**UNIVERSIDADE FEDERAL DE MINAS GERAIS**
**Faculdade de Odontologia**
**Colegiado de Pós-Graduação em Odontologia**

**Tania Mara de Souza**

# EFEITOS DO MODELADOR NASOALVEOLAR (NAM) ASSOCIADO OU NÃO À QUEILOPLASTIA EM INDIVÍDUOS COM FISSURA LABIOPALATINA: *ENSAIO CLÍNICO E REVISÃO SISTEMÁTICA DE LITERATURA*

**Belo Horizonte**
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**Orientadora**: Profa. Dra. Soraia Macari
**Coorientador**: Prof. Dr. Lucas G. Abreu

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**FACULDADE DE ODONTOLOGIA**

**COLEGIADO DO CURSO DE PÓS-GRADUAÇÃO EM ODONTOLOGIA**

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**TÂNIA MARA DE SOUZA**

Tese submetida à Banca Examinadora designada pelo Colegiado do Programa de Pós-Graduação em ODONTOLOGIA, como requisito para obtenção do grau de Doutor em ODONTOLOGIA, área de concentração CLÍNICA ODONTOLÓGICA.

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## RESUMO

Fissuras labiopalatinas ocorrem devido a uma falha na fusão embrionária. O modelador nasoalveolar (NAM) é uma intervenção ortopédica anterior à cirurgia labial. Os objetivos deste trabalho são: avaliar o efeito do NAM na simetria facial/arco maxilar e seu impacto psicossocial. Realizar uma revisão sistemática para investigar o impacto do NAM na simetria nasal. A metodologia utilizada foi avaliar 2 grupos (26 bebês tratados com NAM e 12 bebês não tratados com NAM) em dois tempos; antes do NAM (T1) e depois do NAM (T2). Foram analisados: perímetro do arco maxilar (PA), comprimento do arco maxilar (CA) e ângulo do freio labial (AFL), largura nasal (LN), largura bucal (LB), ângulo da columela (AC) e área da narina (AN). Estes mesmos 2 grupos foram comparados antes do NAM e após queiloplastia. O impacto da condição fissura no bebê na rotina familiar também foi avaliado. E ainda foram realizadas buscas eletrônicas considerando estudos que comparavam indivíduos submetidos à queiloplastia/NAM e indivíduos submetidos apenas à queiloplastia. Foram realizadas meta-análises, avaliação do risco de viés e da força da evidência. Nos resultados pudemos ver que houve aumento de PA e CA nos grupos NAM e Controle no período T2 em relação ao T1. O AFL foi reduzido no grupo NAM em comparação com os períodos NAM-T1 e Controle-T2. O NAM produziu uma redução no LN no período de T2 em relação ao T1. AC foi melhorado após o uso de NAM em T2. A AN foi reduzida no grupo NAM em T2 em relação ao Controle. O grupo NAM apresentou redução na largura nasal pós-NAM e queiloplastia. A largura da boca e o ângulo da columela apresentaram alterações no grupo NAM no pós-operatório. Houve redução na área da narina fissurada após o NAM. As pontuações globais do FIS foram mais altas em T1 do que em T2, configurando um impacto positivo do uso do NAM nas famílias. Nas buscas eletrônicas foram recuperados 416 artigos e nove foram incluídos. No grupo NAM houve aumento na altura das narinas e na largura e comprimento da columela. A largura das narinas e a largura bialar diminuíram no curto prazo e aumentaram no longo prazo nos indivíduos submetidos à queiloplastia e NAM. Seis estudos exibiram risco moderado de viés; três exibiram um sério risco de viés. A força da evidência variou de muito baixa a moderada. Desta forma, pudemos concluir que o tratamento NAM melhorou as medidas AFL, LN e AC, melhorando a simetria maxilar e nasal. O NAM promoveu aumento do ângulo da columela e redução das larguras da boca e do nariz, e ainda, redução da área da narina afetada pela fissura. O NAM mostrou um impacto positivo nas emoções familiares. A altura da narina e largura/comprimento columelar foram favorecidos pela queiloplastia seguida do NAM. O comprimento alar foi impactado positivamente pelo NAM.



Palavras-chave: fissura labiopalatina; modelador nasoalveolar; queiloplastia; indicadores de qualidade de vida; revisão sistemática.

## ABSTRACT

**Effects of Nasoalveolar Molding (NAM) associated or not with cheiloplasty in individuals with cleft lip and palate: clinical trial and systematic literature review**

Cleft lip and palate occur due to a failure in embryonic fusion. The nasoalveolar molding (NAM) is an orthopedic intervention prior to lip surgery. The objectives of this study are: to evaluate the effect of NAM on facial symmetry/maxillary arch and its psychosocial impact. To conduct a systematic review to investigate the impact of NAM on nasal symmetry. The methodology used was to evaluate 2 groups (26 babies treated with NAM and 12 babies not treated with NAM) in two time points; before NAM (T1) and after NAM (T2). The following were analyzed: maxillary arch perimeter (AP), maxillary arch length (AL) and labial frenum angle (LFA), nasal width (NW), buccal width (BW), columella angle (CA) and nostril area (NA). These same 2 groups were compared before NAM and after cheiloplasty. The impact of the cleft condition on the baby's family routine was also evaluated. Electronic searches were also performed considering studies that compared individuals undergoing cheiloplasty/NAM and individuals undergoing only cheiloplasty. Meta-analyses, assessment of risk of bias and strength of evidence were performed. The results showed that there was an increase in AP and AC in the NAM and Control groups in the T2 period compared to T1. LFA was reduced in the NAM group compared to the NAM-T1 and Control-T2 periods. NAM produced a reduction in LN in the T2 period compared to T1. CA was improved after the use of NAM in T2. NA was reduced in the NAM group in T2 compared to the Control. The NAM group showed a reduction in nasal width after NAM and cheiloplasty. The width of the mouth and the angle of the columella showed changes in the NAM group in the postoperative period. There was a reduction in the area of the cleft nostril after NAM. The global FIS scores were higher in T1 than in T2, configuring a positive impact of the use of NAM on families. In the electronic searches, 416 articles were retrieved and nine were included. In the NAM group, there was an increase in nostril height and columella width and length. Nostril width and bialar width decreased in the short term and increased in the long term in individuals undergoing cheiloplasty and NAM. Six studies showed a moderate risk of bias; three showed a serious risk of bias. The strength of evidence ranged from very low to moderate. Thus, we were able to conclude that NAM treatment improved LFA, NW and CA measurements, improving maxillary and nasal symmetry. NAM promoted an increase in the columella angle and a reduction in the widths of the mouth and nose, and also a reduction in the area of the nostril affected by the cleft. NAM showed a positive impact on family emotions. Nostril height and columellar width/length were favored by cheiloplasty followed by NAM. Alar length was positively impacted by NAM.



Keywords: cleft lip and palate; nasoalveolar molding; cheiloplasty; quality of life indicators; systematic review.

## LISTA DE FIGURAS

## LISTA DE ABREVIATURAS E SIGLAS

| | |
|---|---|
| **AC** | Ângulo da Columela |
| **AFL** | Ângulo do Freio Labial |
| **AN** | Área da Narina |
| **ANOVA** | Análise de Variância |
| **AP** | Atividade Parental/Familiar |
| **CA** | Comprimento do Arco |
| **CF** | Conflito Familiar |
| **DP** | Desvio Padrão |
| **EF** | Encargos Financeiros |
| **EP** | Emoções Parentais |
| **FIS** | Familiar Impact Scale |
| **FL** | Frênulo Labial |
| **FLP** | Fissura Labiopalatina |
| **FLP/B** | Fissura Labiopalatina Bilateral |
| **FLP/U** | Fissura Labiopalatina Unilateral |
| **GRADE** | Grading of Recomedations, Assessments, Development and Evaluation |
| **IC** | Intervalo de Confiança |
| **LB** | Largura da Boca |
| **LN** | Largura Nasal |
| **NAM** | Nasoalveolar Molding |
| **PA** | Perímetro do Arco |
| **PPC** | Ponto Posterior Central |
| **PPD** | Ponto Posterior Direito |
| **PPE** | Ponto Posterior Esquerdo |
| **PRISMA** | Preferred Reporting Items for Systematic Reviews and MetaAnalyses |
| **PROSPERO** | International Prospective Register of Systematic Reviews |
| **ROBINS I** | Risk of Bias in Non-Randomized Studies |
| **SMD** | Diferença Média Padronizada |
| **STL** | Standard Triangle Language |
| **SUS** | Sistema Único de Saúde |

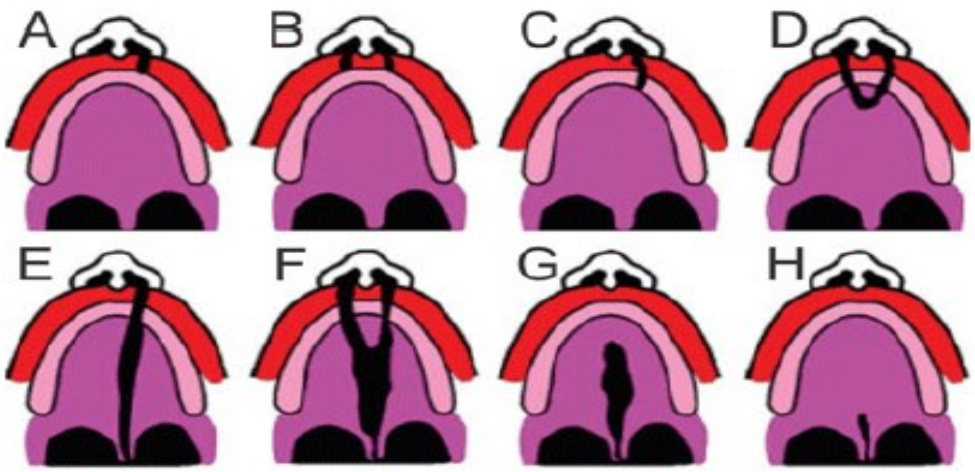
**SUMÁRIO**

# 1 CONSIDERAÇÕES INICIAIS

A fissura labiopalatina é uma má formação craniofacial frequente (Applebaum *et al*., 2024) que afeta estruturas faciais importantes do terço médio da face, podendo apresentar-se isoladamente ou associada a síndromes (Crockett *et al.,* 2014). Ocorre devido a uma falha na fusão dos tecidos da face média entre a quarta e décima segunda semana de vida intrauterina, sendo as má formações congênitas mais comuns da região craniofacial (Kurnik *et al*., 2021).

A fissura labiopalatina apresenta variados graus de envolvimento tecidual e várias classificações têm sido sugeridas no intuito de facilitar a pesquisa e simplificar a comunicação entre as equipes e centros de referência (Applebaum *et al*., 2024). Uma classificação bastante reconhecida estabelece o forame incisivo como ponto de referência para a identificação e localização das fissuras (Spina *et al*., 1973). Desta forma, as fissuras anteriores ao forame incisivo são denominadas pré-forame, podendo ser uni ou bilaterais e podem acometer lábios e osso alveolar (FIGURA 1).

Figura 1 – Classificação de Spina




Legenda: A - Fissura labial esquerda pré-forame incompleta
B – Fissura labial bilateral pré-forame incompleta
C – Fissura labial esquerda pré-forame completa
D – Fissura labial bilateral pré-forame completa
E – Fissura labial esquerda transforame completa
F - Fissura labial bilateral transforame completa
G – Fissura palatina pós-forame completa
H – Fissura palatina pós-forame incompleta

Fonte: SPINA *et al*., 1973

As fissuras pós-forame podem acometer palato duro ou palato mole ou ambos, sendo chamadas completas ou incompletas. As fissuras que atingem as duas

regiões são chamadas transforames (FIGURA 1). E por fim, há ainda um último grupo das fissuras raras da face que estão desvinculadas do forame incisivo, atingindo outras estruturas faciais (Allori *et al*., 2017).

Enquanto a frequência mundial das fissuras é de 1 a cada 700 nascimentos (Worley *et al.,* 2018), no Brasil a proporção é de 1 para cada 1924 nascidos vivos, sendo que esta frequência pode aumentar, especialmente em regiões menos desenvolvidas (Silva *et al., 2022)*. A prevalência pode variar dependendo de vários fatores como localização geográfica, etnia e raça, sexo da criança e presença de outros casos na família, sendo que a menor ocorrência de fissuras aparece em africanos e o sexo masculino mostra-se mais acometido (Vyas *et al*., 2014).

As fissuras podem se apresentar isoladas ou associadas a síndromes como por exemplo a Síndrome Van der Woude, Síndrome velocardiofacial e a Sequência de Pierre Robin (Kulesa-Mrowiecka *et al*., 2024). Sua etiologia é complexa e devido às interações de fatores de risco genéticos e ambientais, ainda não está totalmente compreendida. A participação genética na etiologia das fissuras mostra alguns genes que foram identificados com mutações que podem causar fissuras, mostrando uma conexão entre a mutação e o fenótipo apresentado (Robinson *et al*., 2024). Como fatores ambientais relacionados podemos citar as deficiências nutricionais, tabagismo e uso de álcool/drogas durante a gravidez (Bennaceur *et al*., 2019).

