PRÓ-REITORIA DE PESQUISA E PÓS-GRADUAÇÃO
MESTRADO EM CIÊNCIA ANIMAL

LUANA BEZERRA DE MEDEIROS VASCONCELOS

# COMPORTAMENTO DAS VARIÁVEIS DA DIMENSÃO FRACTAL EM TECIDO CUTÂNEO CICATRICIAL SUBMETIDOS A DIFERENTES MÉTODOS DE INDUÇÃO DE FERIDA E TRATAMENTOS: REVISÃO SISTEMÁTICA DE ESCOPO

Presidente Prudente - SP
2025

PRÓ-REITORIA DE PESQUISA E PÓS-GRADUAÇÃO
MESTRADO EM CIÊNCIA ANIMAL

LUANA BEZERRA DE MEDEIROS VASCONCELOS

# COMPORTAMENTO DAS VARIÁVEIS DA DIMENSÃO FRACTAL EM TECIDO CUTÂNEO CICATRICIAL SUBMETIDOS A DIFERENTES MÉTODOS DE INDUÇÃO DE FERIDA E TRATAMENTOS: REVISÃO SISTEMÁTICA DE ESCOPO

Dissertação apresentada à Pró-Reitoria de Pesquisa e Pós-Graduação, Universidade do Oeste Paulista, como parte dos requisitos para obtenção do título de Mestra – Área de concentração: Fisiopatologia Animal.

Orientadora: Drª. Cecília Laposy Santarém

Presidente Prudente - SP
2025

636.089
V331

Vasconcelos, Luana Bezerra de Medeiros.
Comportamento das variáveis da dimensão fractal em tecido cutâneo cicatricial submetidos a diferentes métodos de indução de ferida e tratamentos: revisão sistemática de escopo / Luana Bezerra de Medeiros Vasconcelos. – Presidente Prudente, 2025.
66f.: il.

Dissertação (Mestrado em Ciência Animal) - Universidade do Oeste Paulista – Unoeste, Presidente Prudente, SP, 2025.
Bibliografia.
Orientador: Cecília Laposy Santarém.

1. Cicatrização. 2. Colágeno. 3. Análise fractal. I. Título.

Catalogação na fonte: Michele Mologni – CRB 8/6204

Unoeste
PRÓ-REITORIA DE PESQUISA E PÓS-GRADUAÇÃO
18 3229-3286
prppg@unoeste.br
Campus II Rodovia Raposo Tavares, KM 572 • Bairro Limoeiro • CEP 19067-175 • Presidente Prudente-SP • www.unoeste.br

# CERTIFICADO DE APROVAÇÃO

**TÍTULO: "COMPORTAMENTO DAS VARIÁVEIS DA DIMENSÃO FRACTAL EM TECIDO CUTÂNEO CICATRICIAL SUBMETIDOS A DIFERENTES MÉTODOS DE INDUÇÃO DE FERIDA E TRATAMENTOS: REVISÃO SISTEMÁTICA DE ESCOPO"**

**AUTOR(A): LUANA BEZERRA DE MEDEIROS VASCONCELOS**
**ORIENTADOR(A): Profa. Dra. CECÍLIA LAPOSY SANTARÉM**

Aprovado(a) como parte das exigências para obtenção do título de MESTRE(A) em CIÊNCIA ANIMAL
Área de Concentração FISIOPATOLOGIA ANIMAL, pela Comissão Examinadora:

**CECÍLIA LAPOSY SANTARÉM (orientadora)**
UNOESTE - Universidade do Oeste Paulista / Presidente Prudente (SP)

**BRUNA CORRAL GARCIA DE ARAÚJO**
UNOESTE - Universidade do Oeste Paulista / Presidente Prudente (SP)

**ANA KARINA MARQUES SALGE MENDONÇA**
UFG – Universidade Federal de Goiás / Goiânia (GO)

Data da realização: Presidente Prudente, 27 de maio de 2025.

**Campus I** Rua José Bongiovani, 700 - Cidade Universitária - CEP 19050-920 - Presidente Prudente-SP - Tel: 18 3229-1000 | **Campus II** Rodovia Raposo Tavares, KM 572 - Bairro Limoeiro - CEP 19067-175 - Presidente Prudente-SP - Tel: 18 3229-2000
**Campus Jaú** Av. Antonio de Almeida Pacheco, 2945 - 2ª Zona Industrial - CEP 17213-700 - Jaú-SP - Tel: 14 3624-1109 | **Campus Guarujá** Rua Albertino Pedro, 75 - Cond. Guarujá Park - Enseada - CEP 11441-225 - Guarujá-SP - Tel: 13 3386-9002

# Central de Assinaturas Eletrônicas

## Sobre o documento

Assunto: Documento eletrônico
Status do documento: Concluído
Data de criação do documento: 28/05/2025 09:06
Fuso horário: (UTC-03:00) Brasília
Número de assinaturas: 3
Solicitante: KEID RIBEIRO KRUGER (#6137299)

## Signatários do documento

CECILIA LAPOSY SANTAREM (PROFESSOR)
claposy@unoeste.br
Recebido em 28/05/2025 09:06
Assinado em 28/05/2025 09:11
Assinatura Interna UNOESTE
Usando endereço IP: 177.131.39.1
ID da assinatura: 4892799

BRUNA CORRAL GARCIA DE ARAUJO (COORDENADOR DE CURSO)
bruna@unoeste.br
Recebido em 28/05/2025 09:06
Assinado em 28/05/2025 09:08
Assinatura Interna UNOESTE
Usando endereço IP: 2804:2af0:29c:af00:2c50:785e:9487:5fed
ID da assinatura: 4892800

ANA KARINA MARQUES SALGE MENDONÇA (SIGNATÁRIO EXTERNO)
anasalge@gmail.com
Recebido em 28/05/2025 09:06
Assinado em 28/05/2025 09:09
Assinatura Interna UNOESTE
Usando endereço IP: 200.137.223.253
ID da assinatura: 4892801

URL do documento: https://www.unoeste.br/ca/d074b188
Assinatura digital do documento: 1c73287c9dbb2e03c938773baeaabdeb994a50d62b5b9f492e19a023add40302
UNOESTE - Universidade do Oeste Paulista
Mantida pela Associação Prudentina de Educação e Cultura - APEC

Utilize o QRCode abaixo para conferir a autenticidade deste documento:

## AGRADECIMENTOS

Agradeço ao meu esposo Tiego e ao meu filho, Alexandre, por toda a compreensão, amor e paciência; mesmo diante de tantas dificuldades nesta trajetória acadêmica, sempre me incentivaram a continuar. Esta conquista também pertence a eles.

Minha gratidão à minha querida mãe, Edileusa, minha melhor amiga, que sempre esteve me apoiando e me auxiliando. Sem ela, não chegaria até aqui.

À minha orientadora, Dr$^{a}$ Cecília Laposy Santarém, meus sinceros agradecimentos por toda a compreensão e confiança depositada a mim, me proporcionando condições para crescer cientificamente e pessoalmente.

Agradeço à Dr$^{a}$ Ana Clara Campagnolo Gonçalves Toledo, minha co-orientadora, por estar sempre presente, me direcionando e ajudando, com muito carinho e paciência, sempre acreditando no meu potencial, me ajudando a me tornar uma profissional melhor.

Agraço às minhas amigas Dr$^{a}$ Bruna Corral Garcia de Araújo e a Médica Veterinária Gabriela da Silva Pinho, pela colaboração no desenvolvimento desse trabalho, o que fez com que esse processo fosse mais tranquilo.

Meus agradecimentos às alunas do curso de Estética e Cosmética da UNOESTE, Maria Luisa Soares e Maria Rita Alves Costa, por contribuírem na construção dessa pesquisa.

E, por fim, agradeço à UNOESTE, especialmente ao Programa de Pós-graduação em Ciência Animal, por toda a estrutura fornecida durante a realização deste trabalho e aos excelentes professores que somaram com minha trajetória acadêmica.

*“Na vida, não existe nada a temer, mas a entender”. (Marie Curie)*

## RESUMO

### Comportamento das variáveis da dimensão fractal em tecido cutâneo cicatricial submetidos a diferentes métodos de indução de ferida e tratamentos: revisão sistemática de escopo

A dimensão fractal tem se mostrado uma ferramenta capaz de interpretar áreas de diagnóstico de tecido biológico a fim de compreender respostas terapêuticas e de seus mecanismos, no processo de indução e cicatrização de feridas. Contudo, compreender o comportamento das variáveis de dimensão fractal mostra-se ainda inconclusivas sobre o tratamento de lesões cutâneas, pois os diferentes tipos de intervenção parecem influenciar diferentes padrões dos aspectos inflamatórios e permeabilidade celular. O presente estudo teve o objetivo de realizar, de maneira sistemática, a busca em bases de dados e seleção dos estudos pré-clínicos quanto à análise fractal no processo de cicatrização de feridas cutâneas. A estratégia de busca incluiu as bases de dados Medline via OVID, EMBASE, Web of Science e CINAHL, considerando os seguintes termos: cicatrização, feridas, colágeno, ratos, coelhos, queimadura, morfometria, histologia e imuno-histoquímica. O processo de seleção de estudo consistiu na seleção do título e, em sequência, no resumo e, por fim, a leitura do texto completo. Para controle e padronização dos processos de seleção dos estudos, foram utilizados a plataforma Rayyan e um formulário de Excel, para que o processo seguisse de maneira cega e padronizados entre os autores, para a posterior dupla checagem. Foram extraídos das bases de dados 407 artigos. Destes, 69 eram duplicados e, portanto, foram excluídos. Após a leitura de títulos e resumos, foram incluídos 8 estudos para a leitura completa. Dois estudos pré-clínicos foram incluídos nesta revisão por comtemplarem todos os critérios de inclusão como a análise fractal realizada em tecidos de ratos e camundongos, por meio de indução de feridas por queimadura ou corte por dermatoscópico ou a emissão de raios-x. Entre os 2 estudos encontrados, o comportamento da análise fractal mostrou-se variável e dependente do processo de indução de feridas, sendo o procedimento de queimaduras aquele que apresentou resultados mais diferenciados, devido à perda de fractalidade do tecido relacionada à desnaturação térmica.



**Palavras-chave:** análise fractal; cicatrização; colágeno; ferimento; queimadura; pele.

## ABSTRACT

### Behavior of fractal dimension variables in scar tissue subjected to different wound induction methods and treatments: a scoping review

Fractal dimension has proven to be a tool capable of interpreting diagnostic areas of biological tissue in order to understand therapeutic responses and their mechanisms in the process of wound induction and healing. However, understanding the behavior of fractal dimension variables is still inconclusive regarding the treatment of skin lesions, since different types of intervention seem to influence different patterns of inflammatory aspects and cell permeability. The present study aimed to systematically search databases and select preclinical studies regarding fractal analysis in the healing process of skin wounds. The search strategy included the Medline databases via OVID, EMBASE, Web of Science and CINAHL, considering the following terms: healing, wounds, collagen, rats, rabbits, burn, morphometry, histology and immunohistochemistry. The study selection process consisted of selecting the title, then the abstract and, finally, reading the full text. To control and standardize the study selection processes, the Rayyan platform and an Excel form were used so that the process would be blinded and standardized among the authors for subsequent double checking. A total of 407 articles were extracted from the databases. Of these, 69 were duplicates and were therefore excluded. After reading the titles and abstracts, 8 studies were included for full reading. Seven preclinical studies were included in this review because they met all the inclusion criteria, such as fractal analysis performed on tissues of rats, mice or rabbits, through induction of burn or dermoscopic cut wounds or emission of X-rays. Among the 7 studies found, the behavior of the fractal analysis was shown to be variable and dependent on the wound induction process, with the burn procedure being the one that presented the most differentiated results, due to the loss of tissue fractality related to thermal denaturation.



**Keywords:** fractal analysis; healing; collagen; wound; burn; skin.

## LISTA DE SIGLAS

DF – Dimensão Fractal
L – Lacunaridade
FMOD – Camundongos Fibromodulin
WT – Camundongos Wild Type
SD – Ratos Sprague Dawley

**SUMÁRIO**

## 1 ARTIGO CIENTÍFICO[1]

# Comportamento das variáveis da dimensão fractal em tecido cutâneo cicatricial submetidos a diferentes métodos de indução de ferida e tratamentos: revisão sistemática de escopo

Luana Bezerra de Medeiros Vasconcelos[1], Cecília Laposy Santarém[1], Ana Clara Campagnolo Gonçalves Toledo[2]

1. Programa de Pós-Graduação em Ciência Animal, Universidade do Oeste Paulista, Presidente Prudente, São Paulo, Brasil. 2. Mestrado em Ciências da Saúde, Universidade do Oeste Paulista, Presidente Prudente, São Paulo, Brasil.

