages principaux l'augmentation de la puissance (et donc une réduction du nombre de sujets à inclure) et la diminution de la variabilité inter-individuelle. Il est particulièrement adapté à certaines pathologies dermatologiques se présentant sous forme de lésions multiples individualisables homogènes chez un patient. Cependant, les contraintes méthodologiques et statistiques liées à ce schéma d'étude sont importantes ; en particulier en cas d'inclusion de plus de 2 lésions par patient. Pour les pathologies dermatologiques fréquentes, l'utilisation d'un essai classique avec randomisation individuelle semble donc à privilégier, quand bien même l'effectif à inclure est plus important.

Nous nous sommes intéressés dans cette thèse aux aspects méthodologiques pour les traitements topiques médicamenteux. Cependant, l'utilisation de ce schéma d'étude n'est pas limitée aux traitements topiques médicamenteux. Il peut être utilisé également pour l'évaluation de dermocosmétiques ou de traitements physiques (photothérapie dynamique ou lasers par exemple) avec des contraintes méthodologiques qui seront différentes. Ainsi, il n'y a pas de risque de contamination inter-groupe du fait de l'absence de passage systémique et l'absence de contamination directe pour les traitements physiques. Par ailleurs, l'administration du traitement physique est habituellement réalisée par le « care provider » parfois lors d'une séance unique permettant de minimiser le risque de non-observance. Néanmoins, la mise en insu du « care provider » pour les traitements physiques n'est pas réalisable et de la même façon, un critère de jugement objectif est privilégié.

4. Acceptabilité du patient et de l'investigateur

L'adhésion du patient et de l'investigateur est également un point majeur à considérer lors de la planification de l'étude et peut varier en fonction de la pathologie dermatologique. Plusieurs « niveaux » d'acceptation doivent être considérés. Dans un 1er temps, le patient doit accepter le protocole de recherche en « within-person » avec l'application simultanée des 2 traitements sur 2 lésions. En effet, un patient est-il prêt à accepter que la moitié de ses lésions soit traitée avec un médicament tandis que l'autre moitié sera traitée avec l'autre médicament ? Cette

problématique est d'autant plus importante dans les pathologies affichantes (par exemple, vitiligo sur zones exposées, acné du visage, pelade). Il doit également accepter les contraintes liées à l'étude notamment en cas d'utilisation de « care provider ». Dans un 2ème temps, au cours de l'étude, en cas d'efficacité d'un des traitements évalués, le patient doit pouvoir accepter d'avoir une partie seulement de ses lésions améliorées et doit accepter de poursuivre les traitements dans le cadre de l'étude. En parallèle, l'investigateur doit également accepter et adhérer au schéma d'étude choisi car c'est lui qui propose le protocole de recherche au patient, lui explique les enjeux d'avoir des lésions traitées différemment et le convainc de participer et d'être observant.

Ces points d'acceptabilité peuvent être décisifs pour le choix du schéma d'étude. Pour illustrer nos propos, nous pouvons prendre l'exemple de l'étude thérapeutique non randomisée de Tosti et al, utilisant un schéma d'étude en « within-person ». Vingt-huit patients présentant une pelade totale ou universelle avaient été traités par corticoïdes topiques d'activité très forte 6 jours par semaine pendant 6 mois sur la moitié du cuir chevelu (Tosti, 2003). L'autre moitié n'était pas traitée. Huit patients ont présenté une repousse complète à 6 mois sur une moitié du cuir chevelu (Figure 10). Dès lors on peut s'interroger sur l'acceptabilité des patients de cette situation, ce d'autant qu'elle est affichante, et sur leur bien-être. On peut aussi s'interroger sur l'acceptabilité des cliniciens investigateurs qui, au final, sont responsables d'avoir proposé à leurs patients cette étude qui a conduit à ce qu'ils soient dans cette situation où une partie des lésions semblent traitées quand l'autre ne l'est pas.



Figure 12 : A gauche, patiente de 35 ans présentant une alopécie universelle avant (A) et après (B) traitement par corticoïdes locaux d'activité très forte. A droite, patiente de 26 ans

présentant une alopécie totale, avant (A) et après (B) traitement (photographies issues de l'article de Tosti et al., 2003).