Indivíduos com fissura labiopalatina passam por um extenso e complexo tratamento de reabilitação, começando nos primeiros meses de vida, com a queiloplastia (Freitas *et al*., 2012). Esse procedimento é um tratamento cirúrgico para fechamento da fissura labial e reconstrução nasal, geralmente realizado por volta dos seis meses de idade. O objetivo da correção da deformidade do lábio é retornar à forma e função adequadas, realizando a união dos tecidos e buscando a reconstrução estética e funcional do lábio, facilitando funções essenciais como alimentação, fala e expressão facial (Al-Qatami *et al*., 2022).

A recuperação da anatomia e simetria da região afetada é importante não apenas para o indivíduo com a fissura, mas também para os responsáveis e cirurgiões (Sasaki *et al*., 2012). No momento da primeira intervenção cirúrgica, considerando diferenças individuais e de gravidade, o cirurgião geralmente se depara com segmentos labiais separados no lado da fissura, alargamento da base da narina e colapso da cartilagem nasal deslocada para lateral e para baixo (Thakur *et al*., 2022; Barillas *et al*., 2009).

Atualmente no Brasil, existem poucos centros de atendimento especializados no tratamento desta condição, concentrados principalmente nas regiões Sudeste e Sul do País. Em 2019, foi aprovado um projeto (Projeto de Lei 1409/24) que obriga o Sistema Único de Saúde (SUS) a oferecer o tratamento com suporte completo ao paciente. Esta proposta, para virar lei, ainda deve passar por nova votação na Câmara dos deputados, mas reflete o importância da reabilitação desta condição na sociedade (https://www.camara.leg.br/noticias/1058600-projeto-obriga-o-sistema-publico-de-saude-a-oferecer-tratamento-completo-para-labio-leporino).

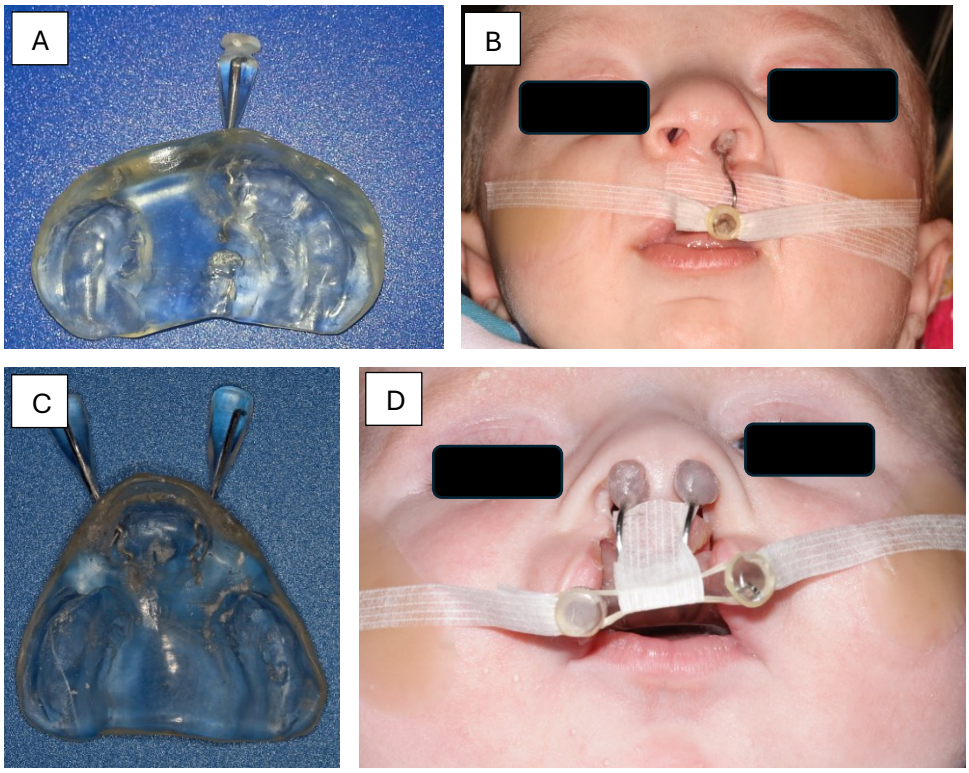
Tratamentos ortopédicos realizados em bebês com fissuras antes da primeira cirurgia corretiva englobam um conjunto de aparelhos que vêm evoluindo há décadas (Georgiade *et al*., 1975; Grayson *et al*., 1993; Latham *et al*., 1976). Este manejo em recém-nascidos antes da cirurgia reconstrutiva do lábio traz benefícios clínicos como melhoria da morfologia facial, estética e da alimentação com resultados cirúrgicos futuros otimizados (Villarreal-Martínez *et al*., 2024).

Uma técnica proposta, no final da década de 90, por Grayson e Cutting (Grayson *et al*., 1999), a fim de amenizar a deformidade facial que caracteriza esta má formação, é o tratamento utilizando o modelador nasoalveolar (NAM). Nesta abordagem a moldagem dos bebês é feita o mais cedo possível após o nascimento e utiliza a expansão tecidual e os princípios de correção de deformidades nas cartilagens proposta por Matsuo e colaboradores (Matsuo *et al*., 1984). O tratamento com NAM, usado antes da cirurgia de lábio, tem por objetivo elevar o nariz, aproximar os segmentos alveolares e labiais, diminuindo o espaço da fissura, sem diminuir as medidas do arco maxilar. Estas modificações anatômicas ortopédicas buscam facilitar os procedimentos operatórios diminuindo a tensão entre os tecidos no momento do fechamento cirúrgico (Kinouche *et al*., 2018; Mustafa *et al*., 2023).

O protocolo completo do tratamento NAM, em sua versão convencional, consiste em um conjunto composto por placa de acrílico, acessórios nasais e fitas labiais (FIGURA 2). O protocolo dura em média 4 meses e em casos unilaterais, busca reduzir o tamanho da fissura e recuperar o colapso das estruturas nasais (Kapadia *et al*., 2020). Em casos de fissuras bilaterais, o tratamento NAM objetiva retrair e centralizar o segmento da pré-maxila, expandindo os segmentos alveolares e aumentar o tecido da columela considerado ponto crítico na reconstrução cirúrgica primária (Grayson *et al*., 1993). Todas as alterações anatômicas conseguidas neste

momento do tratamento ortopédico buscam diminuir as dificuldades na alimentação, reduzir a extensão da deformidade facial e facilitar o ato cirúrgico (Kinouche *et al*., 2018).

Figura 2 – Modelador nasoalveolar NAM convencional




Legenda: A - Placa de acrílico com um acessório nasal
B – Fita labial e placa de acrílico com um acessório nasal (instalados)
C – Placa de acrílico com dois acessórios nasais
D – Fita labial e placa de acrílico com dois acessórios nasais (instalados)

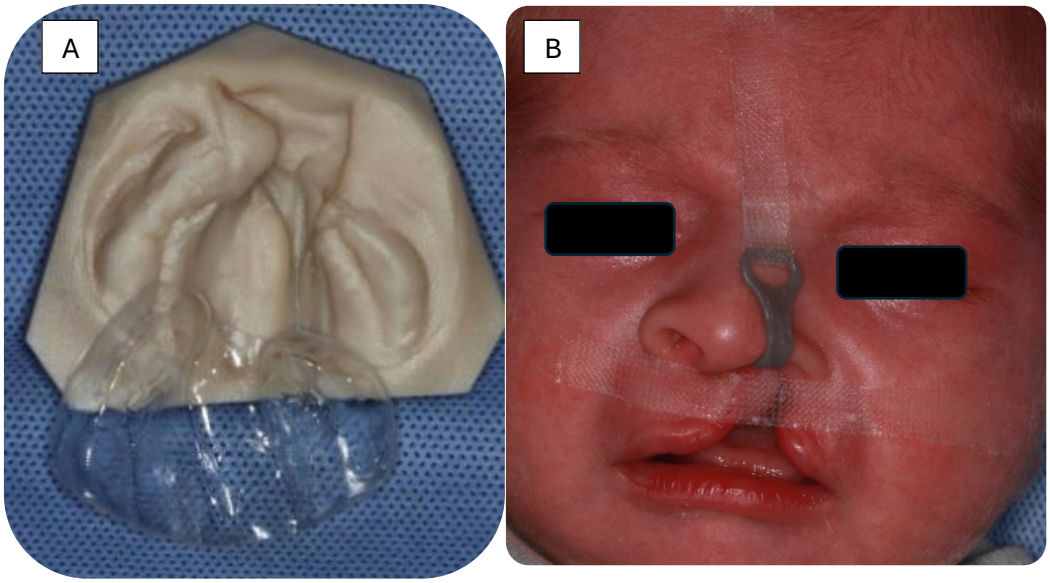
Fonte: Arquivo Projeto NAM-UFMG, 2021

A presença da fissura pode impactar na capacidade do bebê de se alimentar, levando a desafios durante o período de amamentação (Bessel *et al*., 2011). Embora a amamentação exclusiva seja difícil para essas mães, o uso da terapia NAM pode ser vantajoso, pois as placas favorecem uma melhor alimentação com mamadeira (María *et al.,* 2022).

Ferramentas digitais, como scaners ópticos especializados e impressão 3D, estão revolucionando o manejo pré-cirúrgico das fissuras, tornando-o mais eficiente e fácil de usar para as equipes e famílias (Villarreal-Martinez *et al*., 2024). Inconvenientes que dificultam a realização do tratamento com o modelador nasoalveolar convencional (placa de acrílico), como inúmeras consultas de controle e tempo maior de cadeira, têm sido otimizados (Ahmed *et al*., 2019). Essa nova versão de engenharia reversa do modelador nasoalveolar melhora a adesão da família ao

tratamento e diminui o número de consultas para ajuste. De fato, essa nova abordagem do NAM fornece um fluxo de trabalho digital que simplifica o atendimento ao paciente, eleva os padrões de resultados e facilita o compartilhamento e a pesquisa (Carter *et al*., 2023; Villarreal- Martinez *et al*., 2024) (FIGURA 3).

Figura 3 - Modelador nasoalveolar NAM Engenharia reversa




Legenda: A – Modelo de resina da maxila e placa de acetato para movimentação dos segmentos de rebordo
B – NAM Engenharia reversa instalado: acessório nasal, fita labial e placa de acetato.

Fonte: Arquivo Projeto NAM-UFMG, 2021

O tratamento NAM tem sido, nos últimos anos, bastante discutido em torno de sua eficiência, (Thakur *et al*., 2021) pois a carga de custos financeiros e de tempo dispendido, para pais e profissionais, na realização deste tratamento pré-cirúrgico, por vezes tem deixado dúvidas sobre sua validade (Alfonso *et al*., 2020). Embora haja frequentes debates sobre sua importância, a adoção quase global reflete seu valor (Villarreal-Martínez *et al*., 2024).

É reconhecido que a condição bucal da criança com fissura labiopalatina pode afetar a família (Aslan *et al*., 2018), refletindo nos campos emocional, econômico, psicossocial e comportamental. A reabilitação integral dos pacientes com fissuras requer também o acompanhamento das famílias (Francisco *et al*., 2021) e a avaliação do impacto da intervenção do tratamento NAM engenharia reversa e da cirurgia de queiloplastia, por meio de questionários, pode nortear os protocolos e abordagens (Al-Anazi *et al*., 2020).

Desta forma, o objetivo deste trabalho é a busca por evidências em torno da intervenção NAM na simetria facial/nasal, no impacto desta adversidade na família e revisar a literatura em busca de evidências disponíveis sobre ganhos em simetria nasal após cirurgia de queiloplastia, com e sem tratamento NAM.

# 2 OBJETIVOS

## 2.1 Objetivo geral da tese

Avaliar o efeito do NAM na simetria facial, nasal e maxilar, seu impacto psicossocial na família e ainda, revisar a literatura em busca de evidências disponíveis sobre ganhos em simetria nasal após cirurgia de queiloplastia, com e sem tratamento NAM.

## 2.2 Artigo 1

### 2.2.1 Objetivo geral

Avaliar a obtenção da simetria facial, maxilar e nasal em bebês fissurados submetidos e não submetidos ao tratamento ortopédico com modelador nasoalveolar.

### 2.2.2 Objetivos específicos

- Estabelecer para bebês recém nascidos, pontos de referências reproduzíveis para executar as medidas de comprimento do arco maxilar, largura do arco maxilar e ângulo do freio labial.
- Quantificar e comparar entre os grupos controle (sem tratamento ortopédico) e experimental (tratados com NAM), as medidas de perímetro do arco, comprimento do arco e ângulo do freio labial, utilizando modelos digitais em dois tempos: inicial e após uso do NAM.
- Estabelecer pontos faciais reproduzíveis para medir largura nasal, largura bucal e ângulo da columela, por meio de fotografias padronizadas.
- Quantificar e comparar entre os grupos controle e experimental, as medidas de largura nasal, largura bucal e ângulo da columela em dois tempos: inicial e após uso do NAM.