**Autor para correspondência**:
Cecília Laposy Santarém
Pós-Graduação em Ciência Animal, Universidade do Oeste Paulista, Rodovia Raposo Tavares, Km 572, Presidente Prudente, São Paulo, Brasil.
Telefone: +55 (18) 99623-0772;
Fax: +55 (18) 3229-2080;
E-mail: claposy@unoeste.br

Luana Bezerra de Medeiros Vasconcelos: orcid:0009-0004-5912-5649
Cecília Laposy Santarém: orcid:0000-0002-4775-6142
Ana Clara Campagnolo Gongalves Toledo: orcid: 0000-0001-7660-0449

[1] Artigo segue as normas da revista Archives of Dermatological Research. Fator de Impacto: 2,18. CiteScore3,3. Scopus 64%

**Resumo**

A dimensão fractal tem se mostrado uma ferramenta capaz de interpretar áreas de diagnóstico de tecido biológico a fim de compreender respostas terapêuticas e de seus mecanismos, no processo de indução e cicatrização de feridas. Contudo, compreender o comportamento das variáveis de dimensão fractal mostra-se ainda inconclusivas sobre o tratamento de lesões cutâneas, pois os diferentes tipos de intervenção parecem influenciar diferentes padrões dos aspectos inflamatórios e permeabilidade celular. O presente estudo teve o objetivo de realizar, de maneira sistemática, a busca em bases de dados e seleção dos estudos pré-clínicos quanto à análise fractal no processo de cicatrização de feridas cutâneas. A estratégia de busca incluiu as bases de dados Medline via OVID, EMBASE, Web of Science e CINAHL, considerando os seguintes termos: cicatrização, feridas, colágeno, ratos, coelhos, queimadura, morfometria, histologia e imuno-histoquímica. O processo de seleção de estudo consistiu na seleção do título e, em sequência, no resumo e, por fim, a leitura do texto completo. Para controle e padronização dos processos de seleção dos estudos, foram utilizados a plataforma Rayyan e um formulário de Excel, para que o processo seguisse de maneira cega e padronizados entre os autores, para a posterior dupla checagem. Foram extraídos das bases de dados 407 artigos. Destes, 69 eram duplicados e, portanto, foram excluídos. Após a leitura de títulos e resumos, foram incluídos 7 estudos para a leitura completa. Dois estudos pré-clínicos foram incluídos nesta revisão por comtemplarem todos os critérios de inclusão como a análise fractal realizada em tecidos de ratos e camundongos, por meio de indução de feridas por queimadura ou corte por dermatoscópico ou a emissão de raios-x. Entre os 2 estudos encontrados, o comportamento da análise fractal mostrou-se variável e dependente do processo de indução de feridas, sendo o procedimento de queimaduras aquele quem apresentou resultados mais diferenciados, devido à perda de fractalidade do tecido relacionada à desnaturação térmica.

**Palavras-chave:** análise fractal; cicatrização; colágeno; ferimento; queimadura; pele.

## Introdução

A cicatrização de feridas é um processo biológico complexo em que vários tipos de células e moléculas atuam a fim de restaurar a estrutura e função originais da pele [1]. O tempo médio de cicatrização de feridas agudas dura, aproximadamente, entre 8 a 12 semanas, com exceção das feridas crônicas, que necessitam de mais tempo para concluir o processo [2]. Classicamente, o reparo de feridas é dividido em quatro fases: hemostasia, inflamação, proliferação e remodelação dérmica [3].

Na fase de hemostasia, há vasoconstrição e ativação plaquetária, após o contato com a matriz extracelular e fibras de colágeno afetadas. O coágulo de fibrina, uma matriz temporária capaz de suportar a migração celular, é formado [4]. Além disso, as plaquetas ativadas secretam diversos fatores de crescimento, como fatores de

crescimento transformadores (TGF-α, TGF-β), fator de crescimento derivado de plaquetas e fator de crescimento semelhante à insulina que irão auxiliar na migração das células inflamatórias para o local da ferida.

Durante a inflamação, neutrófilos e monócitos são atraídos da circulação para o local da lesão. Na fase de proliferação celular, ocorrem reepitelização, angiogênese e formação do tecido de granulação. Nesse estágio, os fibroblastos produzem colágeno tipo I e se diferenciam em miofibroblastos, promovendo a contração da ferida [5]. A última etapa, a remodelação, é considerada clinicamente a mais relevante, pois é quando a matriz extracelular se transforma em cicatriz [6]. Inicialmente, o colágeno depositado é fino e menos organizado do que o presente na pele saudável. Com o tempo, o colágeno tipo III é gradualmente substituído pelo tipo I, mais denso e alinhado conforme as linhas de tensão, aumentando a resistência tênsil da ferida. A cicatrização é eficaz quando há equilíbrio entre a síntese da nova matriz e a degradação da antiga, sendo considerada bem-sucedida com a predominância de deposição. Ainda assim, mesmo após um ano, a organização do colágeno na área cicatrizada permanece inferior à da pele normal, e a força tênsil nunca atinge o nível original [3, 5]. O colágeno, principal componente da matriz extracelular, é essencial no processo de cicatrização, sendo a proteína mais abundante no tecido conjuntivo. O colágeno tipo I, produzido pelos fibroblastos, predomina em ossos e tendões, enquanto o tipo III é encontrado principalmente em tecidos moles, como vasos sanguíneos, derme e fáscia. A matriz extracelular se organiza como uma rede densa e dinâmica, mantida pela constante deposição e reabsorção do colágeno, resultante do equilíbrio entre síntese e degradação [5].

As lesões cutâneas podem ser classificadas como agudas ou crônicas [7]. Feridas agudas seguem um processo de cicatrização mais rápido e organizado, restaurando de forma permanente a integridade anatômica e funcional da pele. Já as feridas crônicas apresentam cicatrização prolongada, frequentemente associada à insuficiência vascular e infecção, o que pode dificultar a recuperação e prolongar o tratamento, gerando desconforto para o paciente [8, 9].

O monitoramento da cicatrização de feridas é essencial para direcionar a escolha mais adequada para promover a completa cicatrização [10]**.** Diversas tecnologias são utilizadas na avaliação dos parâmetros estruturais e físicos de uma ferida ou cicatriz, considerando as características anatômicas, mecânicas e fisiológicas da cicatrização [11, 12]. Segundo Ud-din e Bayat (2016), os principais parâmetros

avaliados são os anatômicos (espessura da pele, pigmentação, dimensões da ferida, textura e morfologia do tecido), mecânicos (elasticidade e flexibilidade da pele) e fisiológicos (fluxo sanguíneo, função de barreira da pele e glândulas sebáceas) [12]. Além disso, os biomarcadores são grandes aliados para o acompanhamento nos diferentes estágios de cicatrização pois permitem um melhor manejo da ferida. Os biomarcadores mais comumente mensurados são pH, temperatura, oxigenação tecidual e até mesmo a presença de certos microrganismos [13]. No campo da análise quantitativa e tridimensional na avaliação da pele, a análise da dimensão fractal tem sido utilizada pois é uma ferramenta capaz monitorar em tempo real a estrutura de colágeno, permitindo prever a progressão de uma ferida [14].

A análise da dimensão fractal (ou análise fractal) é um conceito geométrico desenvolvido em 1973 pelo matemático Benoit Mandelbrot [15]. Ela permite uma medida da porcentagem de um espaço preenchido por um objeto, no qual o valor aumenta de acordo com o aumento a densidade estrutural [16]. Fractais são uma descrição quantitativa de um objeto, que se caracterizam por irregularidades e autossimilaridades sob mudanças de escala. A forma de um objeto denominado auto semelhante não altera quando a escala de medição é alterada, pois qualquer parte dele pode ser semelhante ao objeto original. Já o tamanho e os parâmetro geométricos de um objeto irregular mudam quando inspecionados em maiores resoluções, mostrando mais detalhes e imperfeições dentro dele [14].

O conceito de dimensão fractal é capaz de descrever a complexidade morfológica das células e tecidos, sendo amplamente utilizado em diversos tecidos biológicos irregulares e complexos, como neurônios e leitos capilares [17–19]. Na medicina, a análise fractal é utilizada durante análises de tomografia por emissão de pósitrons, **imagens radiográficas, tomografia computadorizada e imagens de ressonância magnética** [20–23]**.**

Estudos mostram que o comportamento fractal desempenha um papel importante na cicatrização de diversos tipos de tecidos, incluindo o muscular, cardíaco e tecido liso, cada um exibindo padrões específicos passíveis de análise pela dimensão fractal. No tecido muscular esquelético, a análise fractal revela a organização e alinhamento das fibras durante a regeneração, sendo sensível a intervenções que promovem a recuperação da funcionalidade e resistência. No tecido cardíaco, a dimensão fractal ajuda a identificar alterações na disposição das fibras colágenas e redes capilares, essenciais para restaurar a função contrátil após lesões, como

infartos. Em tecidos lisos, como vasos e órgãos digestivos, a análise fractal auxilia na avaliação da recuperação estrutural das camadas musculares e da integridade do tecido conjuntivo, essenciais para a manutenção da elasticidade e contratilidade. Em todos esses casos, a análise fractal fornece uma ferramenta quantitativa e precisa para rastrear a cicatrização e ajustar intervenções conforme a resposta dos tecidos [24–27].

No caso do tecido tegumentar, a análise fractal da cicatrização mostra que a densidade do colágeno flutua em torno dos níveis normais durante a cicatrização. Contudo, em queimaduras simuladas, não se observa dimensão fractal, possivelmente devido à desnaturação térmica, que altera a estrutura do colágeno e perde a autossimilaridade [12].

Assim, o comportamento do colágeno em quantidade e forma varia conforme a fase de reestruturação da lesão e o tipo de tecido, impactando diretamente o processo de cicatrização. Embora tecidos como o muscular, cardíaco e liso apresentem características específicas na remodelação do colágeno, o tecido tegumentar possui particularidades que requerem acompanhamento especializado. Compreender essas fases e particularidades no tecido tegumentar é fundamental para identificar padrões e necessidades específicas durante a cicatrização, facilitando intervenções direcionadas e eficazes. Dessa forma, o objetivo desta revisão sistemática de escopo é apresentar o estado da arte da análise fractal no processo de cicatrização do tecido tegumentar, consolidando evidências que aprimorem a eficácia das intervenções e favoreçam uma recuperação tecidual otimizada.

## Metodologia

Esta revisão sistemática com meta análise apresentou registro na plataforma de base de dados internacional OSF Institutions [28] (https://doi.org/10.17605/OSF.IO/F62B9), o qual foi realizado de maneira prospectiva, de acordo com as diretrizes seguintes diretrizes: PRISMA (Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation) [29].

## Estratégias de busca

Os estudos foram selecionados por meio de cinco bancos de dados EMBASE, CINAHL, MEDLINE via ovid e WEB OF SCIENCE a partir dos registros mais antigos de cada banco de dados até as publicações mais atuais [30, 31]. Os descritores

foram Medical Subject Headings e outras palavras-chave específicas relacionadas aos seguintes tópicos: cicatrização, feridas, colágeno, ratos, coelhos, queimadura, dimensão fractal, morfometria e imuno-histoquímica. Essas palavras e seus sinônimos foram relacionados também a Ensaio clínico ou pré-clínico in vivo (Anexo 1).

**Critérios de elegibilidade**

Para serem elegíveis, os estudos contiveram os seguintes critérios: 1) Artigos disponíveis em formato completo; 2) Ensaios pré-clínicos e clínicos randomizados que avaliaram a dimensão fractal do tecido tegumentar após a cicatrização de lesões e não foram restringidos os tipos de tratamento que a ferida fora submetida; 3) Inclusão de grupo controle; 4) Estudos realizados com ratos e/ou coelhos saudáveis que foram submetidos a um processo de lesão tecidual; 5) As lesões cutâneas poderiam ser promovidas por corte de bisturi, ou dermatoscópio e/ou queimadura induzida pelo calor, 6) Tempo de intervenção nos períodos antes da lesão, 7, 14 e 21 após indução de lesão; 7) Análise das morfométricas e variáveis da Dimensão Fractal; 8) Análise das variáveis imuno-histoquímicas.

Não houve restrição quanto ao idioma dos estudos e ao período de publicação características dos participantes.

**Tipos de estudo**

Ensaios pré-clínicos randomizados que avaliaram a dimensão fractal do tecido tegumentar após a cicatrização de lesões. Não foram restringidos o tipo de tratamento realizados na ferida.

**Período de intervenção**

Tempo de intervenção nos períodos antes da lesão: 7, 14 e 21 após indução de lesão.

**Desfechos primários e secundários**

Para o desfecho primário, compreenderam-se os tipos das análises, as variáveis estudadas e as interpretações sobre cicatrização do tecido cutâneo em relação a dimensão fractal, tais como, densidade do colágeno e descrição quantitativa da sua expressão.

Já para o desfecho secundário, foram compreendidas análises complementares, como histoquímicas, análises macroscópicas do fechamento das feridas, ou outras análises morfométricas complementares.