5. Perspectives

5.1.Évaluation de l'acceptabilité : méthode de révélation des préférences

Nous souhaitons donc, à l'issue de cette thèse, mener un travail sur l'acceptabilité par les patients et les investigateurs du schéma d'étude en « within-person » à l'aide d'une méthode de révélation des préférences (« discrete choice experiment »). Cette méthodologie, développée initialement en économie, est utilisée de façon croissante dans le domaine de la santé (Ryan, 2008 ; de Bekker-Grob, 2012). Elle consiste à exposer aux participants (patients et investigateurs dans notre étude) une série de scénarios/situations hypothétiques avec plusieurs choix. Les participants sont appelés à indiquer leur préférence entre les différents scénarios présentés (les scénarios étant des schémas d'études). La méthodologie pour ce travail sera réalisée à l'aide d'un économiste de la santé et enseignant-chercheur au sein de l'unité INSERM SPHERE.

5.2.Recherche en méthodologie des essais cliniques

Mon année de mobilité est planifiée pour novembre 2022 au sein de l'équipe du Professeur Hywel Williams et du Professeur Kim Thomas dans le *Centre of Evidence Based Dermatology* de Nottingham, au Royaume-Uni. Ce centre apporte une aide méthodologique nationale au Royaume-Uni pour les essais cliniques institutionnels.

Je prévois, au cours de cette année, de poursuivre mon activité de recherche sur la méthodologie. Il est prévu que j'y coordonne une revue systématique méthodologique sur les effets indésirables spécifiques des médicaments systémiques dans les essais contrôlés randomisés dans la dermatite atopique et le risque de levée de l'aveugle. L'objectif de cette revue systématique est d'évaluer la prévalence des effets indésirables spécifiques et de décrire les méthodes utilisées pour garantir le maintien de l'aveugle, afin de présenter et de proposer pour les futurs essais une classification des méthodes de mise en insu. Ce travail sera un travail collaboratif entre l'Université de Nottingham, le Centre de Preuves en Dermatologie de la Société Française de Dermatologie et le « GREAT Research Group » (Groupe de Recherche

sur l'Eczéma Atopique). Cette année de mobilité sera également l'occasion de collaborations futures entre nos 2 équipes. En effet, la problématique du placebo n'est pas propre aux traitements systémiques mais se pose également pour les traitements topiques et pourra faire l'objet d'une extension du travail qui sera conduit à Nottingham.

5.3.Recherche clinique sur les traitements topiques en dermatologie

Enfin, je souhaiterais en parallèle poursuivre mon activité de recherche clinique au sein de l'unité de Dermatologie Pédiatrique, en lien avec le Centre d'Investigation Clinique du CHRU de Tours et éventuellement l'unité INSERM SPHERE, selon les problématiques méthodologiques rencontrées. L'administration des traitements par voie topique est une voie d'administration privilégiée chez les enfants, pour éviter les traitements invasifs. Avec l'essor de nouvelles molécules avec une administration par voie systémique (par exemple, les inhibiteurs de mTOR, inhibiteurs de Janus Kinase, inhibiteur de la phosphodiestérase 4), l'évaluation de ces molécules par voie topique dans la population pédiatrique dans de nombreuses dermatoses est un enjeu majeur de la recherche en dermatologie. Nous avons obtenu un financement PHRC National en 2020, pour un protocole de recherche évaluant un traitement topique par inhibiteurs de Janus Kinase dans la pelade de l'enfant. Mon double parcours en dermatologie et méthodologie/biostatistique me permet ainsi d'appréhender les problématiques soulevées en méthodologie et leur mise en application dans le cadre de projets de recherche clinique.

Références

1. Adams DM, Trenor CC, Hammill AM, Vinks AA, Patel MN, Chaudry G, et al. Efficacy and safety of sirolimus in the treatment of complicated vascular anomalies. Pediatrics. 2016;137(2):e20153257.
2. Adams G, Gulliford MC, Ukoumunne OC, Eldridge S, Chinn S, Campbell MJ. Patterns of intra-cluster correlation from primary care research to inform study design and analysis. J Clin Epidemiol. 2004;57(8):785-94.
3. Agence nationale de sécurité du médicament et des produits de santé (2022). http://agence-prd.ansm.sante.fr/php/ecodex/index.php
4. Amoric JC. [Absorption cutanée et accidents toxiques des traitements locaux chez l'enfant]. Rev Fr Allergol Immunol Clin. 2000;40(7):747—53.
5. Arda O, Göksügür N, Tüzün Y. Basic histological structure and functions of facial skin. Clinics in Dermatology. 2014;32(1):3-13.
6. Badia P, Ricci K, Gurria JP, Dasgupta R, Patel M, Hammill A. Topical sirolimus for the treatment of cutaneous manifestations of vascular anomalies: A case series. Pediatr Blood Cancer. 2020;67(4):e28088.
7. Bos JD, Meinardi MM. The 500 Dalton rule for the skin penetration of chemical compounds and drugs. Exp Dermatol. 2000;9(3):165-9.
8. Bryant D, Havey TC, Roberts R, Guyatt G. How many patients? How many limbs? Analysis of patients or limbs in the orthopaedic literature: a systematic review. J Bone Joint Surg Am. 2006;88(1):41-5.
9. Caille A, Leyrat C, Giraudeau B. [Cluster randomised trials]. Ann Dermatol Venereol. 2014;141(2):144-6.
10. Cavalié M, Ezzedine K, Fontas E, Montaudié H, Castela E, Bahadoran P, et al. Maintenance therapy of adult vitiligo with 0.1% tacrolimus ointment: a randomized, double blind, placebo–controlled study. J Invest Dermatol. 2015;135(4):970-4.
11. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-7.
12. Chosidow O, Giraudeau B, Cottrell J, Izri A, Hofmann R, Mann SG, et al. Oral ivermectin versus malathion lotion for difficult-to-treat head lice. N Engl J Med. 2010;362(10):896-905.
13. de Bekker-Grob EW, Ryan M, Gerard K. Discrete choice experiments in health economics:

a review of the literature. Health Economics. 2012;21(2):145-72.
14. de Monte F, Pontrelli G, Becker SM. Chapter 10 - Transdermal Drug Delivery and Percutaneous Absorption: Mathematical Modeling Perspectives. In: Becker SM, Kuznetsov AV, éditeurs. Heat Transfer and Fluid Flow in Biological Processes [Internet]. Boston: Academic Press; 2015. p. 273-304.
15. Dodds M, Tollefson M, Castelo-Soccio L, Garzon MC, Hogeling M, Hook K, et al. Treatment of superficial vascular anomalies with topical sirolimus: A multicenter case series. Pediatr Dermatol. 2020;37(2):272-7.
16. Dréno B. [Anatomie et physiologie de la peau et de ses annexes]. Ann Dermatol Venereol. 2009;136:S247-51.
17. Eldridge SM, Ashby D, Kerry S. Sample size for cluster randomized trials: effect of coefficient of variation of cluster size and analysis method. Int J Epidemiol. oct 2006;35(5):1292-300.
18. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)--a simple practical measure for routine clinical use. Clin Exp Dermatol. 1994;19(3):210-6.
19. García-Montero P, Del Boz J, Baselga-Torres E, Azaña-Defez JM, Alcaraz-Vera M, Tercedor-Sánchez J, et al. Use of topical rapamycin in the treatment of superficial lymphatic malformations. J Am Acad Dermatol. 2019;80(2):508-15.
20. Garduno J, Bhosle MJ, Balkrishnan R, Feldman SR. Measures used in specifying psoriasis lesion(s), global disease and quality of life: a systematic review. J Dermatolog Treat. 2007;18(4):223-42.
21. Global Topical Drug Delivery Industry (2021). *https://www.reportlinker.com/p06033143/Global-Topical-Drug-Delivery-Industry.html*
22. Hammer J, Seront E, Duez S, Dupont S, Van Damme A, Schmitz S, et al. Sirolimus is efficacious in treatment for extensive and/or complex slow-flow vascular malformations: a monocentric prospective phase II study. Orphanet J Rare Dis. 2018;13(1):191.
23. Harlow D, Poyner T, Finlay AY, Dykes PJ. Impaired quality of life of adults with skin disease in primary care. Br J Dermatol. 2000;143(5):979-82.
24. Hawkins CM, Chewning RH. Diagnosis and management of extracranial vascular malformations in children: arteriovenous malformations, venous malformations, and lymphatic malformations. Semin Roentgenol. 2019;54(4):337-48.
25. Hon KL, Tsang YCK, Lee VWY, Pong NH, Ha G, Lee ST, et al. Efficacy of sodium hypochlorite (bleach) baths to reduce Staphylococcus aureus colonization in childhood onset

moderate-to-severe eczema: A randomized, placebo-controlled cross-over trial. J Dermatolog Treat. 2016;27(2):156-62.

26. Jain KK. Drug delivery systems - an overview. Methods Mol Biol. 2008;437:1-50.

27. Jones, B, Kenward, MG. Design and analysis of cross-over trials, 2nd ed. London: Chapman and Hall, 2003.

28. Karimkhani C, Dellavalle RP, Coffeng LE, Flohr C, Hay RJ, Langan SM, et al. Global skin disease morbidity and mortality: an update from the global burden of disease study 2013. JAMA Dermatology. 2017;153(5):406-12.