## 2.3 Artigo 2

### 2.3.1 Objetivo geral

Avaliar os efeitos adjuvantes da terapia NAM nos parâmetros de simetria facial pós-queiloplastia e seu impacto psicossocial por meio do questionário FIS.

### 2.3.2 Objetivos específicos

- Estabelecer para bebês recém-nascidos pontos de referências reproduzíveis para executar medidas de largura nasal, distância intercantal, largura da boca, distância interpupilar, ângulo da columela e área da narina
- Quantificar e comparar entre os grupos experimental (tratados com NAM) e controle (sem tratamento com NAM) as medidas de largura nasal, distância intercantal, largura da boca, distância interpupilar, ângulo da columela e área da narina, utilizando fotografias digitais padronizadas em dois tempos: antes e após cirurgia de lábio.
- Avaliar o impacto da fissura labiopalatina na vida familiar, por meio de questionário aplicado para pais/cuidadores.

## 2.4 Artigo 3

### 2.4.1 Objetivo geral

Avaliar o impacto do tratamento com modelador nasoalveolar na obtenção da simetria nasal em bebês fissurados após a queiloplastia.

### 2.4.2 Objetivos específicos

- Realizar buscas por publicações em todas as bases de dados e idiomas disponíveis até outubro de 2023, sobre a avaliação da simetria nasal obtida após a cirurgia de queiloplastia em pacientes fissurados que foram tratados com modelador nasoalveolar e que não foram submetidos a este tratamento.
- Realizar a extração de dados dos artigos selecionados.
- Realizar a análise de risco de viés nos estudos incluídos por meio da ferramenta ROBINS I.
- Verificar a possibilidade de realização de meta análise das medidas extraídas dos estudos incluídos.

- Avaliar a qualidade da evidência obtida nesta revisão sistemática e meta análise por meio da ferramenta GRADE.

# 3 METODOLOGIA EXPANDIDA

Incialmente, será descrita a metodologia comum aos três artigos que fazem parte desta tese. Em seguida, a metodologia específica para cada artigo será descrita.

## 3.1 Aspectos éticos

Este estudo foi submetido e aprovado pelo Comitê de Ética em Pesquisa da Universidade Federal de Minas Gerais (COEP-UFMG) sob protocolo número CAAE – 10111619.1.0000.5149 (ANEXO A).

Todos os pais/responsáveis pelos bebês participantes desta pesquisa assinaram o Termo de Consentimento Livre e Esclarecido (TCLE), autorizando a participação de seus filhos no estudo (APÊNDICE A). Embora tenham consentido, estavam cientes do direito de desistir a qualquer momento do trabalho.

## 3.2 Área de estudo

O estudo foi realizado na cidade de Belo Horizonte, no estado de Minas Gerais e na cidade de Curitiba, no estado do Paraná.

## 3.3 Universo

O universo do estudo foi constituído por bebês fissurados que procuraram atendimento no Projeto NAM da Faculdade de Odontologia da Universidade Federal de Minas Gerais e bebês fissurados agendados para realização de queiloplastia na Faculdade de Medicina da UFPR.

## 3.4 Desenho do estudo

Foi realizado um estudo do tipo ensaio clínico prospectivo nos artigos 1 e 2, de janeiro de 2017 a Junho de 2022. E ainda, uma revisão sistemática com meta-análise no artigo 3, recuperando publicações até Outubro de 2023.

## 3.5 Critérios de elegibilidade

### 3.5.1 Critérios de inclusão

- Bebês com fissura labiopalatina transforame unilateral, não sindrômica, com até 1 mês de vida, de ambos os sexos, em tratamento no Projeto NAM-FAOUFMG.
- Bebês com fissura labiopalatina unilateral não sindrômica, com até 1 mês de vida, de ambos os sexos, em acompanhamento na Faculdade de medicina da UFPR, não submetido a nenhum tratamento anterior a cirurgia de queiloplastia.

### 3.5.2 Critérios de exclusão

- Bebês portadores de síndromes ou cujos pais/responsáveis não assinaram o TCLE.

## 3.6 Plano amostral

### 3.6.1 Seleção da amostra

As amostras que constituem os grupos controle e experimental dos artigos 1 e 2 desta pesquisa são amostras de conveniência. Trata-se, no grupo experimental, de pacientes que procuraram o serviço de atendimento aos bebês fissurados, na Faculdade de Odontologia de UFMG. O grupo controle também é uma amostra de conveniência formada pelos bebês com cirurgia de queiloplastia programada pela Faculdade de Medicina da UFPR.

## 3.7 Coleta de dados

As coletas de dados foram realizadas no período de Janeiro de 2017 a Junho de 2022.

### 3.7.1 Coleta de dados não clínicos

As variáveis não clínicas foram obtidas por meio de questionário aplicado aos pais/responsáveis, quando estavam na sala de espera para atendimento dos bebês.

### 3.7.2 Coleta de dados clínicos

As moldagens e fotografias foram realizadas na primeira consulta, com idade do bebê com até 1 mês de vida, novamente, por volta do 6° mês de vida e, por último, com aproximadamente 1 ano de idade.

Para esta coleta de dados foi realizada uma moldagem de alta precisão da arcada superior do bebê com silicone de adição (ESPE XT, 3M Health Care, Minnesota, EUA) utilizando moldeiras pediátricas de acrílico. A seguir, os modelos foram digitalizados utilizando o software Orthoanalyzer (3Shape, Copenhagen, Dinamarca) e exportados no formato de arquivo estereolitográfico (STL).

Para coleta de dados fotográficos faciais, foram realizadas fotografias nas posições frontal e basilar, utilizando câmera com lente macro de 100 mm (Canon EOS Rebel T3i, Japão) Para a fotografia frontal a criança foi colocada no colo do responsável e a câmera foi fixada em um tripé e posicionada perpendicularmente à criança, a uma distância constante para todos os disparos (40 cm). Para a fotografia basilar, a câmera foi inclinada de forma que a ponta do nariz ficasse entre a linha da sobrancelha e a pálpebra superior e posicionada a uma distância constante para os disparos (40 cm).

## 3.8 Metodologia artigo 1

### 3.8.1 Elenco de variáveis

#### 3.8.1.1 Variáveis clínicas

As imagens digitais da maxila, obtidas pelo escaneamento dos modelos, foram orientadas de forma que o plano oclusal ficasse paralelo à tela do computador onde foi superposta uma tela milimetrada. As medições foram executadas por um mesmo dentista, treinado para este fim. Nos modelos digitais, as medidas realizadas foram:

- Perímetro do arco;
- Comprimento do arco;
- Ângulo do freio labial.

As medidas angulares e lineares nas fotografias foram realizadas através do software ImageJ (National Institute of Mental Health, Bethesda, Maryland, USA), executadas por um mesmo dentista, também treinado para este fim. Com o intuito de

minimizar possíveis erros em mensurações de estruturas tridimensionais de forma bidimensional, as medidas foram expressas em forma de razão. Nas fotografias, as análises realizadas foram:

- Largura nasal/comprimento intercantal;
- Largura bucal/distância interpupilar;
- Ângulo da columela;
- Área da narina;

### 3.8.2 Análise de dados

Os resultados foram apresentados na forma de média ± desvio padrão. A análise estatística das fotografias e dos modelos digitais foi conduzida utilizando-se o GraphPad Prism 8.0 software (GraphPad Prism Version 8.0 for Mac, La Jolla, CA, USA). Através do teste de normalidade Komogorov-Smirnof ficou demonstrado que os escores apresentavam distribuição simétrica. Os dados oriundos dos modelos digitais foram submetidos ao teste estatístico *t-student* ($P<0,05$), e os dados obtidos na análise das fotografias foram submetidos ao teste estatístico *one-way* ANOVA ($P<0,05$).

## 3.9 Metodologia artigo 2

### 3.9.1 Elenco de variáveis

#### 3.9.1.1 Variáveis clínicas

As variáveis clínicas obtidas no artigo 2 seguem a mesma metodologia descrita no item 3.8.1.1 na metodologia do artigo 1. Nas fotografias, as análises realizadas foram:

- Largura nasal/comprimento intercantal;
- Largura bucal/distância interpupilar;
- Ângulo da columela;
- Área da narina.

#### 3.9.1.2 Variáveis não clínicas

As variáveis não clínicas relacionadas ao impacto da condição bucal da criança fissurada na família foram obtidas por meio do questionário FIS (APÊNDICE B). O questionário *Family Impact Scale* (FIS) foi desenvolvido para aferir o impacto das condições bucais das crianças na família. O questionário é composto por 14 questões que devem ser respondidas escolhendo entre cinco opções de resposta em uma escala do tipo Likert: (nunca; uma ou duas vezes; algumas vezes; frequentemente; todos os dias ou quase todos os dias). A combinação de respostas específicas leva a uma pontuação total em 4 domínios: atividade dos pais/familiares, emoções dos pais/familiares, conflito familiar e encargos financeiros. As perguntas referem-se a um período pregresso de 3 meses. Uma pontuação mais alta significa um maior impacto da condição bucal da criança sobre a qualidade de vida dos pais. O uso deste tipo de instrumento no grupo de crianças com fissura labiopalatina tem por finalidade conhecer o impacto da abordagem NAM na qualidade de vida das famílias e poder auxiliar no planejamento dos cuidados e das intervenções clínicas.

### 3.9.2 Análise de dados

A análise estatística das fotografias foi realizada utilizando o software GraphPad Prism 8.0 (GraphPad Prism Versão 8.0 para Mac, La Jolla, Califórnia, EUA). Os dados foram representados por média ± desvio padrão (DP) e submetidos ao teste estatístico ANOVA a dois critérios ($P<0,05$) com pós-teste de comparações múltiplas de Tukey, ($P<0,05$). Foi realizada correlação de Pearson entre as variáveis.

Para o questionário, a análise estatística foi realizada com o Social Package for the Social Sciences (SPSS, versão 22.0, IBM Inc., Armonk USA). Estatística descritiva foi calculada. O teste de Shapiro Wilk demonstrou que os dados quantitativos (scores das subescalas e escores gerais do FIS) exibiram distribuição não normal. As comparações das pontuações gerais e das subescalas do FIS ao longo do tempo foram realizadas com o teste de Friedman. A diferença estatística foi fixada em $p<0,05$. As comparações dos escores da subescala e da pontuação geral do FIS entre os tempos foram realizadas com o teste de Wilcoxon. Foi aplicada a correção de Bonferroni e a diferença estatística foi fixada em $p<0,016$.

## 3.10 Metodologia artigo 3

### 3.10.1 Diretrizes

Esta revisão sistemática segue as diretrizes PRISMA, e um protocolo com o número de registro CRD 42023477752 foi registrado na base de registro de protocolos de revisões sistemáticas PROSPERO.

### 3.10.2 Critérios de elegibilidade

#### 3.10.2.1 Critérios de inclusão

Os trabalhos selecionados para esta revisão sistemática foram aqueles que compararam bebês tratados com NAM, com bebês não tratados com NAM, para desfechos de simetria nasal, após cirurgia de queiloplastia, nos tempos imediato e/ou a longo prazo. Os estudos incluídos foram ensaios clínicos, estudos observacionais originais (caso-controle, transversais e coorte). Estudos em qualquer idioma e data de publicação foram considerados até Outubro de 2023.

#### 3.10.2.2 Critérios de exclusão

Os critérios de exclusão foram estudos com dados insuficientes ou medidas heterogêneas, revisões narrativas, relatos de casos, diretrizes, declarações de consenso, editoriais, cartas, comentários ou resumos de conferências.

### 3.10.3 A pergunta PICO

A questão PICO foi assim elaborada:

P (população): pacientes com fissura labiopalatina
I (intervenção): Queiloplastia + NAM
C (Comparação): queiloplastia somente
O (desfecho): simetria nasal

### 3.10.4 Estratégia de busca

A estratégia de busca foi uma combinação dos termos MESH e palavras-chave unidos por operadores booleanos (*cheiloplasty* ***OR*** *cleft lip surgery* ***OR*** *cleft-lip surgery)* ***AND*** *(nasoalveolar molding* ***OR*** *NAM* ***OR*** *nasoalveolar moulding).*

As bases consultadas foram: Clinical Trials, Scopus, Web of Science, Cochrane Library, Embase e Pubmed.