**Perfil da amostra**

Para esta revisão foram selecionados estudos que envolveram ratos e coelhos, sem restrição de sexo, peso e idade. Todos esses animais foram submetidos a indução de ferida cutânea, por agente térmico ou corte.

**Seleção de estudos**

No início do processo de triagem foram verificados os títulos dos estudos selecionados para a verificação de duplicatas, sendo suas cópias excluídas. Para a continuidade do processo de seleção, o resumo e o texto completo foram verificados de acordo com os critérios de inclusão supracitados. As listas de referência dos textos completos selecionados foram revisadas manualmente para obter estudos potencialmente elegíveis não recuperados eletronicamente.

O processo de seleção dos estudos foi realizado por revisores independentes (LBMV, MLS, MRAC) que examinaram os resultados da busca para obter elegibilidade. As diferenças foram resolvidas por um terceiro revisor independente (CLS) [30, 31]. Esse processo de seleção está representado no fluxograma, figura 1.

**Extração dos dados**

Os dados das variáveis imuno-histoquímicas e anticorpos foram extraídos de acordo com suas características dicotômicas ou contínuas. Caso fosse a primeira, foram extraídos valores iniciais e finais do risco relativo e o número de eventos de cada grupo avaliado. Caso contrário, se os dados fossem contínuos, foram anotados, incluindo valores iniciais e finais de médias, desvios padrão e tamanho da amostra, por revisores independentes (LBMV, MLS, MRAC). Os desacordos entre autores quanto às extrações de dados foram resolvidos por um terceiro revisor independente (CLS) [30, 31].

O processo de extração de dados foi realizado por meio de um formulário padronizado, o qual incluiu detalhes como características dos animais; do processo de intervenção: maneira como foi induzida a ferida, modos, doses, frequências de aplicação do tratamento proposto, e tempo de intervenção; quais variáveis da

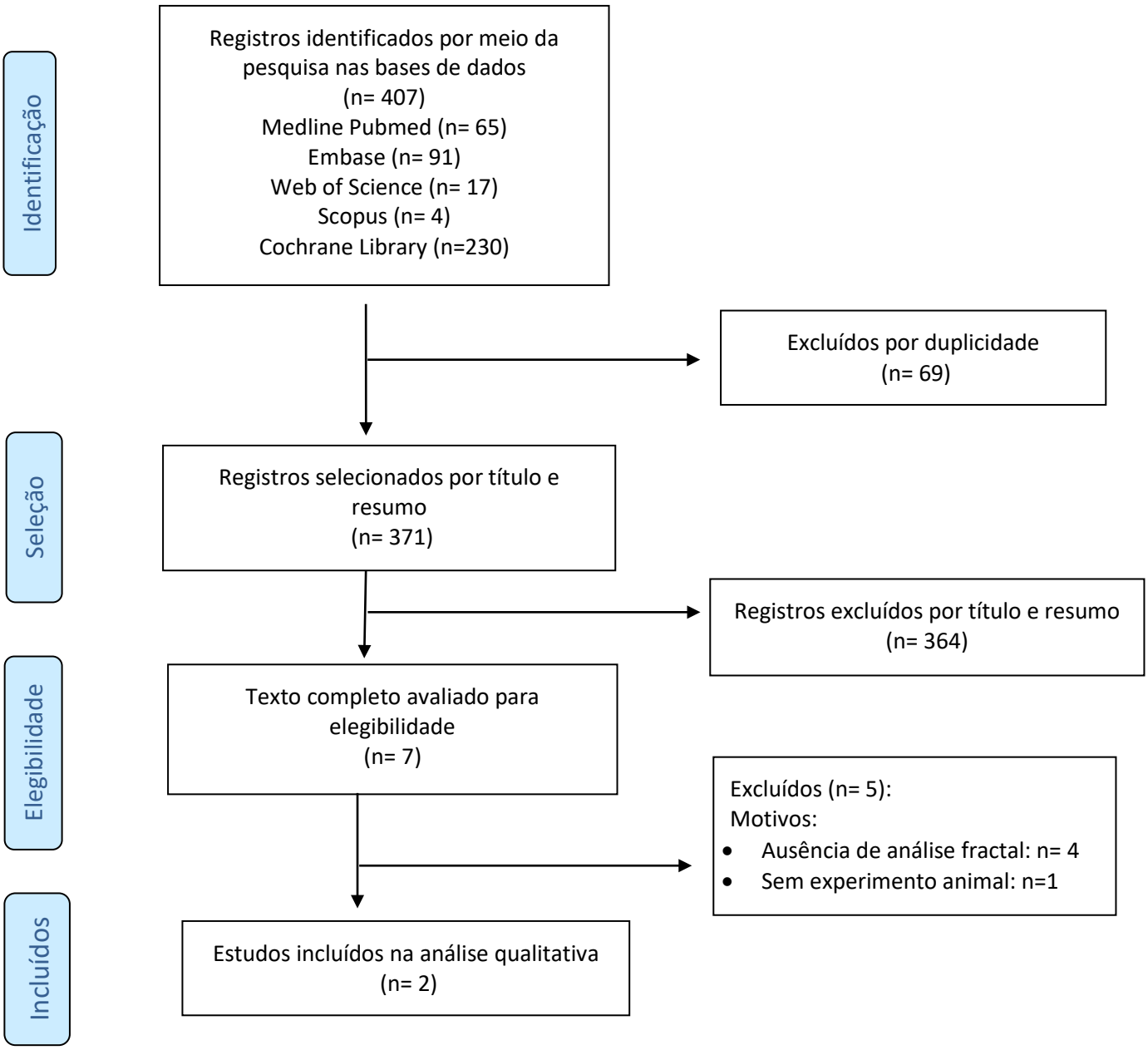
dimensão fractal foram consideradas pelos estudos incluídos incluindo coloração e análises histológicas [30–32]. As características dos estudos incluídos estão apresentadas na tabela 1.

**Resultados**

As buscas nas bases de dados supracitadas identificaram 407 estudos, sendo que 69 foram excluídos como duplicados. Destes, 363 estudos foram retirados por título e por resumo, e somente 7 estudos foram escolhidos para a leitura do texto completo. Em seguida, 5 foram excluídos pelos seguintes motivos: Ausência de análise fractal, ausência de abordagem da análise fractal em tecido cutâneo e/ou ausência de métodos de indução de ferida e tratamentos. Desta forma, foram incluídos 2 estudos nesta revisão, publicados entre os anos de 2011 e 2022. Na figura 1 está a representação do processo de seleção desses estudos.

Os estudos incluídos nesta revisão apresentam alta heterogeneidade metodológica, pois envolvem diferentes critérios e recursos para análise da dimensão fractal, animais como amostra, tipos de indução de feridas e períodos de cicatrização para essas análises. O resumo das características dos estudos incluídos está representado na tabela 1.

**Figura 1** – Fluxograma de Seleção dos Estudos



| Autor | Animais | Grupos de intervenção | Método da Análise Fractal | Outras Análises Realizadas |
|---|---|---|---|---|
| Xu *et al*., 2022 | Ratos SD (250 ± 25 g) | **Grupo1:** Diferentes espessuras de enxerto de pele 0.1, 0.2, 0.3, 0.4, 0.6 mm (n= 10)<br><br>**Grupo 2:** queimadura em 3 profundidades: superficiais (3 seg / contato) (n = 10); parcial (5 seg / contato) (n = 10); total (8 seg / contato) (n = 10)<br><br>**Grupo 3:** Ferida produzida por bisturi, cicatrizada em 2 semanas (n=10) e 4 semanas (n=10).<br><br>**Grupo 4:** ratos diabéticos (estreptozotocina) (n=20), cicatrização 2 semanas (n=10) em 4 semanas (n=10) | Análise da dimensão fractal com espalhamento de raios X de pequeno ângulo | Não avaliado (N/A) |
| Khorasani *et al.*, 2011 | Camundongos machos e fêmeas WT e FMOD (±30 g)<br><br>Camundongos FMOD (±30 g) | 4 excisões de pele de 10 mm x 3 mm de espessura total<br><br>Sutura – primeira intensão<br><br>Feridas foram colhidas 2, 7 e 14 dias após a lesão. | Microscopia eletrônica<br>Dimensão fractal (DF)<br>Lacunaridade (L) | Microscopia óptica<br><br>Microscopia confocal de varredura a laser<br><br>Microscopia eletrônica de transmissão |

Tabela 1 – Características dos Estudos Incluídos

A análise fractal do tecido tegumentar proposta por Xu et al, 2022 aponta que a análise da estrutura fractal do colágeno pode ser realizada utilizando a análise de dimensão fractal com espalhamento de raios X de pequeno ângulo (SAXS, *Small-Angle X-ray Scattering*) [14]. No grupo que analisou os diferentes tipos de tempo de cicatrização, foi possível compreender que a densidade de colágeno variou durante o processo de cicatrização, inicialmente mais esparsa logo após a lesão e tornando-se mais densa com o tempo. Para o grupo dos ratos diabéticos notou-se que os ratos diabéticos apresentaram uma geometria de colágeno mais esparsa, ($D<3$) indicando uma alteração significativa na estrutura do colágeno. O tempo de cicatrização também foi maior em animais diabéticos, sugerindo que a qualidade da cicatrização da pele é inferior aos controles.

Ainda nesse mesmo estudo, mais dois grupos foram estudados, as diferentes espessuras de enxerto de pele como também as diferentes profundidades de pele

queimada. Em relação a dimensão fractal, revelou que a geometria fractal dos enxertos era diferente da pele normal. A pele normal apresentava uma estrutura de colágeno altamente compacta (α > 3), enquanto os valores de α dos enxertos de pele de diferentes espessuras foram menores que 3, sugerindo que a estrutura do tecido dérmico foi danificada durante o corte do enxerto. Os enxertos mais espessos preservam melhor a camada reticular da derme, enquanto os enxertos de espessura intermediária apresentaram uma surpreendente menor densidade de colágeno, possivelmente devido à dificuldade de cortar de forma precisa na interface entre as camadas papilar e reticular. Já em relação ao grupo queimado, a análise revelou a ausência de dimensões fractais, com a presença de picos nas linhas de dados, cuja localização variava conforme a espessura da queimadura, indicando uma alteração na estrutura do colágeno devido à desnaturação térmica.

Já o estudo de Khorasani et al (2011) teve como propósito compreender a morfologia do colágeno em cicatrizes utilizando microscopia confocal, análise de dimensão fractal (FD) e lacunaridade (L) [33]. Foram criadas feridas em camundongos, que foram coletadas 14 dias após a lesão para morfometria, análise de Fourier e análise fractal. Os resultados mostraram que a análise fractal e de lacunaridade é mais sensível do que a análise de Fourier para discriminar entre tecido cicatricial e tecido não ferido. Este método provou ser uma técnica fácil, sensível, reprodutível e objetiva, fornecendo quantificação adequada não apenas da cicatriz, mas também da morfologia do colágeno da derme não ferida. Os resultados revelaram que a análise de FD e L discrimina de maneira eficaz o tecido cicatricial e não ferido, mostrando que o colágeno em cicatrizes apresenta uma arquitetura mais densa e homogênea em comparação ao tecido não ferido. A análise de FD e L se mostrou superior à análise de transformada de Fourier, que não conseguiu detectar diferenças significativas nas mesmas amostras. Além disso, a avaliação da ultraestrutura do colágeno em fibrilas indicou que as fibrilas de cicatrizes de camundongos FMOD eram menores e apresentavam anormalidades, como fusão lateral, contribuindo para a variabilidade na morfologia. Esses achados ressaltam a utilidade da análise de FD e L para entender melhor a cicatrização de feridas e suas implicações clínicas.

**Discussão**

Nesta revisão de escopo, identificamos dois estudos que avaliaram a dimensão fractal no tecido tegumentar após intervenção em feridas em modelos animais [14, 33]. Até o momento, em nosso conhecimento, esta é a primeira revisão sistemática de escopo a investigar o comportamento do colágeno no processo de regeneração do tecido tegumentar utilizando a metodologia de análise fractal.

A análise fractal, conforme demonstrado por Khorasani et al. (2011), representa um avanço significativo na avaliação da morfologia do colágeno durante o processo de cicatrização de feridas [33]. Esse estudo estabeleceu uma metodologia robusta para a análise da arquitetura do colágeno em cicatrizes, mostrando que a análise fractal é mais sensível e reprodutível que métodos tradicionais, como a transformada de Fourier. A utilização de microscopia confocal aprimorou a visualização precisa da estrutura dérmica, eliminando o viés do observador, uma limitação anteriormente presente em técnicas como a microscopia de luz polarizada. Além disso, a partir dessa metodologia permitiu novas perspectivas para a aplicação dessa técnica em diversas condições patológicas.