29. Kezic S, Nielsen JB. Absorption of chemicals through compromised skin. Int Arch Occup Environ Health. 2009;82(6):677-88.

30. Lee CF, Cheng AC, Fong DY. Eyes or subjects: are ophthalmic randomized controlled trials properly designed and analyzed? Ophthalmology. 2012;119(4):869-72.

31. Lim HW, Collins SAB, Resneck JS, Bolognia JL, Hodge JA, Rohrer TA, et al. The burden of skin disease in the United States. J Am Acad Dermatol. 2017;76(5):958-972.e2.

32. Long CC, Finlay AY. The finger-tip unit--a new practical measure. Clin Exp Dermatol. nov 1991;16(6):444-7.

33. Luo Y, Liu L, Rogers D, Su W, Odaka Y, Zhou H, et al. Rapamycin inhibits lymphatic endothelial cell tube formation by downregulating vascular endothelial growth factor receptor 3 protein expression. Neoplasia. 2012;14(3):228-37.

34. Machet L, Pinton J, Patat F, Arbeille B, Pourcelot L,Vaillant L. In vitro phonophoresis of digoxin across hairless mice and human skin: thermal effect of ultrasound. Int J Pharm. 1996;33, 39-45.

35. Machin D, Campbell MJ, Tan SB, Tan SH (2009) Sample size tables for clinical studies. 3rd ed. Chichester: Wiley-Blackwell.

36. Maruani A, Boucaud A, Perrodeau E, Gendre D, Giraudeau B, Machet L. Low-frequency ultrasound sonophoresis to increase the efficiency of topical steroids: a pilot randomized study of humans. Int J Pharm. 2010;395(1-2):84-90.

37. Maruani A, Samimi M, Lorette G, le Cleach L. Comparative effectiveness of topical drugs in dermatologic priority diseases: geometry of randomized trial networks. J Invest Dermatol. 2015;135:76-83.

38. Maruani A, Tavernier E, Boccara O, Mazereeuw-Hautier J, Leducq S, Bessis D, et al. Sirolimus (rapamycin) for slow-flow malformations in children: the observational-phase randomized clinical PERFORMUS trial. JAMA Dermatol. 2021;157(11):1289-98.

39. Murray CJ. Quantifying the burden of disease: the technical basis for disability-adjusted life years. Bull World Health Organ. 1994;72(3):429-45.
40. Pandis N, Chung B, Scherer RW, Elbourne D, Altman DG. CONSORT 2010 statement: extension checklist for reporting within person randomised trials. BMJ. 2017;357:j2835.
41. Pfannenstiel HP, Pandis N, Seehra J, Faggion CM Jr. The reporting quality of split-mouth studies in implant dentistry: a survey. Int J Oral Maxillofac Implants. 2022;37(3):447-454.
42. PubChem. *Clobetasol propionate*. https://pubchem.ncbi.nlm.nih.gov/compound/32798
43. PubChem. *Tretinoin*. https://pubchem.ncbi.nlm.nih.gov/compound/444795
44. Ryan M, Gerard K, Amaya-Amaya M. Using discrete choice experiments to value health and health care (The economics of non-market goods and resources, 11). Springer Academic Publishers 2008.
45. Scharffetter-Kochanek K, Brenneisen P, Wenk J, Herrmann G, Ma W, Kuhr L, et al. Photoaging of the skin from phenotype to mechanisms. Exp Gerontol. 2000;35(3):307-16.
46. Schmieder S, Patel P, Krishnamurthy K. Research techniques made simple: drug delivery techniques, part 1: concepts in transepidermal penetration and absorption. J Invest Dermatol. 2015;135(11):1-5.
47. Schofield J, Grindlay D, Williams H. Skin conditions in the UK : a health care needs assessment. Centre of Evidence Based Dermatology, University of Nottingham. 2009. http://uhra.herts.ac.uk/handle/2299/5622.
48. Schulz KF, Altman DG, Moher D; CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c332.
49. Seneschal J, Duplaine A, Maillard H, Passeron T, Andreu N, Lassalle R, et al. Efficacy and safety of tacrolimus 0.1% for the treatment of facial vitiligo: a multicenter randomized, double-blinded, vehicle-controlled study. J Invest Dermatol. 2021;141(7):1728-1734.
50. Smith RJH. Lymphatic malformations. Lymphat Res Biol. 2004;2(1):25-31.
51. Tosti A, Piraccini BM, Pazzaglia M, Vincenzi C. Clobetasol propionate 0.05% under occlusion in the treatment of alopecia totalis/universalis. J Am Acad Dermatol. 2003;49(1):96-8.
52. Vaillant L. Traitements locaux en dermatologie. Dermatologie pratique 1996.
53. Wester, RC, HI. Maibach. Regional variation in percutaneous absorption. Pp. 107-116 in Percutaneous absorption, 3rd ed. New York: Marcel Dekker, Inc. 1999.
54. Zhai H, Maibach HI. Effects of skin occlusion on percutaneous absorption: an overview. Skin Pharmacol Appl Skin Physiol. 2001;14(1):1-10.