### 3.10.5 Seleção de estudos

A seleção de estudos foi realizada seguindo 3 etapas:

- Identificação: Publicações identificadas por meio de pesquisa em bases de dados;
- Triagem: Realizada em duas fases. Na fase 1 foi feita a exclusão das duplicatas e leitura de título e resumo das publicações, por dois autores independentes. Na fase 2 foi realizada a leitura do texto completo dos artigos escolhidos na fase 1, pelos mesmos autores;
- Inclusão: Os artigos que preencheram os critérios de elegibilidade foram incluídos.

### 3.10.6 Extração de dados

Na fase de extração de dados, cada estudo selecionado foi alocado em uma tabela e as seguintes informações foram extraídas: último nome do primeiro autor, ano de publicação, país onde o estudo foi conduzido, desenho do estudo, número de participantes do grupo experimental (G1) e do grupo controle (G2), tipo de fissura labiopalatina avaliada, sexo e idade média dos participantes nos tempos avaliados, momentos de avaliação do desfecho, medidas objetivas realizadas na comparação entre os dois grupos e resultados das comparações dos desfechos entre os dois grupos.

### 3.10.7 Elenco de variáveis

#### 3.10.7.1 Variáveis clínicas

As medidas extraídas de cada estudo para avaliar a simetria nasal foram:

- **Altura da narina:** Distância do ponto mais alto da borda interna superior da narina até a linha da base alar;
- **Largura da narina** distância do ponto médio da superfície lateral da crista columelar até o ponto médio da borda interna da asa lateral;

- **Largura bialar** maior distância entre os pontos mais laterais da asa lateral;
- **Comprimento alar:** distância entre o ponto de inserção facial da base alar e o ponto pronasal;
- **Comprimento columelar:** distância ao longo da crista da columela entre a base da columela e o ponto pronasal;
- **Largura columelar:** maior distância laterolateral do ponto médio da columela.

### 3.10.8 Avaliação do risco de viés

A avaliação do risco de viés foi realizada em cada estudo individualmente, empregando a ferramenta ROBINS-I. Este instrumento contém sete critérios avaliados em três domínios; Pré-intervenção, na intervenção e pós-intervenção. No domínio *Pré-intervenção* foram avaliados os critérios: confundidores e selecionando participantes para o estudo. No domínio *Na intervenção* foi avaliado o critério: classificando as intervenções. Por fim, no domínio *Pós-intervenção* foram avaliados os critérios: desvios da intervenção pretendida, dados faltantes, medindo resultados, selecionando resultados relatados.

### 3.10.9 Meta-análise

Para realização da meta análise, os dados dos estudos metodologicamente homogêneos foram agrupados em meta-análises de desfechos contínuos. Foram utilizados média, desvio padrão (DP) e tamanho da amostra. Nos artigos em que foram fornecidos mediana, mínimo e máximo, a média e o Desvio Padrão foram calculados com as seguintes equações:

$$Mean = \frac{minimum + (2\ x\ median) + maximum}{4}$$

$$SD = \frac{maximum - minimum}{4}$$

Os resultados das meta-análises foram apresentados em diferença média padronizada (SMD) e intervalo de confiança (IC) de 95% (HIGGINS et al., 2023). Em todas as meta-análises foi utilizado o modelo de efeito aleatório. A inconsistência foi medida com $I^2$.

### 3.10.10 Avaliação da evidência

As evidências obtidas nesta pesquisa foram avaliadas por meio do instrumento GRADE. Esse sistema atribui níveis de evidência e classifica a força da recomendação para questões em saúde, representando a confiança na informação obtida. Neste sistema, é possível verificar o grau de recomendação de um tratamento.

## 4 ARTIGO 1

Artigo publicado no periódico *The Journal of Craniofacial Surgery*

### The effects of NAM on the symmetry of the face and maxillary arch in Babies with unilateral cleft

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**Abstract:**

The study aimed to evaluate the effect of nasoalveolar molding (NAM) therapy through reverse engineering, or its absence, to obtain symmetry of the face and maxillary arch. Twenty-six babies with unilateral cleft lip and palate received treatment with NAM, and 12 babies with unilateral cleft lip and palate without presurgical orthopedics (control group). Patients were molded and photographed in 2-stages: the first month of life (T1/pre) and after the use of NAM/before the cheiloplasty (T2/post). In the digital models, the analyses performed were arch perimeter, arch length, and labial frenulum angle. The photographs allowed us to analyze nasal width, mouth width, columella angle, and nostril area. The results demonstrated that there was an increase in arch perimeter and arch length in control and NAM groups in the T2 period in comparison to T1. Labial frenulum angle was reduced in the NAM group compared to the NAM-T1 and control-T2 periods. Treatment with NAM yielded a reduction in nasal width in the period of T2 compared with T1. Columella angle was enhanced after NAM use in T2 and, was different from control group. The nostril area was reduced in the NAM group in T2 compared with control group. Nasoalveolar molding therapy reduced the labial frenulum angle, contributing to a reduction in the extension of the cleft. The NAM protocol improved facial symmetry, mainly through nasal effects, whereas the absence of orthopedic therapy yielded a commitment to the face and maxillary arch symmetry.

**Keywords:** Arch length, arch perimeter, cleft lip and palate, facial symmetry, nasoalveolar molding

## Introduction

Patients with unilateral cleft lip and palate (UCL/P) have anatomical changes in the nose and maxilla, in the trans verse, sagittal, and vertical planes.1 Abnormal nasal morphology with alar width inclination and columella tissue deficiency is a common condition that can compromise the results of first repair surgery.2 Seeking better bone and cartilage relationships before surgical intervention is highly desirable. Since the 1950s, different techniques have been presented to bring soft and hard tissue closer together.3,4 The nasoalveolar molding (NAM) technique is a treatment modality described by Grayson et al,5 which seeks to alleviate asymmetries and cleft severity before surgery6–8 while promoting important modifications on immature nasal cartilage, taking advantage of its malleability.9,10 The clinical benefit of NAM therapy is hotly debated.11–15 The diversity of study models, evaluation times, size and heterogeneity of the samples, different protocols performed, and poorly detailed descriptions of the methods make it difficult to safely evaluate studies that use the NAMprotocol.13Amongthemethodsusedby studies to assess the effects of NAM therapy are the use of 2 dimensional images,7,10,14,16,17 and even 3-dimensional records.18–24 Results of the studies have shown improvement in the aesthetics of the nose, lip, alveolar bone, palate, and nasal wings.14 In addition, NAM therapy has been shown to decrease surgical scars associated with columella reconstruction.25 Treatment with NAM seems to be a promising tech nique3,12,15,26,27; however, there is a lack of studies with methodological consistency comparing treated and nontreated patients that may confirm its benefits. Therefore, this study aimed to evaluate the effectiveness of NAM reverse engineering therapy, and the consequences of its absence, in patients with UCL/P through the conformation of the maxillary arch and facial symmetry in comparison to babies with UCL/P without presurgical orthopedics.

## Methods

In this prospective trial from January 2017 to June 2022, patients with UCL/P treated with NAM reverse engineering therapy associated with lip taping technique and nasal stent (NAM group) were compared with nontreated patients (control group) (Fig. 1). Nasoalveolar molding group consisted of 26 patients from both sexes (18 boys and 8 girls), aged up to 1 month, presenting no syndromic UCL/P, with scheduled cheiloplasty

surgery. All participants were from a convenience sample, derived from the population undergoing treatment/follow-up by the NAM project from the Faculty of Dentistry, Federal University of Minas Gerais, Brazil. The control group comprised 12 nonsyndromic babies of either sex (7 boys and 5 girls) with UCL/P and about 1 month of age without presurgical orthopedics and/or lip taping technique and nasal stent from the Plastic Surgery Unit, Department of Surgery, School of Medicine, Federal University of Parana (UFPR), Brazil. This study is following the Declaration of Helsinki and was approved by the Research Ethics Committee from the Federal University of Minas Gerais and the Federal University of Paraná. Parents/guardians of eligible children were invited to participate in the research and instructed about the treatment, acceptance being granted by signing an informed consent form. Patients were molded and photographed in 2 stages: the first month of life (T1—pre/Initial) and after the use of NAM therapy or before the cheiloplasty (around 6 months of age) (T2— post).

*Children With UCL/P Without Presurgical Orthopedics and/or Lip Taping Technique and Nasal Stent—Control Group*

The maxillary arch impressions were taken during the aforementioned periods and the plaster models were scanned using a high-sensitivity 3D sensors machine (Ceramill Map 400 þ) and exported using the stereolithographic file format (STL). Treatment With NAM Using the Reverse Engineering Technique Associated with Lip Taping Technique and Nasal Stent—NAM Group For the manufacture of plates used in the reverse engineering NAMprotocol,28 in the first visit, a highly accurate impression was performed on the upper arch of children with additional silicone (ESPE XT, 3M Health Care) using acrylic pediatric trays. This treatment time was defined as T1 (pre). After molding, virtual models exported using the STL were obtained through digital scanning using the Orthoanalyzer software (3Shape, Copenhagen, Denmark) for making the NAM plates. In these models, the fabrication of the devices was conducted to gradually approximate the alveolar bone segments.

Upon receiving the plates, those responsible were carefully instructed as to their use and weekly changes. To help close the cleft, 6 mm×100 mm tapes (Micropore, 3M Health Care) were installed on the upper lip, below the alar width, joining the 2 segments affected by the cleft, since the beginning of therapy (T1—pre). A nasal stent with tape support on the child’s forehead was incorporated at the start of treatment. After the use of the plates, and before cheiloplasty surgery, new molding and scanning

procedures were performed to verify the success of the treatment. Treatment time was called (T2—post).

*Analysis of Digital Maxilla Models*

To assess the maxillary changes, the digital models were measured and the parameters analyzed were: the perimeter and length of the maxillary arch and, the angle of the labial frenulum (LF) with the midline of the maxilla. The images obtained from the models were oriented so that the occlusal plane was parallel to the computer screen where a millimeter screen was superimposed so that measurements could be performed. To perform these measurements, the following reference points were established: LF—point corresponding to the center of the edge at the level of the LF, right posterior point (RPP)—most posterior point in the center of the right-side edge, left posterior point (LPP)—most posterior point in the center of the left-side edge, posterior center point (PCP)—point that corresponds to half the distance between the RPP and LPP points (Fig. 2). From these reference points, the following measures were taken: (1) arch perimeter (AP): size in millimeters (mm) of the line that goes around the entire edge from RPP to LPP, passing through the center of the edge; (2) arch length (AL): distance (mm) between the LF and PCP points; (3) angle of the LF with the midline of the maxilla: angle (degree) formed between the line of the AL (LF and PCP) and the posterior line of the ridge (RPP and LPP), on the cleft side (Fig. 2).

*Photographic Analysis of Facial Symmetry*

A limitation of the NAM protocol is the need for frequent visits to the pediatric dentist clinic during treatment.24 In this study, we had understandable absences of 8 patients because of the distance from where they lived, which caused the non-acquisition of the facial photographs (Fig. 1). The evaluation of changes in facial symmetry was performed through photographs in frontal and basilar positions, using a camera with a 100 mm macro lens (Canon EOS Rebel T3i, Japan). The child remained on the guardian’s lap and the camera was fixed on a tripod at a constant distance for all shots (40 cm). The camera was positioned perpendicular to the child for the frontal photo. For basic photography, the camera was positioned so that the tip of the nose was between the eyebrow line and the upper eyelid. The following measures were taken: (1) columella angle (CA): the angle formed between the nasal reference line (the line connecting the left and right alar width) and the line that passes through the center of

the columella, starting at the alar width to the apex of the nose, measured on the side affected by the cleft; (2) nasal width (NW)/intercanthal length ratio: the ratio between the nasal reference line and the mean between the left and right eye widths; (3) mouth width (MW)/interpupillary distance ratio: the ratio between the distance of the 2 labial commissures and the distance between the centers of the ocular pupils (Fig. 3). In addition, the nostril orifice of the NAM group was marked carefully with digital ballpoint, and area measurement was automatically calculated. Angular and linear measurements and nostril area (NA) in the photographs were performed using the ImageJ software (National Institute of Mental Health), performed by the same dentist, and trained for this purpose. To minimize possible errors in measurements of 3-dimensional structures in a 2-dimensional manner, the measures were expressed in the form of ratio.2

**Statistical Analysis**

Statistical analysis of photographs and digital models was conducted using the GraphPad Prism 8.0 software (GraphPad Prism Version 8.0 for Mac, La Jolla, CA). The data were represented by mean± SD and submitted to the 2-way ANOVA statistical test ($P<0.05$) with Tukey's multiple comparison posttest, and *t* test ($P< 0.05$). Pearson correlation was performed among the variables.