De maneira complementar, Xu et al. (2021) ampliaram o escopo dessa análise ao investigar a cicatrização em ratos diabéticos e com queimaduras, destacando a importância da fractalidade na compreensão da morfologia do colágeno em condições patológicas [14]. No grupo de ratos com queimaduras. A ausência de fractalidade no grupo com queimaduras indicou disfunções no reparo tecidual, enquanto as alterações estruturais no colágeno dos ratos diabéticos contribuíram para entender o tempo prolongado de cicatrização. Esses achados são clinicamente relevantes, uma vez que podem guiar intervenções terapêuticas mais adequadas, considerando as diferenças nos mecanismos biológicos envolvidos nas cicatrizações comprometidas, como em casos de queimaduras graves ou [34].

A capacidade de discriminar entre tecidos saudáveis e lesionados, bem como entre diferentes condições patológicas, pode orientar a escolha de intervenções mais apropriadas, contribuindo para o aprimoramento dos resultados terapêuticos. A sua aplicação em tecidos cicatriciais, especialmente em casos de cicatrização comprometida, oferece uma nova abordagem para monitorar a evolução do processo de reparo tecidual.

É importante ressaltar que a fractalidade do tecido tegumentar se comporta de forma distinta em comparação com outros tecidos, como o tecido músculo-esquelético,

cardíaco, cerebral e pulmonar. Estudos demonstram que o comportamento fractal nesses diferentes tecidos não só é diferenciado, mas também varia conforme o tipo de agressão sofrida. No tecido músculo-esquelético, por exemplo, a regeneração de fibras musculares e a recuperação funcional após lesões tendem a seguir padrões de fractalidade mais organizados, refletindo a capacidade de regeneração do tecido [35]. Em contraste, no coração, especialmente em modelos de infarto do miocárdio, a fractalidade pode ser alterada, evidenciando a desorganização das fibras de colágeno no processo de fibrose, com impacto direto na função cardíaca [36]. O cérebro também apresenta comportamentos fractais distintos, com variações observadas em condições patológicas como acidente vascular cerebral (AVC), onde a reorganização da arquitetura tecidual tem um padrão fractal alterado, refletindo o processo de cicatrização neuronal [37]. O pulmão, em modelos de doenças respiratórias, como fibrose pulmonar, também exibe padrões fractais que refletem a fibrose tecidual e a dificuldade de regeneração estrutural [38].

Essas diferenças entre os tecidos são acompanhadas por variações na interpretação das variáveis fractais, como a dimensão fractal (D), que pode indicar diferentes processos biológicos e estruturais dependendo do contexto. Em tecidos como o tegumentar, que geralmente apresenta menor fractalidade, a perda de colágeno e a alteração nos padrões fractais estão frequentemente associadas a processos patológicos como queimaduras ou diabetes, que afetam o processo de cicatrização e resultam em defeitos estruturais [14, 33]. Já em tecidos como os musculares ou cardíacos, um aumento na fractalidade pode estar relacionado a uma regeneração desorganizada, como observado em cicatrizes patológicas, como queloides e cicatrizes hipertróficas, onde a proliferação excessiva de colágeno gera uma estrutura fractal mais densa e menos ordenada [14, 33].

## Conclusão

Dessa forma, os estudos incluídos nessa revisão apresentam que a análise fractal e a lacunaridade mostram-se mais sensíveis a análise da distribuição dos colágenos no tecido cicatricial bem como expandiram esse conhecimento ao demonstrar a importância da fractalidade em tecidos com cicatrização comprometida, como em ratos diabéticos e queimados. Contudo, futuros estudos são necessários para a exploração mais ampla das condições patológicas e apliquem a análise fractal

podem contribuir para uma melhor compreensão dos mecanismos biológicos envolvidos na cicatrização.

**Declarações:**

**Contribuição dos autores:** L.B.M.V. contribuiu no planejamento, coleta dos dados, pesquisa e redação final do artigo, ACCGT e CLS contribuíram na concepção do projeto, redação e revisão do artigo.

**Conflito de interesses:**

Os autores declaram que não têm afiliações ou envolvimento com qualquer organização ou entidade com qualquer interesse financeiro ou não financeiro discutidos neste manuscrito.

**Financiamento:**

Nenhum financiamento foi recebido para ajudar na preparação deste manuscrito.

**Referências**

1. Zhao H, Lou Z, Chen Y, et al (2023) Tea polyphenols (TPP) as a promising wound healing agent: TPP exerts multiple and distinct mechanisms at different phases of wound healing in a mouse model. Biomedicine & Pharmacotherapy 166:115437. https://doi.org/10.1016/j.biopha.2023.115437
2. Gupta A, Kowalczuk M, Heaselgrave W, et al (2019) The production and application of hydrogels for wound management: A review. Eur Polym J 111:134–151. https://doi.org/10.1016/j.eurpolymj.2018.12.019
3. Broughton G, Janis JE, Attinger CE (2006) Wound Healing: An Overview. Plast Reconstr Surg 117:1e-S-32e-S. https://doi.org/10.1097/01.prs.0000222562.60260.f9
4. Stan D, Tanase C, Avram M, et al (2021) Wound healing applications of creams and “smart” hydrogels. Exp Dermatol 30:1218–1232. https://doi.org/10.1111/exd.14396

5. Campos ACL, Borges-Branco A, Groth AK (2007) Cicatrização de feridas. ABCD Arquivos Brasileiros de Cirurgia Digestiva (São Paulo) 20:51–58. https://doi.org/10.1590/S0102-67202007000100010

6. Astaneh ME, Fereydouni N (2023) A focused review on hyaluronic acid contained nanofiber formulations for diabetic wound healing. Int J Biol Macromol 253:127607. https://doi.org/10.1016/j.ijbiomac.2023.127607

7. Tavakoli S, Kisiel MA, Biedermann T, Klar AS (2022) Immunomodulation of Skin Repair: Cell-Based Therapeutic Strategies for Skin Replacement (A Comprehensive Review). Biomedicines 10:118. https://doi.org/10.3390/biomedicines10010118

8. Abu Bakar N, Mydin RBSMN, Yusop N, et al (2023) Understanding the ideal wound healing mechanistic behavior using in silico modelling perspectives: A review. J Tissue Viability. https://doi.org/10.1016/j.jtv.2023.11.001

9. Smythe P, Wilkinson HN (2023) The Skin Microbiome: Current Landscape and Future Opportunities. Int J Mol Sci 24:3950. https://doi.org/10.3390/ijms24043950

10. Kenworthy P, Phillips M, Grisbrook TL, et al (2018) Monitoring wound healing in minor burns—A novel approach. Burns 44:70–76. https://doi.org/10.1016/j.burns.2017.06.007

11. Paul DW, Ghassemi P, Ramella-Roman JC, et al (2015) Noninvasive imaging technologies for cutaneous wound assessment: A review. Wound Repair and Regeneration 23:149–162. https://doi.org/10.1111/wrr.12262

12. Ud-Din S, Bayat A (2016) Non-invasive objective devices for monitoring the inflammatory, proliferative and remodelling phases of cutaneous wound healing and skin scarring. Exp Dermatol 25:579–585. https://doi.org/10.1111/exd.13027

13. Youssef K, Ullah A, Rezai P, et al (2023) Recent advances in biosensors for real time monitoring of pH, temperature, and oxygen in chronic wounds. Mater Today Bio 22:100764. https://doi.org/10.1016/j.mtbio.2023.100764

14. Xu H, Zhang J, Jiang Y, et al (2022) Fractal analysis of rat dermal tissue in the different injury states. Int Wound J 19:1016–1022. https://doi.org/10.1111/iwj.13698

15. Cross SS (1997) Fractals in pathology. J Pathol 182:1–8. https://doi.org/10.1002/(SICI)1096-9896(199705)182:1<1::AID-PATH808>3.0.CO;2-B

16. Tian F, Jiang Y, Liu Y, et al (2021) Can fractal dimension analysis be used in quantitating collagen structure? Exp Dermatol 30:1825–1828. https://doi.org/10.1111/exd.14417

17. Eblen-Zajjur A, Salas R, Vanegas H (1996) Fractal analysis of spinal dorsal horn neuron discharges by means of sequential fractal dimension D. Comput Biol Med 26:87–95. https://doi.org/10.1016/0010-4825(95)00043-7

18. Guidolin D, Vacca A, Nussdorfer GG, Ribatti D (2004) A new image analysis method based on topological and fractal parameters to evaluate the angiostatic activity of docetaxel by using the Matrigel assay in vitro. Microvasc Res 67:117–124. https://doi.org/10.1016/j.mvr.2003.11.002

19. Korolj A, Wu H-T, Radisic M (2019) A healthy dose of chaos: Using fractal frameworks for engineering higher-fidelity biomedical systems. Biomaterials 219:119363. https://doi.org/10.1016/j.biomaterials.2019.119363

20. Chaber R, Łasecki M, Kuczyński K, et al (2020) Hounsfield units and fractal dimension (test HUFRA) for determining PET positive/negative lymph nodes in pediatric Hodgkin's lymphoma patients. PLoS One 15:e0229859. https://doi.org/10.1371/journal.pone.0229859

21. Goutzanis LP, Papadogeorgakis N, Pavlopoulos PM, et al (2009) Vascular fractal dimension and total vascular area in the study of oral cancer. Head Neck 31:298–307. https://doi.org/10.1002/hed.20959

22. Irie MS, Rabelo GD, Spin-Neto R, et al (2018) Use of Micro-Computed Tomography for Bone Evaluation in Dentistry. Braz Dent J 29:227–238. https://doi.org/10.1590/0103-6440201801979

23. Southard TE, Southard KA, Jakobsen JR, et al (1996) Fractal dimension in radiographic analysis of alveolar process bone. Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontology 82:569–576. https://doi.org/10.1016/S1079-2104(96)80205-8

24. Arsos GA, Dimitriu PP (1995) A fractal characterization of the type II fiber distribution in the extensor digitorum longus and soleus muscles of the adult rat. Muscle Nerve 18:961–968. https://doi.org/10.1002/mus.880180907

25. Tian F, Jiang Y, Liu Y, et al (2021) Can fractal dimension analysis be used in quantitating collagen structure? Exp Dermatol 30:1825–1828. https://doi.org/10.1111/exd.14417

26. Mostaço-Guidolin LB, Smith MSD, Hewko M, et al (2019) Fractal dimension and directional analysis of elastic and collagen fiber arrangement in unsectioned arterial tissues affected by atherosclerosis and aging. J Appl Physiol 126:638–646. https://doi.org/10.1152/japplphysiol.00497.2018

27. Shang C, McGrath J, Daly C, Barker J (2000) Modelling and classification ofvascular smooth muscle cell images. Electron Lett 36:1532–1533. https://doi.org/10.1049/el:20001106

28. de Vries RBM, Hooijmans CR, Langendam MW, et al (2015) A protocol format for the preparation, registration and publication of systematic reviews of animal intervention studies. Evid Based Preclin Med 2:1–9. https://doi.org/10.1002/ebm2.7

29. Tricco AC, Lillie E, Zarin W, et al (2018) PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med 169:467–473. https://doi.org/10.7326/M18-0850

30. Leenaars M, Hooijmans CR, van Veggel N, et al (2012) A step-by-step guide to systematically identify all relevant animal studies. Lab Anim 46:24–31. https://doi.org/10.1258/la.2011.011087

31. PT Higgins J, Green S (2011) Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration

32. Kim KY, Lee E, Kim Y (2019) The Association between Bisphenol A Exposure and Obesity in Children—A Systematic Review with Meta-Analysis. Int J Environ Res Public Health 16:2521. https://doi.org/10.3390/ijerph16142521

33. Khorasani H, Zheng Z, Nguyen C, et al (2011) A Quantitative Approach to Scar Analysis. Am J Pathol 178:621–628. https://doi.org/10.1016/j.ajpath.2010.10.019

34. Meyer TR, Gallagher K (214AD) The role of collagen in the wound healing process. Wound Repair and Regeneration 22:245–252

35. Oliveira BM de, Moschini GA de L, Dias R de JD, et al (2020) Evaluation by fractal dimension of muscle regeneration after photobiomodulation. Fisioterapia em Movimento 33:. https://doi.org/10.1590/1980-5918.033.ao39

36. Michallek F, Dewey M (2017) Fractal analysis of the ischemic transition region in chronic ischemic heart disease using magnetic resonance imaging. Eur Radiol 27:1537–1546. https://doi.org/10.1007/s00330-016-4492-2

37. Rajagopalan V, Das A, Zhang L, et al (2019) Fractal dimension brain morphometry: a novel approach to quantify white matter in traumatic brain injury. Brain Imaging Behav 13:914–924. https://doi.org/10.1007/s11682-018-9892-2

38. Mancini M, Bargiacchi L, De Vitis C, et al (2023) Histologic Analysis of Idiopathic Pulmonary Fibrosis by Morphometric and Fractal Analysis. Biomedicines 11:1483. https://doi.org/10.3390/biomedicines11051483

## ANEXO A – NORMAS DA REVISTA ARCHIVES OF DERMATOLOGICAL RESEARCH

https://link.springer.com/journal/403/submission-guidelines#Instructions%20for%20Authors

# Submission guidelines

Contents

## Instructions for Authors

**Types of Manuscripts**

All manuscripts (except "Correspondence") must include an abstract and a structured text body (e. g. introduction, methods, results, discussion and references). For details regarding special requirements please see "notes" below.