55. Zhang M, Silverberg JI, Kaffenberger BH. Prescription patterns and costs of acne/rosacea medications in Medicare patients vary by prescriber specialty. J Am Acad Dermatol. 2017;77(3):448-455.e2.
56. Global Topical Drug Delivery Industry (2021). *https://www.reportlinker.com/p06033143/Global-Topical-Drug-Delivery-Industry.html*
57. World Health Organization (2021). *International Statistical Classification of Diseases and Related Health Problems (ICD)*. https://www.who.int/standards/classifications/classification-of-diseases

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Aspects méthodologiques et statistiques des « within-person randomised trials » évaluant un traitement topique en dermatologie

Résumé en français :

Lors de l'évaluation d'un traitement topique en dermatologie, on peut recourir à un « within-person design ». Les unités de randomisation ne sont alors pas les patients mais les lésions (ou régions anatomiques), et les traitements à comparer sont appliqués de façon concomitante sur les différentes lésions. Ce schéma d'étude réduit la variabilité inter-observations, et donc le nombre de patients à inclure dans l'essai. Cependant il présente des contraintes méthodologiques majeures, notamment la nécessité de s'assurer qu'il n'y a pas de risque de contamination intergroupe (« carry across effect »). L'objectif de cette thèse était d'étudier les aspects méthodologiques et statistiques des « within-person trials ». La 1ère partie de ce travail présente une synthèse des aspects méthodologiques à considérer lorsqu'on envisage ce type de schéma d'étude. Cette synthèse a été réalisée par un groupe de travail comportant des dermatologues et biostatisticiens. Dans la 2ème partie, nous avons réalisé une revue méthodologique des « within-person trials » publiés entre 2017 et 2021. Les aspects méthodologiques identifiés dans le 1er travail ont été recueillis et discutés dans cette revue. Le 3ème travail portait sur les méthodes d'analyse potentielles pour ce type d'essai. A l'aide d'une étude de simulation de Monte-Carlo, nous avons comparé les propriétés statistiques de plusieurs méthodes d'analyse (modèles mixtes et generalized estimating equations). Enfin, à titre d'illustration, la 4ème partie présente un protocole de « within-person trial » visant à évaluer le sirolimus topique dans les malformations lymphatiques superficielles. Le schéma d'étude en « within-person » présente de multiples spécificités à la fois méthodologiques et statistiques qui doivent être pris en compte lors de la planification et de l'analyse de l'étude. Les dermatologues et méthodologistes doivent également tenir compte de l'acceptabilité du patient.

Mots-clés : within-person design, administration par voie topique, essai contrôlé randomisé, traitement topique, dermatologie, méthodologie, étude de simulation

Summary:

To assess a topical treatment in dermatology, we may use a within-person (also called split-body) design. Randomization units are no longer patients but rather lesions or body sites. Experimental and control treatments are then applied simultaneously on the different lesions. This study design reduces the inter-observation variability, and therefore the number of patients to be included in the trial. However, this study design presents methodological constraints, notably a risk of intergroup contamination, named the "carry across effect". The objective of this PhD thesis was to study the methodological and statistical aspects of within-person randomized clinical trials. The first part of this work presents a synthesis of the methodological aspects to be considered when using this design. This work was conducted by a group associating dermatologists and biostatisticians. In the second part, we performed a methodological review of within-person randomized trials published between 2017 and 2021. The methodological aspects identified in the first work were assessed and discussed in this review. The third work focused on the statistical analysis. Using a Monte-Carlo simulation study, we compared the statistical properties of several analysis methods (mixed models and generalized estimating equations). Finally, as an illustration, the last part presents a within-person randomized trial protocol for evaluating topical sirolimus in superficial lymphatic malformations. The within-person design has multiple methodological and statistical specificities that must be taken into account when planning and analyzing the study. Dermatologists and methodologists must also consider patient acceptability.

Keywords: within-person, topical treatment, randomized clinical trial, dermatology, methodology, simulation study