**Results**

There was good adherence and acceptability of the protocol by the families in the treatment with NAM. The average length of treatment with NAM was 4.88 months. In this research, there was no adversity or damage to the studied patients. The analysis of the digital models to verify changes in the maxillary arch showed the following results:

- Arch perimeter: There was no significant difference between the control and NAM groups within the same period. A significant increase in perimeter was exhibited in the T2 period (post control: 75.97 mm±6.963 mm; post NAM: 76.61 mm±5.888 mm) compared with T1 (pre control: 65.53 mm±3.749 mm; pre-NAM: 70.26 mm± 4.895 mm) in both groups (an increase of 10.44 mm for control group, and 6.35 mm for NAM group), as seen in Figures 4A, B.
- Arch length: The AL of the NAM group was statistically enhanced compared with control group in the T1 period (Figs. 4A, B). Figures 4A and B shows a significant

increase in the length of the maxillary arch in T2 (post control: 27.23 mm±2.901 mm; post-NAM: 27.44 mm±2.734 mm) compared with T1 (pre control: 22.34 mm±1.826 mm; pre-NAM: 24.71 mm±2.185 mm) in both groups. There was an increase in the AL of 4.89 mm for the control group and 2.73 mm for the NAM group in the T2period compared to T1.

- The angle of the LF with the midline of the maxilla: The LF angle (LFA) was similar between control and NAM groups in the T1 period (pre-control: 106.4±7.166 degree; pre-NAM: 101.5±8.05 degrees) (Figs. 4A, B). The post-NAM group (T2) exhibited a significant reduction of 6.7 degrees in the angle of the LF with the midline of the maxilla compared to the pre-NAM group (T1) (pre-NAM: pre-NAM: 101.5±8.05 degree; post-NAM: 94.80±5.426 degrees), with no difference between the pre-control and post control groups (reduction of 2.1 degrees in post control group). There was a significant reduction of 9.5 degrees (reduction of 9.1%) between the post control (104.3±5.855 degrees) and post NAM(94.80±5.426 degrees) groups in the T2 period. There was a positive correlation between the LFA and the AL of the maxilla in the period T2 period (Fig. 4C).

The facial symmetry was analyzed and the photographs demonstrated the following results:

- Nasal width/intercanthal length ratio: nasal width was similar between pre-control and pre-NAM groups (pre control: 1.45 mm±0.1818 mm; pre-NAM: 1.506 mm±0.1373 mm) (Figs. 5A, B). Post-NAM (T2 period) group showed a significant reduction in the NW/intercanthal length ratio compared with pre-NAM (T1 period) (pre-NAM: 1.506 mm±0.1373 mm; post-NAM: 1.387 mm±0.093 mm). However, no significance was verified between post control and post-NAM groups (post control: 1.379 mm±0.093 mm; post NAM: 1.387 mm±0.1588 mm) (Figs. 5A, B).
- Mouth width/interpupillary distance ratio: No significant changes in MW/interpupillary distance were verified between groups and periods (Figs. 5A, B) (T1, pre-control: 0.8233 mm±0.059 mm; pre-NAM: 0.7641 mm±0.078 mm; T2, post control: 0.8032 mm±0.0815 mm; and post-NAM: 0.8055 mm±0.072 mm). Columella angle: the angle was similar between pre control and pre-NAM groups (pre-control: 37.48±5.056 degree; pre-NAM: 42.31±8.556 degree) (Figs.

5C, D). As seen in Figures 5C, D, the NAM treatment caused enhancement of the CA to a more vertical position in the T2 (post) period compared with T1 (pre) (pre-NAM: 42.31±8.556 degree; post-NAM: 56.58±9.918 degree). The CA was significantly increased in the post NAM group compared with post control (post control: 41.83±5.429 degrees, post-NAM: 56.58±9.918 degrees) (Figs. 5C, D).

After verifying the clinical improvement of the CA with NAM therapy through reverse engineering, the NA of the NAM group was analyzed. No difference was verified in the NA of the noncleft side comparing pre-NAM (T1) and post NAM periods (T2) (Figs. 6A, B). However, it was demonstrated a decrease in the NA on the post-NAM-cleft side in comparison to the pre-NAM-cleft side (Figs. 6A, B). The NA of the cleft side was enlarged concerning the noncleft side in the pre (T1) and post (T2) periods compared to the noncleft side (Fig. 6C).

No correlation was exhibited in the facial parameters in the T2 period (post) (Supplemental Fig. 1, Supplemental Digital Content 1, http://links.lww.com/SCS/F110). In the NAM group at the post period (T2), a positive correlation in the maxillary arch parameters was shown between the angle of the LF and the AL (Supplemental Fig. 2, Supplemental Digital Content 2, http://links.lww.com/SCS/F111). Also, in the same group and period, a negative correlation was exhibited between the LFA (maxillary arch parameter) versus CA (facial parameter), and negative correlation was verified between the MW and the AL and AP parameters (Supplemental Fig. 3, Supplemental Digital Content 3, http://links.lww.com/SCS/F112).

## Discussion

Surgical treatment of patients with cleft lip and palate is challenging.2 In addition to nasal asymmetry and cleft lip, the maxillary alveolar structure may also be split. The repair of these tissues by primary nonsurgical intervention is a great opportunity to deconstruct the stigma that cleft lip and palate may produce. The idea of using presurgical orthopedics is to improve the symmetry of the upper arch5 and enhance the symmetry of the immature nasal cartilage through nasal stents before the primary surgery.10,30 In this context, the evaluation of the changes that the NAM protocol promotes, or the con sequences of its absence, in nasal and maxillary symmetry seeks to confirm its importance, providing evidence for choosing the best treatment available

for the child with a cleft. This study found that the treatment with NAM through the reverse engineering technique yielded maxillary and facial growth effects towards better symmetry in patients with complete UCL/P. The treatment provided improvement in the maxillary arch, allowing its adequate growth with an increase in the perimeter and length of the arch, as well as a reduction in the angle of the LF concerning the midline of the maxilla. Treatment with NAM provided prominent balance on the face as perceived through the significant increase in the CA, reduction in the NW /inter canthal length ratio, and decrease in the NA. The babies without NAM therapy exhibited similar growth patterns although with a strong commitment to the LF and CAs in their first 6-month of life.

Arch perimeter is considered one of the most important parameters for orthodontic diagnosis and treatment planning.31 It is defined as the distance from the mesial surface of the first permanent molar around the dental arch to the same point on the opposite side. In this study, using the widths of this concept, we made an analogy to the dental AP to analyze the dimension and changes that occurred in the alveolar arch of babies with cleft lip and palate who used NAM as an early treatment. The maxillary AP, assessed using digital models, showed an increase after NAM therapy. This increase can be attributed to the continuous growth of the alveolar ridges, guided by the forces exerted by the devices of this therapy. This result corroborates with some studies found in the literature,31,32 which demonstrated an increase in the AP in this phase.

Guided by the concept of AL, as a line that starts on the palatal surface of the central incisor, passing through the palatine raphe until it finds an imaginary line perpendicularly, that passes through the mesial surface of the first permanent molars, this measurement was performed in babies. Fitting this imaginary line to the most posterior point of the ridge on the left and right sides, the length of the arch was measured. Thus, changes in the size of the maxillary arch were evaluated, in the Antero posterior direction, in babies with a cleft but not treated with NAM and before and after NAM therapy. Our study demonstrated a significant increase in this measure, which disagrees with the findings by Khateeb et al,31 who observed a decrease. This increase can be attributed to the large growth observed in the alveolar arches at this stage of childhood, and an increase in this measure is desirable for a therapy that guides growth without impeding the normal development of facial structures.32 Further

prospective studies are needed to clarify AL behavior during the active phase of the NAM protocol.

In the angle of the LF concerning the midline of the maxilla, a significant decrease was seen in this measure, showing a de crease in the width of the cleft. This dimensional change is particularly important when considering the difficulties encountered in bringing the ridge segments together, especially during surgical repair procedures.4,15 These improvements re duce the perception of cleft severity, creating, especially among parents and caregivers, a more optimistic image of adversity, such as greater adherence to treatment.16 Other authors have also reported a reduction in this measure, in varying amounts, probably due to factors such as cleft severity or age at treatment initiation.7,33 Uprighting and increasing the extension of the columella before the lip repair surgery favors the surgical procedure, offering better surgical results.4,5 The findings of this study corroborate with other studies,7,31 showing; however, small quantitative discrepancies, probably due to differences in methodologies.

This study demonstrated that children who received NAM therapy obtained significant improvement in nasal symmetry. There was a reduction in the width of the nose with values that approached the intercantal width and a reduction of the NA of the cleft side, which is desirable in a harmonic face. This significant reduction in the size of the slit-side nostril, width, is in line with the findings of other researchers7,33 that met the goals of this therapy. The use of nasal stents also modifies this immature alar cartilage,30 contributing to the success of the therapy. The verticalization of the columella and the significant reduction in the angle of the LF with the midline of the maxilla, observed in the analyzes of this study and other investigations,7,18 show a decrease in the width of the cleft lip and palate and can help reduce the number of soft tissue surgery revisions and grafts. These findings have a positive impact on surgical repair surgery. In this study, we evaluated the changes that occurred in structures markedly affected by the cleft, such as the nose, lip, and maxilla. The babies with UCL/P and not treated with orthopedic therapy had jeopardized facial symmetry. Quantitative changes were observed in these structures, showing a deficient nasal verticalization and width reduction of the cleft in the maxillary arch. Facial symmetry was achieved by NAM therapy and these changes improved facial esthetics, reducing the stigma of the patients with a cleft.16 The distance between the labial commissures must present, in

a harmonic face, the same values of the interpupillary distance, and when placed in the ratio form, they must approach the number 1.34 In this study, the treatment with NAM therapy or its absence did not show significance in this measure. These results are positive because of the reduction of the cleft in the lips and alveolar bone did not affect the width between the labial commissures, which would be an undesirable effect of this treatment.

The clinical benefits of therapy are widely discussed among re searchers and clinicians,3,13,26,27 and NAM is often associated with a positive change in nasal esthetics and decreased cleft width.16,23,29 In the present study, measurements of the maxilla and soft tissue structures of the face showed significant improvements in the treatment of patients with clefts. The reverse engineering technique overcame an important limitation when compared to conventional NAM therapy: by delivering all the devices in a single consultation, so that they can be installed by the parents, the patient avoided the weekly visits for care, which had always been a difficulty in complying with the treatment. The results of the present study are useful to reinforce the importance of NAM therapy with professionals who develop treatment strategies in terms of aesthetic, anatomical, and functional aspects. A consensus among researchers around the methodology, such as standardizing measurement times and outcome variables, may bring greater consistency to the evidence regarding the benefits of the NAM protocol, offering further improvements in this therapy and a greater understanding of its strengths and limitations.

In agreement with our results, a previous study demonstrated that UCL/P babies had a significant spontaneous palatal narrow with no intervention performed.35 Although this study did not measure the cleft gap and arch width in nontreated babies, such as Pontes et al,35 our results demonstrate that the orthopedic apparatus allowed the normal maxillary growth of the palate of the cleft babies with the increase in the AP and length.

Studies have analyzed the maxillary arch and soft tissue features morphology of children with cleft lip and palate.36–38 Agell Sogbe et al38 compared patients with UCL/P who underwent presurgical orthopedics with UCL/P with no presurgical intervention and cheilorhinoplasty. The cleft distance and maxillary width (anterior, medium, and posterior) were measured, but not facial parameters. Both, surgery and orthopedics procedures allowed the closure of the cleft at different sites.38 Hood et

al36 analyzed unilateral cleft lip (UCL) and UCL/P before primary surgery and compare them with noncleft control group using 3 dimensional stereophotogrammetry (C3D) system. Facial parameters, such as nostril dimensions, alar wing angulation, CA, and alar base to corner of mouth dimension; alar base width; and soft tissue defect in nose and the lip and philtrum length bordering the cleft, but not maxillary arch parameters. The use of C3D system facilitated the standardization of facial parameters before surgery and during follow-up. Duffy et al37 verified the facial surface of UCL/P compared with noncleft patients. The interocular width, nose base width, MWs, and nose base/MW ratios were increased in the UCL/P group; however, no maxillary arch measurements were performed. Our study showed that a negative correlation was verified between the MW and the AL and AP parameters. This study was the first to correlate facial parameters with maxillary arch dimensions. Limitations to this study include the lack of a 3D facial analysis that could be a source of concern when claims of enhanced results. The authors strongly believe that future studies using the same approach are needed with 3D techniques.

## Conclusions

Early nonsurgical NAM treatment through the reverse engineering technique did not interfere with the growth of the perimeter and length of the alveolar arch of UCL/P babies, allowing normal development of this structure. It also improved the LFA, NW, and CA of the nose. Nasoalveolar molding proved to be effective, promoting maxillary symmetry and improving nasal symmetry, which makes the face more harmonious. The absence of orthopedic therapy yielded no consequences for the growth process although had caused commitment to the face and maxillary arch symmetry.

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**Figure 1 –** Consolidated Standards of Reporting Trials (CONSORT) flow diagram. NAM indicates nasoalveolar molding; UCL/P, unilateral cleft lip and palate.