- Research

  All scientific contributions describing novel findings in the entire field of dermatology and cutaneous research with a maximum length of 3,500 words. No limit on references and figures/tables. Abstract must be 350 words, unstructured.

- Review

  State-of-the art narrative or systematic review articles written by experts in the field either upon request or by unsolicited submission with a maximum length of 3,500 words. No limit on references and figures/tables. Abstract must be 350 words, unstructured.

- Study Protocol

  A platform for publishing innovative clinical trial data regardless of their outcome as publication of negative results is of similar importance as of positive ones with a maximum length of 3,000 words. No limit on references and figures/tables. Abstract must be 350 words, unstructured.

- Correspondence

  Research Letters to the Editor with a maximum length of 500 words, 5 references, and a total of 2 figures/tables.

- Brief Report

  Small, preliminary studies; survey studies with low response rate, with a maximum length of 1,200 words, 15 references and no more than total of 2 figures/tables. Abstract must be 350 words, unstructured.

- Guideline

  Clinical practice guidelines; applications of guidelines into practice, development of guidelines; issues surrounding guidelines, with a maximum length of 5,000 words. No limit on references and figures/tables. Abstract must be 350 words, unstructured.

- Consensus Article

  Proceedings of consensus meetings or conferences, work offering recommendations or setting policy, with a maximum length of 5,000 words. No limit on references and tables/figures. Abstract must be 350 words, unstructured.

- Protocol

  Study protocols of proposed or ongoing trials. No maximum length and no restrictions on references and tables/figures. Abstract must be 350 words, unstructured.

**Important Notes:**

- Manuscripts describing mutations

  Reports describing mutation(s) will not be considered for review in Archives of Dermatological Research unless at least one of the following conditions is met:

  1. No more than three mutation reports implicating the same gene in the same disease have already been published.

  2. The findings provide new insights into genotype-phenotype correlation.

  3. The findings provide new insights into population genetics, such as founder effect, genetic drift, or bottlenecks.

- Manuscripts describing effects of natural compounds

  Reports describing the effect(s) of plant extracts or natural compounds will not be considered for review in Archives of Dermatological Research unless the following conditions are met:

  1. Chemical definition of the investigated compound(s). The chemical structure(s) must be shown as a figure.

  2. The compound(s) investigated must be accessible for other researchers in order to repeat the described experiments. The source must be named and full address supplied.

3. No more than three publications describing similar effects of the investigated compound(s) in the same or similar in vitro or in vivo models.

## Manuscript Submission

### *Manuscript Submission*

Submission of a manuscript implies: that the work described has not been published before; that it is not under consideration for publication anywhere else; that its publication has been approved by all co-authors, if any, as well as by the responsible authorities – tacitly or explicitly – at the institute where the work has been carried out. The publisher will not be held legally responsible should there be any claims for compensation.

### *Permissions*

Authors wishing to include figures, tables, or text passages that have already been published elsewhere are required to obtain permission from the copyright owner(s) for both the print and online format and to include evidence that such permission has been granted when submitting their papers. Any material received without such evidence will be assumed to originate from the authors.

### *Online Submission*

Please follow the hyperlink "Submit manuscript" and upload all of your manuscript files following the instructions given on the screen.

### *Source Files*

Please ensure you provide all relevant editable source files at every submission and revision. Failing to submit a complete set of editable source files will result in your article not being considered for review. For your manuscript text please always submit in common word processing formats such as .docx or LaTeX.

### *Submitting Declarations*

Please note that Author Contribution information and Competing Interest information must be provided at submission via the submission interface. Only the information submitted via the interface will be used in the final published version. Please make sure that if you are an editorial board member and also a listed author that you also declare this information in the Competing Interest section of the interface.

Please see the relevant sections in the submission guidelines for further information on these statements as well as possible other mandatory statements.

***Important note:***

- **The approval document has to be submitted with the manuscript for all studies requiring review by the responsible local or national ethical committee.**

***Proposal of Expert Reviewer***

To shorten the time of the editorial process and to increase the quality of manuscripts published in AODR at least 5 reviewers must be proposed. Three of the proposed experts must be from outside of the country of the corresponding author. Members of the Board of Associate Editors cannot be proposed as reviewer.

It is advisable to suggest experts who are active in the respective field and have recently published articles related to topic of the submission. Suggestion of people who are well known in global dermatology but are no longer active as scientist and/or clinician is not advisable. Successful manuscript processing requires at least 2 qualified expert evaluations.

***General Remark***

Please provide text and figures of your manuscript as separate electronic files (one file for each figure). The text file should include references, figure legends and tables; it should not include figures. Tables and figure legends are placed within the text file at the end of the main text. Depending on the type of paper the text file should contain the following sections:

Manuscript sections (Download xlsx, 11 kB)

***Further Useful Information***

please follow the link below

Further useful information

The Springer Author Academy is a set of comprehensive online training pages mainly geared towards first-time authors. At this point, more than 50 pages offer advice to authors on how to write and publish a journal article.

Springer Author Academy

***Scientific style***

Generic names of drugs and pesticides are preferred; if trade names are used, the generic name should be given at first mention.

**Title Page**

Please make sure your title page contains the following information.

## Title

The title should be concise and informative.

## Author information

- The name(s) of the author(s)
- The affiliation(s) of the author(s), i.e. institution, (department), city, (state), country
- A clear indication and an active e-mail address of the corresponding author
- If available, the 16-digit ORCID of the author(s)

If address information is provided with the affiliation(s) it will also be published.

For authors that are (temporarily) unaffiliated we will only capture their city and country of residence, not their e-mail address unless specifically requested.

Large Language Models (LLMs), such as ChatGPT, do not currently satisfy our authorship criteria. Notably an attribution of authorship carries with it accountability for the work, which cannot be effectively applied to LLMs. Use of an LLM should be properly documented in the Methods section (and if a Methods section is not available, in a suitable alternative part) of the manuscript. The use of an LLM (or other AI-tool) for "AI assisted copy editing" purposes does not need to be declared. In this context, we define the term "AI assisted copy editing" as AI-assisted improvements to human-generated texts for readability and style, and to ensure that the texts are free of errors in grammar, spelling, punctuation and tone. These AI-assisted improvements may include wording and formatting changes to the texts, but

do not include generative editorial work and autonomous content creation. In all cases, there must be human accountability for the final version of the text and agreement from the authors that the edits reflect their original work.

#### *Abstract*

Please provide an abstract of 150 to 250 words. The abstract should not contain any undefined abbreviations or unspecified references.

*For life science journals only (when applicable)*

- Trial registration number and date of registration for prospectively registered trials
- Trial registration number and date of registration, followed by "retrospectively registered", for retrospectively registered trials

#### *Keywords*

Please provide 4 to 6 keywords which can be used for indexing purposes.

#### *Statements and Declarations*

The following statements should be included under the heading "Statements and Declarations" for inclusion in the published paper. Please note that submissions that do not include relevant declarations will be returned as incomplete.

- **Competing Interests:** Authors are required to disclose financial or non-financial interests that are directly or indirectly related to the work submitted for publication. Please refer to "Competing Interests and Funding" below for more information on how to complete this section.

Please see the relevant sections in the submission guidelines for further information as well as various examples of wording. Please revise/customize the sample statements according to your own needs.

### Text

#### *Text Formatting*

Manuscripts should be submitted in Word.

- Use a normal, plain font (e.g., 10-point Times Roman) for text.
- Use italics for emphasis.
- Use the automatic page numbering function to number the pages.

- Do not use field functions.
- Use tab stops or other commands for indents, not the space bar.
- Use the table function, not spreadsheets, to make tables.
- Use the equation editor or MathType for equations.
- Save your file in docx format (Word 2007 or higher) or doc format (older Word versions).

Manuscripts with mathematical content can also be submitted in LaTeX. We recommend using Springer Nature's LaTeX template.

#### *Headings*

Please use no more than three levels of displayed headings.

#### *Abbreviations*

Abbreviations should be defined at first mention and used consistently thereafter.

#### *Footnotes*

Footnotes can be used to give additional information, which may include the citation of a reference included in the reference list. They should not consist solely of a reference citation, and they should never include the bibliographic details of a reference. They should also not contain any figures or tables.

Footnotes to the text are numbered consecutively; those to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data). Footnotes to the title or the authors of the article are not given reference symbols.

Always use footnotes instead of endnotes.

#### *Acknowledgments*

Acknowledgments of people, grants, funds, etc. should be placed in a separate section on the title page. The names of funding organizations should be written in full.

### References

#### *Citation*

Reference citations in the text should be identified by numbers in square brackets. Some examples:

1. Negotiation research spans many disciplines [3].

2. This result was later contradicted by Becker and Seligman [5].

3. This effect has been widely studied [1-3, 7].

***Reference list***

The list of references should only include works that are cited in the text and that have been published or accepted for publication. Personal communications and unpublished works should only be mentioned in the text.

Reference list entries should be alphabetized by the last names of the first author of each work and numbered consecutively.

If available, please always include DOIs as full DOI links in your reference list (e.g. “https://doi.org/abc”).

- Journal article

  Gamelin FX, Baquet G, Berthoin S, Thevenet D, Nourry C, Nottin S, Bosquet L (2009) Effect of high intensity intermittent training on heart rate variability in prepubescent children. Eur J Appl Physiol 105:731-738. https://doi.org/10.1007/s00421-008-0955-8

  Ideally, the names of all authors should be provided, but the usage of “et al” in long author lists will also be accepted:

  Smith J, Jones M Jr, Houghton L et al (1999) Future of health insurance. N Engl J Med 965:325–329

- Article by DOI

  Slifka MK, Whitton JL (2000) Clinical implications of dysregulated cytokine production. J Mol Med. https://doi.org/10.1007/s001090000086

- Book

  South J, Blass B (2001) The future of modern genomics. Blackwell, London

- Book chapter

Brown B, Aaron M (2001) The politics of nature. In: Smith J (ed) The rise of modern genomics, 3rd edn. Wiley, New York, pp 230-257

- Online document

  Doe J (1999) Title of subordinate document. In: The dictionary of substances and their effects. Royal Society of Chemistry. Available via DIALOG. http://www.rsc.org/dose/title of subordinate document.

  Accessed 15 Jan 1999

Always use the standard abbreviation of a journal's name according to the ISSN List of Title Word Abbreviations, see

ISSN.org LTWA

If you are unsure, please use the full journal title.

***Citation of Patents***

- Lenssen KC, Jantscheff P, Kiedrowski G, Massing, U (2004) Cationic Lipids with Serine Backbone for Transfecting Biological Molecules. Eur. Pat. Appl. 1457483

***Please note:***

References should be in alphabetical order using the first author's name and should be numbered consecutively. Please note that this numbering is not chronologically – it does not reflect the citation order within the text.

**Tables**

- All tables are to be numbered using Arabic numerals.
- Tables should always be cited in text in consecutive numerical order.
- For each table, please supply a table caption (title) explaining the components of the table.
- Identify any previously published material by giving the original source in the form of a reference at the end of the table caption.
- Footnotes to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data) and included beneath the table body.

***Please note:***

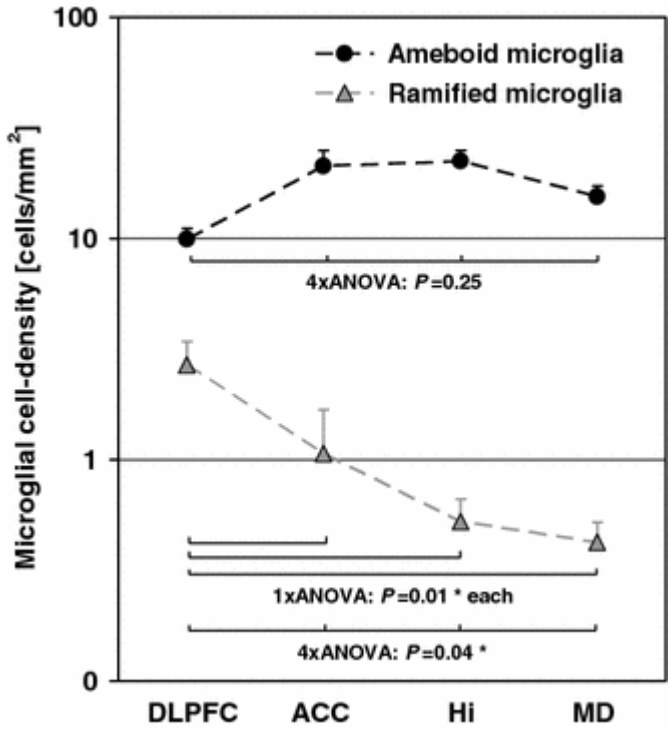
A table should have a title and a legend explaining any abbreviation used in the table. Tables should be placed within the manuscript text file at the end of the main text.