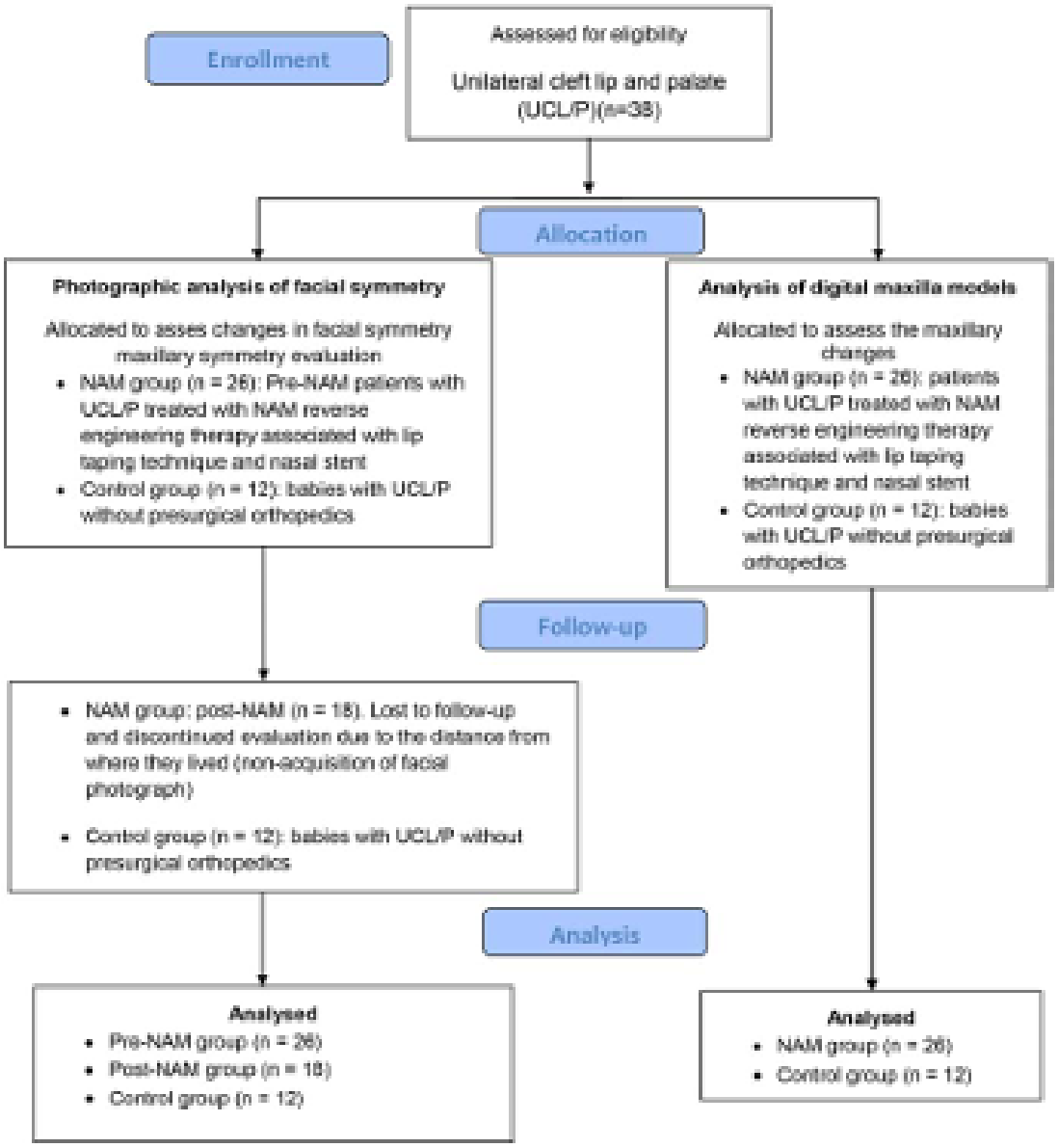


**Figure 2 –** Digital models analysis. (A) Arch perimeter (mm). (B) Arch length (mm). (C) Angle of the labial frenulum with the midline of the maxilla. LF indicate labial frenulum; LPP, left posterior point; PCP, posterior center point; RPP, right posterior point.

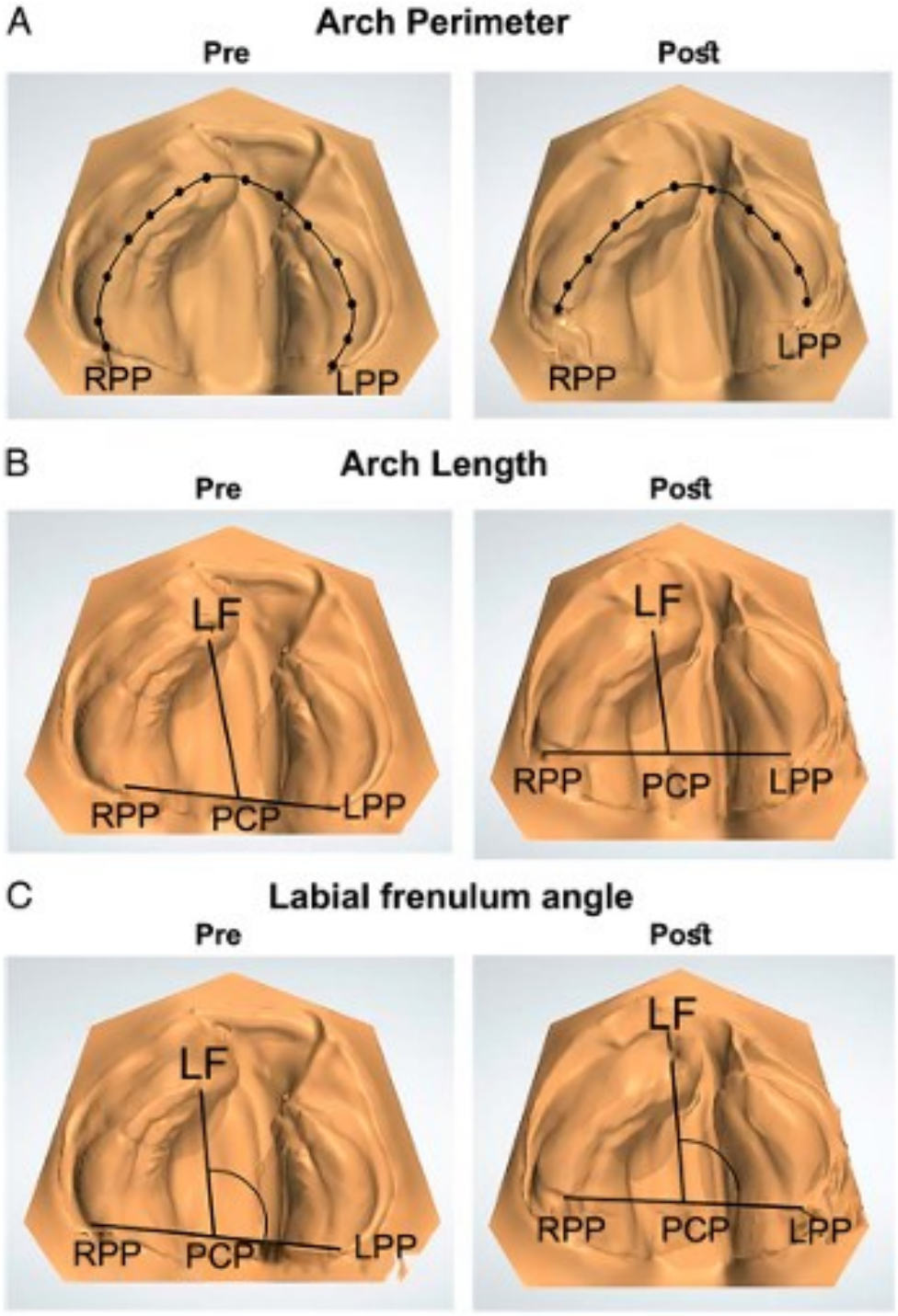


**Figure 3 –** Photographic analysis. (A) Nasal base/intercantal lenght ratio measure. (B) Mouth width/interpupillary distance ratio. (C) Columella angle measurement.

**Figure 4 -** The analysis of the digital models to verify changes in the maxillary arch. Two-way Analysis of Variance (ANOVA) statistical test (P<0.05) with Tukey's multiple comparison posttest. Pearson correlation. NAM indicates nasoalveolar molding. *Different from Pre period. +difference between Control and NAM groups.

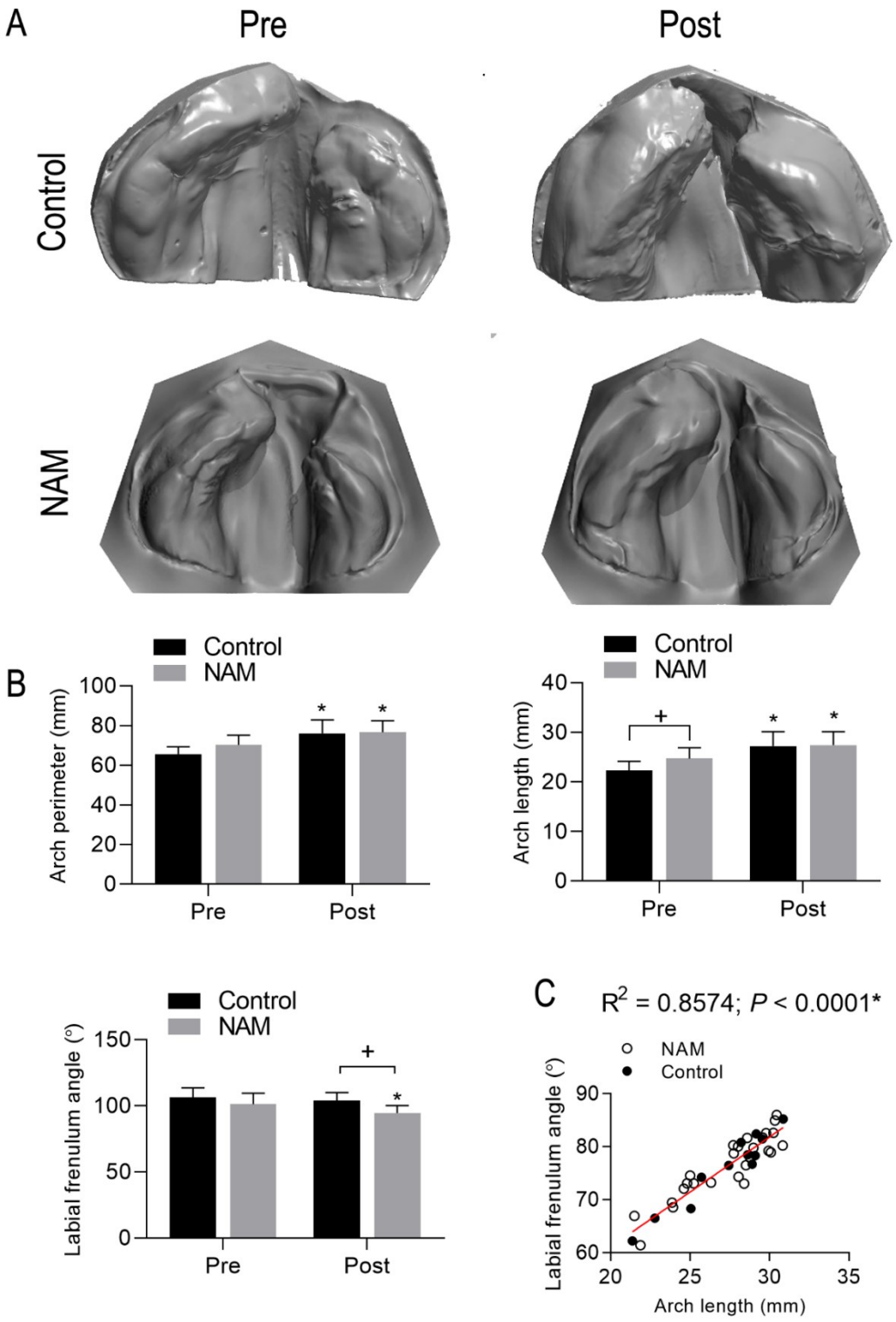


**Figure 5 –** The analysis of the facial symmetry using photographs. Two-way Analysis of Variance (ANOVA) statistical test (P<0.05) with Tukey's multiple comparison posttest. NAM indicates nasoalveolar molding. #different from Pre period. *Difference between Control and NAM groups.