**Artwork and Illustrations Guidelines**

***Electronic Figure Submission***

- Supply all figures electronically.
- Indicate what graphics program was used to create the artwork.
- For vector graphics, the preferred format is EPS; for halftones, please use TIFF format. MSOffice files are also acceptable.
- Vector graphics containing fonts must have the fonts embedded in the files.
- Name your figure files with "Fig" and the figure number, e.g., Fig1.eps.

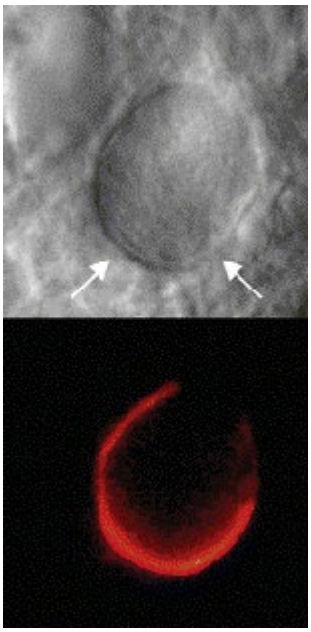
***Line Art***




- Definition: Black and white graphic with no shading.
- Do not use faint lines and/or lettering and check that all lines and lettering within the figures are legible at final size.
- All lines should be at least 0.1 mm (0.3 pt) wide.

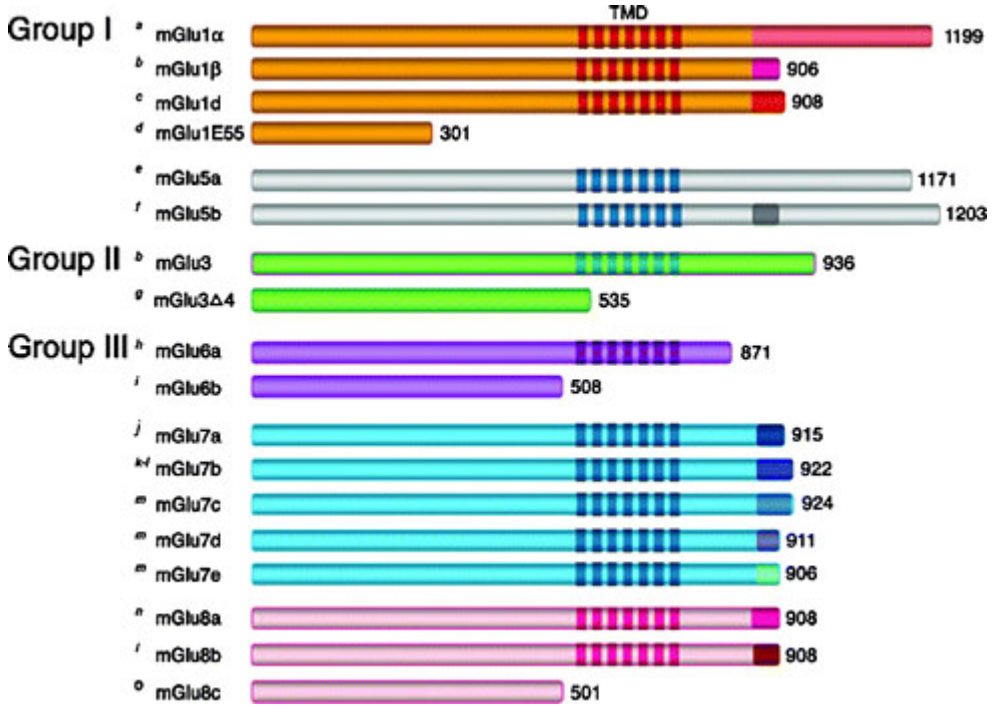
- Scanned line drawings and line drawings in bitmap format should have a minimum resolution of 1200 dpi.
- Vector graphics containing fonts must have the fonts embedded in the files.

***Halftone Art***



- Definition: Photographs, drawings, or paintings with fine shading, etc.
- If any magnification is used in the photographs, indicate this by using scale bars within the figures themselves.
- Halftones should have a minimum resolution of 300 dpi.

***Combination Art***




- Definition: a combination of halftone and line art, e.g., halftones containing line drawing, extensive lettering, color diagrams, etc.
- Combination artwork should have a minimum resolution of 600 dpi.

***Color Art***

- Color art is free of charge for online publication.
- If black and white will be shown in the print version, make sure that the main information will still be visible. Many colors are not distinguishable from one another when converted to black and white. A simple way to check this is to make a xerographic copy to see if the necessary distinctions between the different colors are still apparent.
- If the figures will be printed in black and white, do not refer to color in the captions.
- Color illustrations should be submitted as RGB (8 bits per channel).

***Figure Lettering***

- To add lettering, it is best to use Helvetica or Arial (sans serif fonts).
- Keep lettering consistently sized throughout your final-sized artwork, usually about 2–3 mm (8–12 pt).
- Variance of type size within an illustration should be minimal, e.g., do not use 8-pt type on an axis and 20-pt type for the axis label.

- Avoid effects such as shading, outline letters, etc.
- Do not include titles or captions within your illustrations.

***Figure Numbering***

- All figures are to be numbered using Arabic numerals.
- Figures should always be cited in text in consecutive numerical order.
- Figure parts should be denoted by lowercase letters (a, b, c, etc.).
- If an appendix appears in your article and it contains one or more figures, continue the consecutive numbering of the main text. Do not number the appendix figures,"A1, A2, A3, etc." Figures in online appendices [Supplementary Information (SI)] should, however, be numbered separately.

***Figure Captions***

- Each figure should have a concise caption describing accurately what the figure depicts. Include the captions in the text file of the manuscript, not in the figure file.
- Figure captions begin with the term Fig. in bold type, followed by the figure number, also in bold type.
- No punctuation is to be included after the number, nor is any punctuation to be placed at the end of the caption.
- Identify all elements found in the figure in the figure caption; and use boxes, circles, etc., as coordinate points in graphs.
- Identify previously published material by giving the original source in the form of a reference citation at the end of the figure caption.

***Figure Placement and Size***

- Figures should be submitted within the body of the text. Only if the file size of the manuscript causes problems in uploading it, the large figures should be submitted separately from the text.
- When preparing your figures, size figures to fit in the column width.
- For large-sized journals the figures should be 84 mm (for double-column text areas), or 174 mm (for single-column text areas) wide and not higher than 234 mm.
- For small-sized journals, the figures should be 119 mm wide and not higher than 195 mm.

### *Permissions*

If you include figures that have already been published elsewhere, you must obtain permission from the copyright owner(s) for both the print and online format. Please be aware that some publishers do not grant electronic rights for free and that Springer will not be able to refund any costs that may have occurred to receive these permissions. In such cases, material from other sources should be used.

### *Accessibility*

In order to give people of all abilities and disabilities access to the content of your figures, please make sure that

- All figures have descriptive captions (blind users could then use a text-to-speech software or a text-to-Braille hardware)
- Patterns are used instead of or in addition to colors for conveying information (colorblind users would then be able to distinguish the visual elements)
- Any figure lettering has a contrast ratio of at least 4.5:1

### *Generative AI Images*

Please check Springer's policy on generative AI images and make sure your work adheres to the principles described therein.

### Supplementary Information (SI)

Springer accepts electronic multimedia files (animations, movies, audio, etc.) and other supplementary files to be published online along with an article or a book chapter. This feature can add dimension to the author's article, as certain information cannot be printed or is more convenient in electronic form.

Before submitting research datasets as Supplementary Information, authors should read the journal's Research data policy. We encourage research data to be archived in data repositories wherever possible.

### *Submission*

- Supply all supplementary material in standard file formats.
- Please include in each file the following information: article title, journal name, author names; affiliation and e-mail address of the corresponding author.

- To accommodate user downloads, please keep in mind that larger-sized files may require very long download times and that some users may experience other problems during downloading.

***Audio, Video, and Animations***

- Aspect ratio: 16:9 or 4:3
- Maximum file size: 2 GB
- Minimum video duration: 1 sec
- Supported file formats: avi, wmv, mp4, mov, m2p, mp2, mpg, mpeg, flv, mxf, mts, m4v, 3gp

***Text and Presentations***

- Submit your material in PDF format; .doc or .ppt files are not suitable for long-term viability.
- A collection of figures may also be combined in a PDF file.

***Spreadsheets***

- Spreadsheets should be submitted as .csv or .xlsx files (MS Excel).

***Specialized Formats***

- Specialized format such as .pdb (chemical), .wrl (VRML), .nb (Mathematica notebook), and .tex can also be supplied.

***Collecting Multiple Files***

- It is possible to collect multiple files in a .zip or .gz file.

***Numbering***

- If supplying any supplementary material, the text must make specific mention of the material as a citation, similar to that of figures and tables.
- Refer to the supplementary files as “Online Resource”, e.g., "... as shown in the animation (Online Resource 3)", “... additional data are given in Online Resource 4”.
- Name the files consecutively, e.g. “ESM_3.mpg”, “ESM_4.pdf”.

***Captions***

- For each supplementary material, please supply a concise caption describing the content of the file.

***Processing of supplementary files***

- Supplementary Information (SI) will be published as received from the author without any conversion, editing, or reformatting.

***Accessibility***

In order to give people of all abilities and disabilities access to the content of your supplementary files, please make sure that

- The manuscript contains a descriptive caption for each supplementary material
- Video files do not contain anything that flashes more than three times per second (so that users prone to seizures caused by such effects are not put at risk)

***Generative AI Images***

Please check Springer's policy on generative AI images and make sure your work adheres to the principles described therein.

**Ethical Responsibilities of Authors**

This journal is committed to upholding the integrity of the scientific record. As a member of the Committee on Publication Ethics (COPE) the journal will follow the COPE guidelines on how to deal with potential acts of misconduct.

Authors should refrain from misrepresenting research results which could damage the trust in the journal, the professionalism of scientific authorship, and ultimately the entire scientific endeavour. Maintaining integrity of the research and its presentation is helped by following the rules of good scientific practice, which include*:

- The manuscript should not be submitted to more than one journal for simultaneous consideration.
- The submitted work should be original and should not have been published elsewhere in any form or language (partially or in full), unless the new work concerns an expansion of previous work. (Please provide transparency on the re-use of material to avoid the concerns about text-recycling ('self-plagiarism').

- A single study should not be split up into several parts to increase the quantity of submissions and submitted to various journals or to one journal over time (i.e. 'salami-slicing/publishing').
- Concurrent or secondary publication is sometimes justifiable, provided certain conditions are met. Examples include: translations or a manuscript that is intended for a different group of readers.
- Results should be presented clearly, honestly, and without fabrication, falsification or inappropriate data manipulation (including image based manipulation). Authors should adhere to discipline-specific rules for acquiring, selecting and processing data.
- No data, text, or theories by others are presented as if they were the author's own ('plagiarism'). Proper acknowledgements to other works must be given (this includes material that is closely copied (near verbatim), summarized and/or paraphrased), quotation marks (to indicate words taken from another source) are used for verbatim copying of material, and permissions secured for material that is copyrighted.

**Important note: the journal may use software to screen for plagiarism.**

- Authors should make sure they have permissions for the use of software, questionnaires/(web) surveys and scales in their studies (if appropriate).
- Research articles and non-research articles (e.g. Opinion, Review, and Commentary articles) must cite appropriate and relevant literature in support of the claims made. Excessive and inappropriate self-citation or coordinated efforts among several authors to collectively self-cite is strongly discouraged.
- Authors should avoid untrue statements about an entity (who can be an individual person or a company) or descriptions of their behavior or actions that could potentially be seen as personal attacks or allegations about that person.
- Research that may be misapplied to pose a threat to public health or national security should be clearly identified in the manuscript (e.g. dual use of research). Examples include creation of harmful consequences of biological agents or toxins, disruption of immunity of vaccines, unusual hazards in the use of chemicals, weaponization of research/technology (amongst others).
- Authors are strongly advised to ensure the author group, the Corresponding Author, and the order of authors are all correct at

submission. Adding and/or deleting authors during the revision stages is generally not permitted, but in some cases may be warranted. Reasons for changes in authorship should be explained in detail. Please note that changes to authorship cannot be made after acceptance of a manuscript.

*All of the above are guidelines and authors need to make sure to respect third parties rights such as copyright and/or moral rights.

Upon request authors should be prepared to send relevant documentation or data in order to verify the validity of the results presented. This could be in the form of raw data, samples, records, etc. Sensitive information in the form of confidential or proprietary data is excluded.

If there is suspicion of misbehavior or alleged fraud the Journal and/or Publisher will carry out an investigation following COPE guidelines. If, after investigation, there are valid concerns, the author(s) concerned will be contacted under their given e-mail address and given an opportunity to address the issue. Depending on the situation, this may result in the Journal's and/or Publisher's implementation of the following measures, including, but not limited to:

- If the manuscript is still under consideration, it may be rejected and returned to the author.
- If the article has already been published online, depending on the nature and severity of the infraction:

  - an erratum/correction may be placed with the article

  - an expression of concern may be placed with the article

  - or in severe cases retraction of the article may occur.