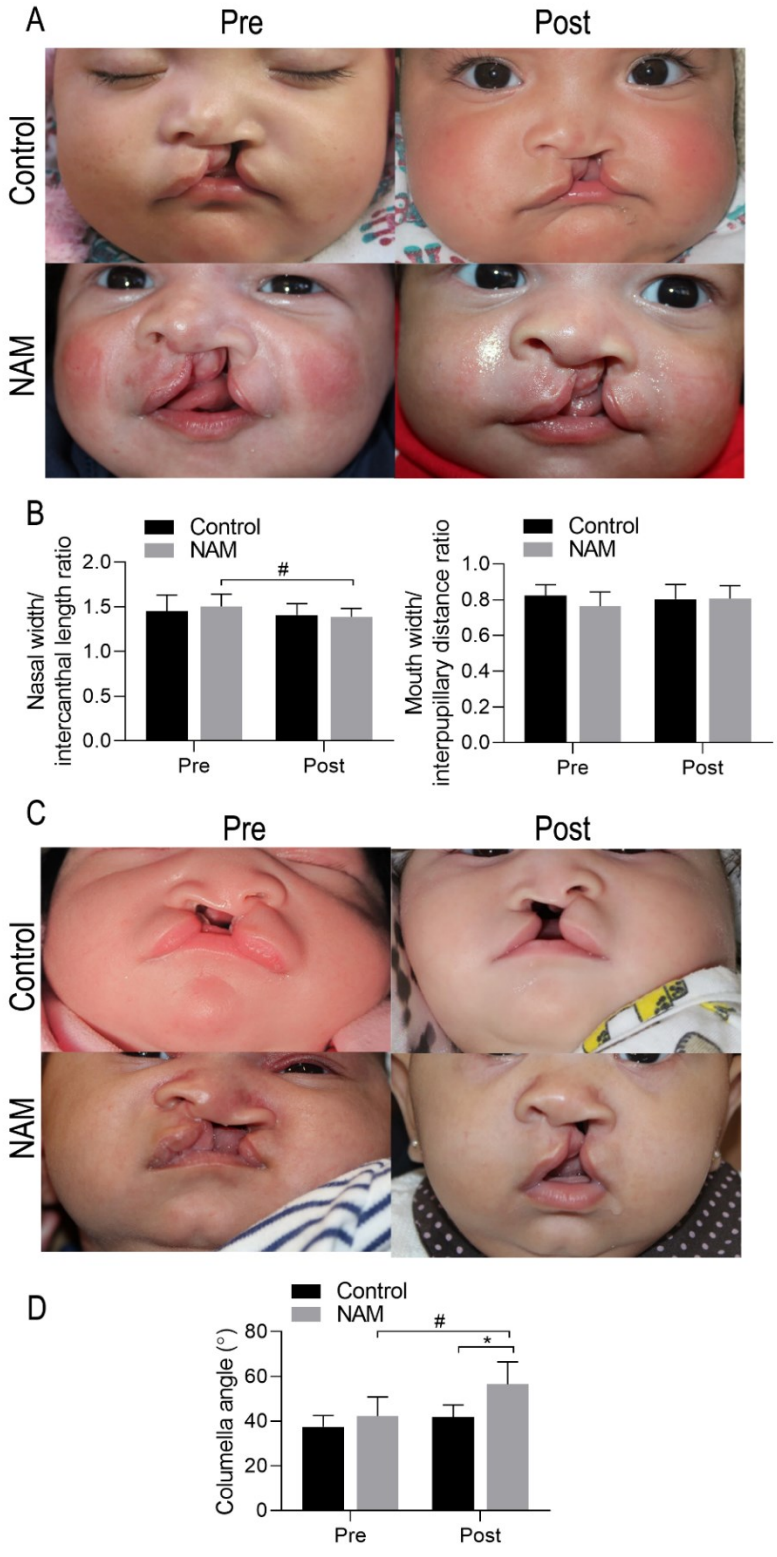
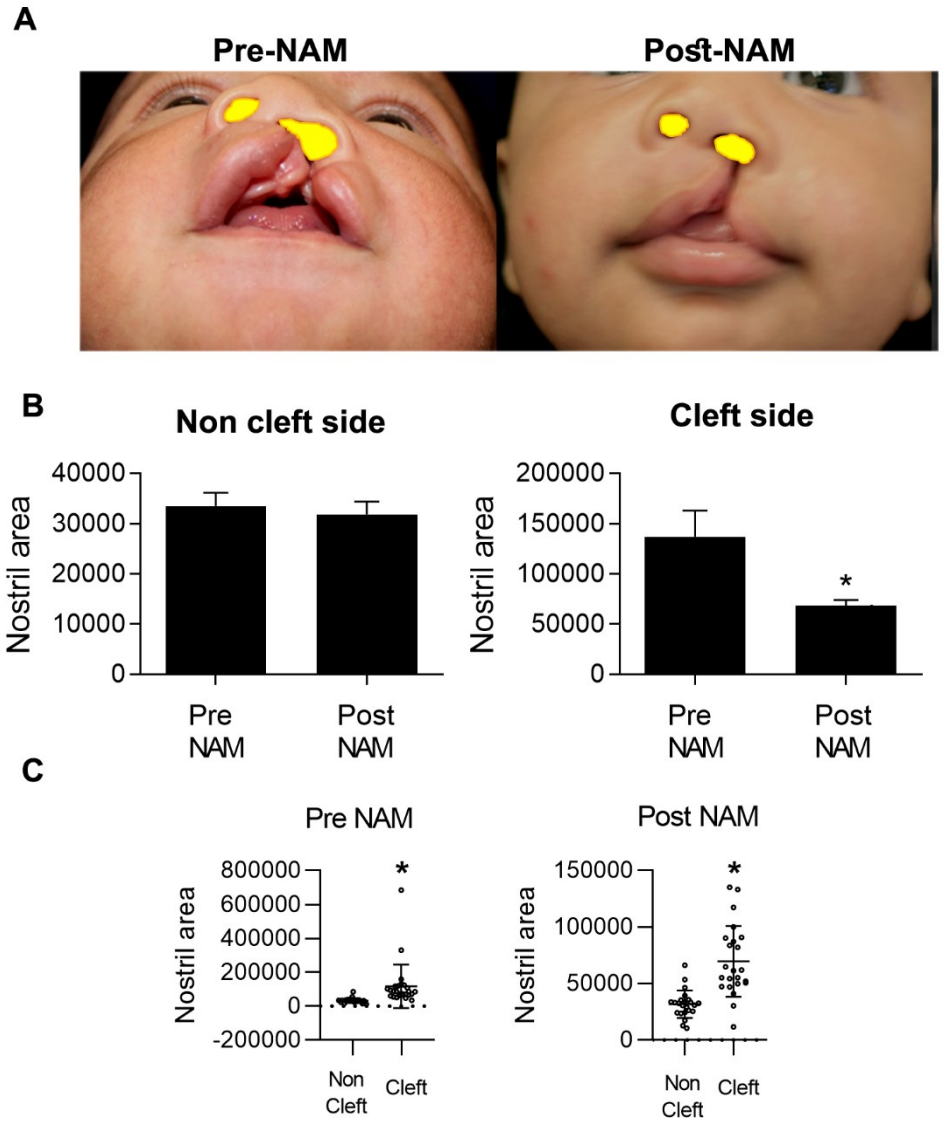


**Figure 6 –** The analysis of the nostril area. One-way Analysis of Variance (ANOVA) statistical test (P<0.05) with Tukey's multiple comparison posttest. NAM indicates nasoalveolar molding. B: *different from Pre NAM period. C: *difference between Non-Cleft and Cleft sides.



## 5 ARTIGO 2

Artigo submetido e sob revisão no periódico *International Journal of Oral & Maxillofacial Surgery*

# Psychosocial impact on families and NAM facial effects of babies with unilateral cleft lip and palate after using NAM and cheiloplasty

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**Abstract**

The study focused to assess the adjunctive effects of NAM therapy on facial symmetry parameters post-cheiloplasty and its impact on family's quality of life. Twenty-six unilateral cleft lip and palate (UCLP) patients undergoing NAM therapy were compared with 12 untreated UCLP infants undergoing cheiloplasty. Parents/caregivers of the UCLP patients treated with NAM and cheiloplasty self-completed the Family Impact Scale (FIS) to measure the impact of oral conditions on family's quality of life. Pre- and post-cheiloplasty photos were taken, and statistical analyses were conducted. Positive correlations between facial parameters were noted, with the NAM group showing reduced nasal width/intercanthal distance ratio post-treatment. The NAM group exhibited a reduction in the nasal width/intercanthal distance ratio post-NAM therapy and cheiloplasty compared to pre-treatment. Mouth width/interpupillary distance and increased columella angle showed significant changes in the NAM group post-surgery. However, no difference in the non-cleft side nostril area was observed, yet a reduction in the cleft side nostril was noted post-NAM treatment. The FIS questionnaire evaluation revealed significant differences overall FIS score ($p$=0.042), initially with higher parental emotions scores (P = 0.008). NAM therapy benefits UCLP treatment, with notable improvements in post-cheiloplasty outcomes and in the impact on family's quality of life.

**Keywords:** Cleft lip and palate; Nasoalveolar molding; Cheiloplasty; Quality of life indicators

## Introduction

Cleft lip and palate are the most frequent congenital malformations of the head and neck, affecting 1 in every 1,924 live births in Brazil[1] and an average of 1 per 700 newborn births worldwide[2]. Cleft lip and palate often occur simultaneously in the form of complete unilateral (UCLP)[3] or bilateral cleft lip and palate (BCL/P)[4]. Individuals with cleft lip and palate present several anatomical, esthetic, functional (suction, breathing, speech, chewing and swallowing) and dental disturbances, directly related to the extent and type of cleft, besides psychological disorders, and difficulties in social relationships [5]. In cases of UCLP, the affected side exhibits a widened nostril base and a gap between the lip segments. The lower lateral nasal cartilage, which is affected by the cleft, is displaced outward and downward, resulting in a depressed nasal tip, a slanted columella, an apparent widening of the nasal wing, and a protruding nostril. When the cleft palate is also present, the nasal septum deviates towards the non-cleft side, causing a shift in the position of the nasal base[6].

Individuals with cleft lip and palate undergo an extensive and complex rehabilitation treatment, starting in the first months of life, with cheiloplasty[7, 8]. This procedure is a surgical management to close the cleft lip, usually performed around six months of age in newborns. The aim of correction of the deformity of the lip is to return to proper shape and function, resulting in the union of the tissue and aesthetic, and functional reconstruction of the lip, facilitating essential functions such as feeding, speech and facial expression[9]. The pre-surgical orthopedics nasoalveolar molding (NAM) device was developed in 1993 by Grayson[10] with the objective of improving the columella length, and reducing the deformities before the surgery[11, 12]. An improvement of the technique for presurgical NAM occurred in 2011[13] using computer-aided reverse engineering and rapid prototyping.

It is recognized that the oral condition of children with cleft lip and palate can affect the family[14], affecting the emotional, economic, psychosocial, and behavioral fields. The comprehensive rehabilitation of patients with fissures also requires monitoring the families[15] and evaluating the impact of the NAM reverse engineering treatment intervention and cheiloplasty surgery, through questionnaires may guide better protocols and approaches[16].

Based on this initial premise, this descriptive and quantitative clinical study aims to evaluate the effects of adjunct therapy with the use of the NAM for facial symmetry parameters on post-cheiloplasty outcomes in newborns with UCLP and to assess the psychosocial impact on the family of children with a cleft.

## Material and Methods

*Participants and study design*

A prospective study was conducted from January 2017 to June 2022, with patients with UCLP treated with reverse engineering therapy of the NAM device compared to babies with UCLP without NAM (control group). The NAM group consisted of 26 patients of both sexes (18 boys and eight girls), who were under treatment at the Faculty of Dentistry of the Federal University of Minas Gerais (UFMG, Brazil), aged up to one month, without syndromic, with scheduled cheiloplasty surgery from the Baleia Hospital, MG, Brazil. The Control group comprised 12 non-syndromic babies (seven boys and five girls) with UCLP and about one month of age without presurgical orthopedics and with scheduled cheiloplasty surgery from the Plastic Surgery Unit, Department of Surgery, School of Medicine, Federal University of Parana (UFPR), Brazil. This study follows the Declaration of Helsinki and was approved by the Research Ethics Committee from the Federal University of Minas Gerais and the Federal University of Paraná. Parents/guardians of eligible children were invited to participate in the research and instructed about the treatment, acceptance being granted by signing an informed consent form.

Patients were subjected to photographic documentation at two distinct stages: firstly, within the initial month of life (Pre - prior undergoing NAM treatment and/or cheiloplasty surgery), and subsequently, at approximately 1-year-old (After cheiloplasty - following the completion of cheiloplasty surgery in the control group and post the utilization of NAM followed by cheiloplasty surgery in the test group). In the previously mentioned group, there were understandable absences of some patients due to the distance from where they lived, which caused the non-acquisition of the follow-up of 11 patients (Figure 1). The treatment with NAM using the reverse engineering technique associated with lip taping technique and nasal stent (NAM group) was performed according to Souza et al.[17].

*Surgical procedures for cheiloplasty*

The participants from the Control group were operated on by the surgeon R.S.F and the surgical protocol was Fisher. The NAM group was operated by two surgeons S.E.R. and M.S.A., and the surgical protocols were Millard or Fisher, respectively.