The reason will be given in the published erratum/correction, expression of concern or retraction note. Please note that retraction means that the article is **maintained on the platform**, watermarked "retracted" and the explanation for the retraction is provided in a note linked to the watermarked article.

- The author's institution may be informed
- A notice of suspected transgression of ethical standards in the peer review system may be included as part of the author's and article's bibliographic record.

### *Fundamental errors*

Authors have an obligation to correct mistakes once they discover a significant error or inaccuracy in their published article. The author(s) is/are requested to contact the journal and explain in what sense the error is impacting the article. A decision on how to correct the literature will depend on the nature of the error. This may be a correction or retraction. The retraction note should provide transparency which parts of the article are impacted by the error.

### *Suggesting / excluding reviewers*

Authors are welcome to suggest suitable reviewers and/or request the exclusion of certain individuals when they submit their manuscripts. When suggesting reviewers, authors should make sure they are totally independent and not connected to the work in any way. It is strongly recommended to suggest a mix of reviewers from different countries and different institutions. When suggesting reviewers, the Corresponding Author must provide an institutional email address for each suggested reviewer, or, if this is not possible to include other means of verifying the identity such as a link to a personal homepage, a link to the publication record or a researcher or author ID in the submission letter. Please note that the Journal may not use the suggestions, but suggestions are appreciated and may help facilitate the peer review process.

## Authorship principles

These guidelines describe authorship principles and good authorship practices to which prospective authors should adhere to.

### *Authorship clarified*

The Journal and Publisher assume all authors agreed with the content and that all gave explicit consent to submit and that they obtained consent from the responsible authorities at the institute/organization where the work has been carried out, **before** the work is submitted.

The Publisher does not prescribe the kinds of contributions that warrant authorship. It is recommended that authors adhere to the guidelines for authorship that are applicable in their specific research field. In absence of specific guidelines it is recommended to adhere to the following guidelines*:

All authors whose names appear on the submission

1) made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work;

2) drafted the work or revised it critically for important intellectual content;

3) approved the version to be published; and

4) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

* Based on/adapted from:

ICMJE, Defining the Role of Authors and Contributors,

Transparency in authors' contributions and responsibilities to promote integrity in scientific publication, McNutt at all, PNAS February 27, 2018

***Disclosures and declarations***

All authors are requested to include information regarding sources of funding, financial or non-financial interests, study-specific approval by the appropriate ethics committee for research involving humans and/or animals, informed consent if the research involved human participants, and a statement on welfare of animals if the research involved animals (as appropriate).

The decision whether such information should be included is not only dependent on the scope of the journal, but also the scope of the article. Work submitted for publication may have implications for public health or general welfare and in those cases it is the responsibility of all authors to include the appropriate disclosures and declarations.

***Data transparency***

All authors are requested to make sure that all data and materials as well as software application or custom code support their published claims and comply with field standards. Please note that journals may have individual policies on (sharing) research data in concordance with disciplinary norms and expectations.

***Role of the Corresponding Author***

**One author** is assigned as Corresponding Author and acts on behalf of all co-authors and ensures that questions related to the accuracy or integrity of any part of the work are appropriately addressed.

The Corresponding Author is responsible for the following requirements:

- ensuring that all listed authors have approved the manuscript before submission, including the names and order of authors;
- managing all communication between the Journal and all co-authors, before and after publication;*
- providing transparency on re-use of material and mention any unpublished material (for example manuscripts in press) included in the manuscript in a cover letter to the Editor;
- making sure disclosures, declarations and transparency on data statements from all authors are included in the manuscript as appropriate (see above).

* The requirement of managing all communication between the journal and all co-authors during submission and proofing may be delegated to a Contact or Submitting Author. In this case please make sure the Corresponding Author is clearly indicated in the manuscript.

***Author contributions***

In absence of specific instructions and in research fields where it is possible to describe discrete efforts, the Publisher recommends authors to include contribution statements in the work that specifies the contribution of every author in order to promote transparency. These contributions should be listed at the separate title page.

**Examples of such statement(s) are shown below:**

• Free text:

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [full name], [full name] and [full name]. The first draft of the manuscript was written by [full name] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Example: CRediT taxonomy:

• Conceptualization: [full name], …; Methodology: [full name], …; Formal analysis and investigation: [full name], …; Writing - original draft preparation: [full name, …]; Writing - review and editing: [full name], …; Funding acquisition: [full name], …; Resources: [full name], …; Supervision: [full name],….

For **review articles** where discrete statements are less applicable a statement should be included who had the idea for the article, who performed the literature search and data analysis, and who drafted and/or critically revised the work.

For articles that are based primarily on the **student's dissertation or thesis**, it is recommended that the student is usually listed as principal author:

A Graduate Student's Guide to Determining Authorship Credit and Authorship Order, APA Science Student Council 2006

***Affiliation***

The primary affiliation for each author should be the institution where the majority of their work was done. If an author has subsequently moved, the current address may additionally be stated. Addresses will not be updated or changed after publication of the article.

***Changes to authorship***

Authors are strongly advised to ensure the correct author group, the Corresponding Author, and the order of authors at submission. Changes of authorship by adding or deleting authors, and/or changes in Corresponding Author, and/or changes in the sequence of authors are **not** accepted **after acceptance** of a manuscript.

- **Please note that author names will be published exactly as they appear on the accepted submission!**

Please make sure that the names of all authors are present and correctly spelled, and that addresses and affiliations are current.

Adding and/or deleting authors at revision stage are generally not permitted, but in some cases it may be warranted. Reasons for these changes in authorship should be explained. Approval of the change during revision is at

the discretion of the Editor-in-Chief. Please note that journals may have individual policies on adding and/or deleting authors during revision stage.

***Author identification***

Authors are recommended to use their ORCID ID when submitting an article for consideration or acquire an ORCID ID via the submission process.

***Deceased or incapacitated authors***

For cases in which a co-author dies or is incapacitated during the writing, submission, or peer-review process, and the co-authors feel it is appropriate to include the author, co-authors should obtain approval from a (legal) representative which could be a direct relative.

***Authorship issues or disputes***

In the case of an authorship dispute during peer review or after acceptance and publication, the Journal will not be in a position to investigate or adjudicate. Authors will be asked to resolve the dispute themselves. If they are unable the Journal reserves the right to withdraw a manuscript from the editorial process or in case of a published paper raise the issue with the authors' institution(s) and abide by its guidelines.

***Confidentiality***

Authors should treat all communication with the Journal as confidential which includes correspondence with direct representatives from the Journal such as Editors-in-Chief and/or Handling Editors and reviewers' reports unless explicit consent has been received to share information.

**Compliance with Ethical Standards**

To ensure objectivity and transparency in research and to ensure that accepted principles of ethical and professional conduct have been followed, authors should include information regarding sources of funding, potential conflicts of interest (financial or non-financial), informed consent if the research involved human participants, and a statement on welfare of animals if the research involved animals.

Authors should include the following statements (if applicable) in a separate section entitled "Compliance with Ethical Standards" when submitting a paper:

- Disclosure of potential conflicts of interest
- Research involving Human Participants and/or Animals

- Informed consent

Please note that standards could vary slightly per journal dependent on their peer review policies (i.e. single or double blind peer review) as well as per journal subject discipline. Before submitting your article check the instructions following this section carefully.

The corresponding author should be prepared to collect documentation of compliance with ethical standards and send if requested during peer review or after publication.

The Editors reserve the right to reject manuscripts that do not comply with the above-mentioned guidelines. The author will be held responsible for false statements or failure to fulfill the above-mentioned guidelines.

**Disclosure of potential conflicts of interest**

Authors must disclose all relationships or interests that could have direct or potential influence or impart bias on the work. Although an author may not feel there is any conflict, disclosure of relationships and interests provides a more complete and transparent process, leading to an accurate and objective assessment of the work. Awareness of a real or perceived conflicts of interest is a perspective to which the readers are entitled. This is not meant to imply that a financial relationship with an organization that sponsored the research or compensation received for consultancy work is inappropriate. Examples of potential conflicts of interests **that are directly or indirectly related to the research** may include but are not limited to the following:

- Research grants from funding agencies (please give the research funder and the grant number)
- Honoraria for speaking at symposia
- Financial support for attending symposia
- Financial support for educational programs
- Employment or consultation
- Support from a project sponsor
- Position on advisory board or board of directors or other type of management relationships
- Multiple affiliations
- Financial relationships, for example equity ownership or investment interest

- Intellectual property rights (e.g. patents, copyrights and royalties from such rights)
- Holdings of spouse and/or children that may have financial interest in the work

In addition, interests that go beyond financial interests and compensation (non-financial interests) that may be important to readers should be disclosed. These may include but are not limited to personal relationships or competing interests directly or indirectly tied to this research, or professional interests or personal beliefs that may influence your research.

The corresponding author collects the conflict of interest disclosure forms from all authors. In author collaborations where formal agreements for representation allow it, it is sufficient for the corresponding author to sign the disclosure form on behalf of all authors. Examples of forms can be found

here:

The corresponding author will include a summary statement in the text of the manuscript in a separate section before the reference list, that reflects what is recorded in the potential conflict of interest disclosure form(s).

Please make sure to submit all Conflict of Interest disclosure forms together with the manuscript.

See below examples of disclosures:

**Funding:** This study was funded by X (grant number X).

**Conflict of Interest:** Author A has received research grants from Company A. Author B has received a speaker honorarium from Company X and owns stock in Company Y. Author C is a member of committee Z.

If no conflict exists, the authors should state:

Conflict of Interest: The authors declare that they have no conflict of interest.

## Research involving human participants, their data or biological material

### *Ethics approval*

When reporting a study that involved human participants, their data or biological material, authors should include a statement that confirms that the study was approved (or granted exemption) by the appropriate institutional and/or national research ethics committee (including the name of the ethics committee) and certify that the study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. If doubt exists whether the research was conducted in accordance with the 1964 Helsinki Declaration or comparable standards, the authors must explain the reasons for their approach, and demonstrate that an independent ethics committee or institutional review board explicitly approved the doubtful aspects of the study. If a study was granted exemption from requiring ethics approval, this should also be detailed in the manuscript (including the reasons for the exemption).

### *Retrospective ethics approval*

If a study has not been granted ethics committee approval prior to commencing, retrospective ethics approval usually cannot be obtained and it may not be possible to consider the manuscript for peer review. The decision on whether to proceed to peer review in such cases is at the Editor's discretion.

### *Ethics approval for retrospective studies*

Although retrospective studies are conducted on already available data or biological material (for which formal consent may not be needed or is difficult to obtain) ethics approval may be required dependent on the law and the national ethical guidelines of a country. Authors should check with their institution to make sure they are complying with the specific requirements of their country.

### *Ethics approval for case studies*

Case reports require ethics approval. Most institutions will have specific policies on this subject. Authors should check with their institution to make sure they are complying with the specific requirements of their institution and seek ethics approval where needed. Authors should be aware to secure informed consent from the individual (or parent or guardian if the participant is a minor or incapable) See also section on **Informed Consent**.

### *Cell lines*

If human cells are used, authors must declare in the manuscript: what cell lines were used by describing the source of the cell line, including when and from where it was obtained, whether the cell line has recently been authenticated and by what method. If cells were bought from a life science company the following need to be given in the manuscript: name of company (that provided the cells), cell type, number of cell line, and batch of cells.

It is recommended that authors check the NCBI database for misidentification and contamination of human cell lines. This step will alert authors to possible problems with the cell line and may save considerable time and effort.

Further information is available from the International Cell Line Authentication Committee (ICLAC).

Authors should include a statement that confirms that an institutional or independent ethics committee (including the name of the ethics committee) approved the study and that informed consent was obtained from the donor or next of kin.

### *Research Resource Identifiers (RRID)*

Research Resource Identifiers (RRID) are persistent unique identifiers (effectively similar to a DOI) for research resources. This journal encourages authors to adopt RRIDs when reporting key biological resources (antibodies, cell lines, model organisms and tools) in their manuscripts.

**Examples:**

**Organism:** *Filip1*$^{tm1a(KOMP)Wtsi}$ **RRID:MMRRC_055641-UCD**

**Cell Line:** RST307 cell line **RRID:CVCL_C321**

**Antibody:** Luciferase antibody DSHB Cat# LUC-3, **RRID:AB_2722109**

**Plasmid:** mRuby3 plasmid **RRID:Addgene_104005**

**Software:** ImageJ Version 1.2.4 **RRID:SCR_003070**

RRIDs are provided by the Resource Identification Portal. Many commonly used research resources already have designated RRIDs. The portal also provides authors links so that they can quickly register a new resource and obtain an RRID.

### *Clinical Trial Registration*

The World Health Organization (WHO) definition of a clinical trial is "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes". The WHO defines health interventions as “A health intervention is an act performed for, with or on behalf of a person or population whose purpose is to assess, improve, maintain, promote or modify health, functioning or health conditions” and a health-related outcome is generally defined as a change in the health of a person or population as a result of an intervention.

To ensure the integrity of the reporting of patient-centered trials, authors must register prospective clinical trials (phase II to IV trials) in suitable publicly available repositories. For example www.clinicaltrials.gov or any of the primary registries that participate in the WHO International Clinical Trials Registry Platform.

The trial registration number (TRN) and date of registration should be included as the last line of the manuscript abstract.

For clinical trials that have not been registered prospectively, authors are encouraged to register retrospectively to ensure the complete publication of all results. The trial registration number (TRN), date of registration and the words 'retrospectively registered’ should be included as the last line of the manuscript abstract.

### *Standards of reporting*

Springer Nature advocates complete and transparent reporting of biomedical and biological research and research with biological applications. Authors are recommended to adhere to the minimum reporting guidelines hosted by the EQUATOR Network when preparing their manuscript.

Exact requirements may vary depending on the journal; please refer to the journal’s Instructions for Authors.

Checklists are available for a number of study designs, including:

Randomised trials (CONSORT) and Study protocols (SPIRIT)

Observational studies (STROBE)

Systematic reviews and meta-analyses (PRISMA) and protocols (Prisma-P)

Diagnostic/prognostic studies (STARD) and (TRIPOD)

Case reports (CARE)

Clinical practice guidelines (AGREE) and (RIGHT)

Qualitative research (SRQR) and (COREQ)

Animal pre-clinical studies (ARRIVE)

Quality improvement studies (SQUIRE)

Economic evaluations (CHEERS)

***Summary of requirements***

The above should be summarized in a statement and placed in a 'Declarations' section before the reference list under a heading of 'Ethics approval'.

Examples of statements to be used when ethics approval has been obtained:

• All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Bioethics Committee of the Medical University of A (No. ...).

• This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University B (Date.../No. ...).

• Approval was obtained from the ethics committee of University C. The procedures used in this study adhere to the tenets of the Declaration of Helsinki.

• The questionnaire and methodology for this study was approved by the Human Research Ethics committee of the University of D (Ethics approval number: ...).

Examples of statements to be used for a retrospective study:

• Ethical approval was waived by the local Ethics Committee of University A in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

• This research study was conducted retrospectively from data obtained for clinical purposes. We consulted extensively with the IRB of XYZ who determined that our study did not need ethical approval. An IRB official waiver of ethical approval was granted from the IRB of XYZ.

• This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of University B approved this study.

Examples of statements to be used when no ethical approval is required/exemption granted:

• This is an observational study. The XYZ Research Ethics Committee has confirmed that no ethical approval is required.

• The data reproduced from Article X utilized human tissue that was procured via our Biobank AB, which provides de-identified samples. This study was reviewed and deemed exempt by our XYZ Institutional Review Board. The BioBank protocols are in accordance with the ethical standards of our institution and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Authors are responsible for correctness of the statements provided in the manuscript. See also Authorship Principles. The Editor-in-Chief reserves the

right to reject submissions that do not meet the guidelines described in this section.

#### Informed consent

All individuals have individual rights that are not to be infringed. Individual participants in studies have, for example, the right to decide what happens to the (identifiable) personal data gathered, to what they have said during a study or an interview, as well as to any photograph that was taken. This is especially true concerning images of vulnerable people (e.g. minors, patients, refugees, etc) or the use of images in sensitive contexts. In many instances authors will need to secure written consent before including images.

Identifying details (names, dates of birth, identity numbers, biometrical characteristics (such as facial features, fingerprint, writing style, voice pattern, DNA or other distinguishing characteristic) and other information) of the participants that were studied should not be published in written descriptions, photographs, and genetic profiles unless the information is essential for scholarly purposes and the participant (or parent/guardian if the participant is a minor or incapable or legal representative) gave written informed consent for publication. Complete anonymity is difficult to achieve in some cases. Detailed descriptions of individual participants, whether of their whole bodies or of body sections, may lead to disclosure of their identity. Under certain circumstances consent is not required as long as information is anonymized and the submission does not include images that may identify the person.

Informed consent for publication should be obtained if there is any doubt. For example, masking the eye region in photographs of participants is inadequate protection of anonymity. If identifying characteristics are altered to protect anonymity, such as in genetic profiles, authors should provide assurance that alterations do not distort meaning.

Exceptions where it is not necessary to obtain consent:

• Images such as x rays, laparoscopic images, ultrasound images, brain scans, pathology slides unless there is a concern about identifying information in which case, authors should ensure that consent is obtained.

• Reuse of images: If images are being reused from prior publications, the Publisher will assume that the prior publication obtained the relevant

information regarding consent. Authors should provide the appropriate attribution for republished images.

## Consent and already available data and/or biologic material

Regardless of whether material is collected from living or dead patients, they (family or guardian if the deceased has not made a pre-mortem decision) must have given prior written consent. The aspect of confidentiality as well as any wishes from the deceased should be respected.

## Data protection, confidentiality and privacy

When biological material is donated for or data is generated as part of a research project authors should ensure, as part of the informed consent procedure, that the participants are made aware what kind of (personal) data will be processed, how it will be used and for what purpose. In case of data acquired via a biobank/biorepository, it is possible they apply a broad consent which allows research participants to consent to a broad range of uses of their data and samples which is regarded by research ethics committees as specific enough to be considered “informed”. However, authors should always check the specific biobank/biorepository policies or any other type of data provider policies (in case of non-bio research) to be sure that this is the case.

### *Consent to Participate*

For all research involving human subjects, freely-given, informed consent to participate in the study must be obtained from participants (or their parent or legal guardian in the case of children under 16) and a statement to this effect should appear in the manuscript. In the case of articles describing human transplantation studies, authors must include a statement declaring that no organs/tissues were obtained from prisoners and must also name the institution(s)/clinic(s)/department(s) via which organs/tissues were obtained. For manuscripts reporting studies involving vulnerable groups where there is the potential for coercion or where consent may not have been fully informed, extra care will be taken by the editor and may be referred to the Springer Nature Research Integrity Group.

### *Consent to Publish*

Individuals may consent to participate in a study, but object to having their data published in a journal article. Authors should make sure to also seek consent from individuals to publish their data prior to submitting their paper

to a journal. This is in particular applicable to case studies. A consent to publish form can be found

here. (Download docx, 36 kB)

***Summary of requirements***

The above should be summarized in a statement and placed in a 'Declarations' section before the reference list under a heading of 'Consent to participate' and/or 'Consent to publish'. Other declarations include Funding, Competing interests, Ethics approval, Consent, Data and/or Code availability and Authors' contribution statements.

Please see the various examples of wording below and revise/customize the sample statements according to your own needs.

Sample statements for **"Consent to participate"**:

Informed consent was obtained from all individual participants included in the study.

Informed consent was obtained from legal guardians.

Written informed consent was obtained from the parents.

Verbal informed consent was obtained prior to the interview.

Sample statements for **"Consent to publish"**:

The authors affirm that human research participants provided informed consent for publication of the images in Figure(s) 1a, 1b and 1c.

The participant has consented to the submission of the case report to the journal.

Patients signed informed consent regarding publishing their data and photographs.

Sample statements if identifying information about participants is available in the article:

Additional informed consent was obtained from all individual participants for whom identifying information is included in this article.

Authors are responsible for correctness of the statements provided in the manuscript. See also Authorship Principles. The Editor-in-Chief reserves the right to reject submissions that do not meet the guidelines described in this section.

Images will be removed from publication if authors have not obtained informed consent or the paper may be removed and replaced with a notice explaining the reason for removal.

**Research Data Policy and Data Availability Statements**

This journal follows Springer Nature research data policy. Sharing of all relevant research data is strongly encouraged and authors must add a Data Availability Statement to original research articles.

Research data includes a wide range of types, including spreadsheets, images, textual extracts, archival documents, video or audio, interview notes or any specialist formats generated during research.

***Data availability statements***

All original research must include a data availability statement. This statement should explain how to access data supporting the results and analysis in the article, including links/citations to publicly archived datasets analysed or generated during the study. Please see our full policy here.

If it is not possible to share research data publicly, for instance when individual privacy could be compromised, this statement should describe how data can be accessed and any conditions for reuse. Participant consent should be obtained and documented prior to data collection. See our guidance on sensitive data for more information.

When creating a data availability statement, authors are encouraged to consider the minimal dataset that would be necessary to interpret, replicate and build upon the findings reported in the article.

Further guidance on writing a data availability statement, including examples, is available at:

Data availability statements

***Data repositories***

Authors are strongly encouraged to deposit their supporting data in a publicly available repository. Sharing your data in a repository promotes the integrity, discovery and reuse of your research, making it easier for the research community to build on and credit your work.

See our data repository guidance for information on finding a suitable repository.

We recommend the use of discipline-specific repositories where available. For a number of data types, submission to specific public repositories is mandatory.

See our list of mandated data types.

The journal encourages making research data available under open licences that permit reuse. The journal does not enforce use of particular licences in third party repositories. You should ensure you have necessary rights to share any data that you deposit in a repository.

***Data citation***

The journal recommends that authors cite any publicly available data on which the conclusions of the paper rely. This includes data the authors are sharing alongside their publication and any secondary data the authors have reused. Data citations should include a persistent identifier (such as a DOI), should be included in the reference list using the minimum information recommended by DataCite (Dataset Creator, Dataset Title, Publisher [repository], Publication Year, Identifier [e.g. DOI, Handle, Accession or ARK]) and follow journal style.

See our further guidance on citing datasets.

***Research data and peer review***

If the journal that you are submitting to uses double-anonymous peer review and you are providing reviewers with access to your data (for example via a

repository link, supplementary information or data on request), it is strongly suggested that the authorship in the data is also anonymised. There are data repositories that can assist with this and/or will create a link to mask the authorship of your data.

#### *Support with research data policy*

Authors who need help understanding our data sharing policy, finding a suitable data repository, or organising and sharing research data can consult our Research Data Helpdesk for guidance.

See our FAQ page for more information on Springer Nature's research data policy.

### After Acceptance

Upon acceptance, your article will be exported to Production to undergo typesetting. Shortly after this you will receive two e-mails. One contains a request to confirm your affiliation, choose the publishing model for your article, as well as to arrange rights and payment of any associated publication cost. A second e-mail containing a link to your article's proofs will be sent once typesetting is completed.

#### *Article publishing agreement*

Depending on the ownership of the journal and its policies, you will either grant the Publisher an exclusive licence to publish the article or will be asked to transfer copyright of the article to the Publisher.

#### *Offprints*

Offprints can be ordered by the corresponding author.

#### *Color illustrations*

Publication of color illustrations is free of charge.

#### *Proof reading*

The purpose of the proof is to check for typesetting or conversion errors and the completeness and accuracy of the text, tables and figures. Substantial changes in content, e.g., new results, corrected values, title and authorship, are not allowed without the approval of the Editor.

After online publication, further changes can only be made in the form of an Erratum, which will be hyperlinked to the article.

***Online First***

The article will be published online after receipt of the corrected proofs. This is the official first publication citable with the DOI. After release of the printed version, the paper can also be cited by issue and page numbers.

**Open Choice**

Open Choice allows you to publish open access in more than 1850 Springer Nature journals, making your research more visible and accessible immediately on publication.

Article processing charges (APCs) vary by journal – view the full list

Benefits:

- Increased researcher engagement: Open Choice enables access by anyone with an internet connection, immediately on publication.
- Higher visibility and impact: In Springer hybrid journals, OA articles are accessed 4 times more often on average, and cited 1.7 more times on average*.
- Easy compliance with funder and institutional mandates: Many funders require open access publishing, and some take compliance into account when assessing future grant applications.

It is easy to find funding to support open access – please see our funding and support pages for more information.

*) Within the first three years of publication. Springer Nature hybrid journal OA impact analysis, 2018.

Open Choice

Funding and Support pages

***Copyright***

Open Choice articles do not require transfer of copyright as the copyright remains with the author. In opting for open access, the author(s) agree to publish the article under a Creative Commons license. Details of the OA licences offered to authors can be found on the individual journal website, in the journal's **How to publish with us** guide.

### Editing Services

***English***

How can you help improve your manuscript for publication?

Presenting your work in a well-structured manuscript and in well-written English gives it its best chance for editors and reviewers to understand it and evaluate it fairly. Many researchers find that getting some independent support helps them present their results in the best possible light. The experts at Springer Nature Author Services can help you with manuscript preparation—including **English language editing, developmental comments, manuscript formatting, figure preparation, translation**, and more.

Get started and save 15%

You can also use our free Grammar Check tool for an evaluation of your work.

Please note that using these tools, or any other service, is not a requirement for publication, nor does it imply or guarantee that editors will accept the article, or even select it for peer review.