*Photographic analysis of facial symmetry*

The evaluation of changes in facial symmetry was performed through photographs in frontal and basilar positions, using a camera with a 100 mm macro lens (Canon EOS Rebel T3i, Japan), according to a previous study [17]. The following measures were taken: (1) Nasal width/intercanthal length ratio (millimeters – mm), (2) Mouth width/interpupillary distance ratio (mm), (3) Columella angle (degree - °), and (4) The nostril area of the orifice (pixels – no measure unit). ImageJ software (National Institute of Mental Health, Bethesda, Maryland, USA) was used to measure the linear, angular and area measurements in the photographs [17].

*Family impact scale (FIS) questionnaire*

Parents/guardians of eligible ULCP children who underwent NAM therapy and cheiloplasty were invited to participate in the research and instructed about the questionnaire application. The FIS measures the impact of child's oral condition on the family quality of life. The questionnaire consists of 14 items divided into three subscales: parental/family activity (PA), parental emotions (PE), and family conflict (FC). The financial burden subscale (FB) is the only one that is evaluated separately since it comprises a single item and addresses economic rather than psychosocial or behavioral impact. The questionnaire was cross-culturally adapted into the Brazilian Portuguese language[18] and administered to parents of babies with UCLP before and after the treatment with NAM reverse engineering therapy associated with lip taping technique, nasal stent and the cheiloplasty surgery (Figure 1). The FIS survey was applied at the first month of life of the children with the cleft and before NAM therapy (T1 – Pre NAM), and after the NAM treatment and the surgery of the cheiloplasty, but before de palatoplasty (T2 – After cheiloplasty) (Figure 1). The FIS survey was not applied to the control group.

## Statistical analysis

Statistical analysis of photographs was conducted using the GraphPad Prism 8.0 software (GraphPad Prism Version 8.0 for Mac, La Jolla, California, USA). The data were represented by mean ± standard deviation (SD) and submitted to the two-way ANOVA statistical test ($P<0.05$) with Tukey´s multiple comparison post-test, ($P<0.05$). Pearson´s correlation was performed among the variables. For the questionnaire, the statistical analysis was run with the Social Package for the Social Sciences (SPSS, version 22.0, IBM Inc., Armonk USA). Descriptive statistics was calculated. The Shapiro Wilk test demonstrated that quantitative data (subscale and overall, FIS scores) exhibited non-normal distribution. Comparisons of subscale and overall, FIS scores over time were performed with the Fridman test. Comparisons of subscale and overall, FIS scores between pairs of times were performed with the Wilcoxon test. Statistical difference was set at $p<0.05$.

## Results

*NAM treatment associated with cheiloplasty increased facial symmetry in babies with ULCP*

There was a high level of compliance and acceptance of the treatment protocol involving NAM by the participating families of the babies of the NAM group. On average, the duration of NAM treatment was approximately five months. Importantly, there were no adverse events or harm observed in any of the patients under investigation.

The Control and NAM groups were similar in the periods pre and after cheiloplasty with no significant differences in the nasal width/intercanthal length ratio, mouth width/interpupillary distance ratio and columella angle (Figure 2). After cheiloplasty, significant decreased nasal width/intercanthal length ratio and increase values for columella angle were exhibited for both groups in comparison to Pre period (Figure 2). Mouth width/interpupillary distance ratio was increased after cheiloplasty only in the NAM group compared to Pre period. The treatment with NAM reverse engineering therapy associated with lip taping technique, nasal stent (NAM group) associated with the cheiloplasty showed statistical increase in mouth

width/interpupillary distance ratio and columella angle in comparison to Control group after the surgery (Figure 2). No correlation was found between the facial parameters in the two groups after cheiloplasty (Suppl. Figure 1).

Following the assessment of the clinical improvement in the columella angle through NAM therapy, the nostril area of the NAM group was thoroughly examined. The nostril area in the cleft and non-cleft sides of NAM group was similar to Control group before NAM treatment and/or cheiloplasty (Pre period) (Figure 3A-C). In both groups, noteworthy differences were observed in the nostril area on the non-cleft side after cheiloplasty, which showed a notable increase compared to the Pre period. When analyzing the nostril area on the cleft side, a significant reduction was exclusively observed in the NAM group after cheiloplasty compared to the initial consultation. However, no difference was exhibited between NAM and Control group after the surgery of cheiloplasty in the non-cleft and cleft sides (Figure 3C). A positive correlation was notably established between the parameters of the columella angle and the area of the nostril on the cleft side after the cheiloplasty (Figure 3D), but not with the other facial parameters.

*The NAM treatment and the surgery of the cheiloplasty improved the quality of life of the families compared to the initial month of life of the baby*

Among the twenty-six participants in the NAM group with ULCP, only eight children responded to the questionnaires at all time points. There was a lost of 18 participants of FIS questionnaire whose parents refused to answer the survey. Among the babies, there were four boys (50.0%) and four (50.0%) were girls. Most caregivers completed a university degree (49.9%) (Table 1). Significant differences occurred in the PE subscale ($p$=0.008) and in the overall FIS score ($p$=0.042) over the follow-up period (Table 2).

**Discussion**

Children born with cleft lip and palate undergo multiple surgical interventions in the fields of plastic and maxillofacial surgery throughout their developmental journey. There is a notable recurrence rate in procedures such as cheiloplasty and palatoplasty[19]. Given this context, with the aim of enhancing the effectiveness of

surgical outcomes, it is widely recognized as crucial to incorporate complementary therapies, such as NAM therapy, during the early months of life for patients with cleft lip and palate[17]. It is imperative to emphasize that early correction of the aesthetic and functional implications of this congenital anomaly is of paramount importance, not only for the children themselves but also their parents, as the facial appearance of the baby is significantly affected, resulting in psychosocial challenges for the family[20]. In this context, our results demonstrated that the use of NAM improved the facial symmetry with the increase of the columella angle after cheiloplasty. The comparison between the period before treatment with NAM and the period after cheiloplasty demonstrated that the overall family quality of life improved, with the main positive effect being upon parental emotions.

The current literature still presents several gaps with respect to the optimal approach for repairing and treating unilateral complete transforaminal cleft lip and palate using[21, 22]. Among the techniques employed, some surgeons option for standalone surgical correction through cheiloplasty, while others prefer to adopt a multidisciplinary pre-surgical treatment protocol, which has shown more promising outcomes[20]. Thus, NAM therapy, followed by primary cheiloplasty in the early months of life, is suggested as a means to significantly improve corrective outcomes for the facial deformities resulting from unilateral complete cleft lip and palate, as demonstrated by the results of this study[23].

Infants born with an unilateral complete cleft lip and palate undergo changes in nasal anatomy due to the failure of fusion between nasal and maxillary[24]. The nasal deformities observed in patients with cleft lip and palate result from three fundamental anatomical changes[25]. The misalignment of the alveolar and maxillary arches exerts a caudal force on the nasal wing and all nasal structures, representing the primary anatomical limitation in achieving the desired final nasal symmetry[17]. This results in the inferior, posterior, and lateral displacement of the lateral inferior nasal cartilage, leading to a concave nasal shape, a depressed nasal dome, and a reduced columella angle, particularly on the affected side[26]. The ideal relationship between the columella and the nasal wing should not exceed 2-3 mm below a line parallel to the inferior margin of the nasal wing when observed in profile[27]. The use of pre-surgical orthopedic correction of soft nasal tissues, particularly with the utilization of a nasal elevator, represents a significant advancement in the treatment of unilateral complete cleft lip

and palate[28]. The results of the present study revealed that both the control group and the group subjected to NAM exhibited an increase in the columella angle following cheiloplasty[20, 28]. However, upon analyzing the difference in angular increase between participants, it became evident that the NAM group achieved a significantly greater increase compared to the control group, resulting in noteworthy improvements in facial symmetry[12, 27, 29].

The width and area of the nostrils were shown to become more symmetrical following pre-surgical therapy with NAM and cheiloplasty[30]. In our study, one of the parameters measured was the area of the nasal nostrils, both on the affected and unaffected sides. It was observed that the area of the nostril on the unaffected side remained unchanged, while changes in the reduction of the nostril area on the affected side were observed exclusively in the NAM group, leading to enhanced aesthetic symmetry in the external nose of patients undergoing NAM therapy.

Reverse NAM therapy includes, in addition to the nasal elevator, the use of lip tape and acetate plates, which are replaced weekly. The adhesive tape facilitates the approximation of lip segments, reducing post-surgical tensions and assisting in cheiloplasty[31, 32]. It is important to emphasize that achieving facial symmetry is a primary goal for patients with cleft lip. Ideally, the distance between the lip commissures should harmonize with the interpupillary distance. When expressed as a ratio, this relationship should approach a value of one[17]. Another parameter under scrutiny was the relationship between nasal width/intercanthal length ratio. It was proposed that from an aesthetic perspective when the nasal width aligns with the intercanthal distance, it can contribute to a more symmetrical appearance in patients, particularly when the ratio between these measurements approaches[33]. Furthermore, some studies employing the technique of dissection just below the alar base and suture tightening suggest that these factors play a significant role in mitigating alar widening[33]. Regarding our results, both study groups displayed a considerable reduction in this ratio. However, the NAM group exhibited values even closer to 1, setting our findings apart from certain earlier studies which concluded that the preoperative nasal elevator's impact had limited influence on the nasal width/intercanthal length ratio[30].

The proportion between mouth width and interpupillary distance is a crucial indicator of facial symmetry. The NAM group showed an increase in this proportion, approaching 1, while the Control group experienced a reduction after cheiloplasty. In

complement to our findings, the results of de Souza et al. (2023)[17] in their clinical studies reinforce the positivity of these results, emphasizing that the reduction of cleft lip and alveolar bone did not adversely affect the width between the lip commissures. This is an important development, as maintaining this width is a crucial goal of NAM therapy and essential for achieving desirable aesthetic outcomes[34].

Families with a child with an orofacial cleft experience a great overall effect on the family routine, elevated impact on parental emotions and increased influence on family activities. Primary rhinoplasty appears to enhance the patient's well-being and social interactions[35]. In this sense, the mental and psychological aspects of parents concerning the anomaly and its correction must be assessed, encompassing the significance of prenatal diagnosis, relational dynamics with the child, self-perception, and quality of life[36]. This study was the first to exhibit the impact of the NAM pre-operative therapy associated with the cheiloplasty on the family. A significant improvement was observed for the PE and the overall FIS score over time when the period before NAM treatment was compared to the period after cheiloplasty.

The impact of NAM in conjunction with cheiloplasty may be contingent upon specific aspects of the technique and treatment protocol employed by healthcare professionals. It's worth noting that the skill set of the plastic surgeon, dentist, and other involved professionals can also play a pivotal role in achieving enhanced facial and nasal symmetry. Additionally, factors such as the width of the cleft, the nasal and facial anatomy and texture, and the patient's ethnic background can act as significant facilitating or hindering factors in reshaping the facial profile of cleft patients[37]. In our study, different plastic surgeons performed cheiloplasty using varying surgical techniques; therefore, the results may exhibit variations. Another limitation of this study was the utilization of 2D photographs for analysis, as more advanced imaging equipment can provide three-dimensional data, enabling the assessment of additional parameters[17]. Finally, the FIS questionnaire was applied only to the NAM plus cheiloplasty group, but not the control group, due to the difficulties of the same research applied to the survey at different states in Brazil. More studies are necessary to improve the results of the impact of the NAM treatment in the family of individuals with UCLP.

It's imperative to emphasize that the literature is currently limited and inconsistent concerning the facial analysis of cleft patients. Thus, there is a pressing

need for more randomized, standardized, and cohesive clinical studies that can establish clear parameters for the validation of specific pre- or post-surgical therapies. The present study demonstrated that early non-surgical NAM treatment using the reverse engineering technique appears to contribute to improved outcomes in cheiloplasty surgery for infants with unilateral cleft lip and palate. This treatment allows for the development and enhanced symmetry among facial structures and nasal aesthetics, resulting in a more harmonious facial appearance, and also improving the quality of life of the family.

**Acknowledgments**

Patient consent was required for the publication of the clinical photographs, and all single case reports, including those where the data was anonymized.

**Declaration of interest:** none

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**Data Availability Statement**: Data available on request (*The data underlying this article will be shared on reasonable request to the corresponding author*).

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**Table 1.** Demographic characteristics of the sample

| | Number (%) |
|---|---|
| Child's sex | |
| Male | 04 (50.0) |
| Females | 04 (50.0) |
| | |
| Caregiver's schooling | |
| Secondary incomplete | 01 (16.7) |
| Secondary complete | 01 (16.7) |
| University incomplete | 01 (16.7) |
| University complete | 03 (49.9) |

**Table 2.** Comparisons of subscale and overall FIS scores over time

| | T1 Median (Min – Max) | T2 Median (Min – Max) | *p* value* |
|---|---|---|---|
| PA | 4.0 (2 – 8) | 2.5 (1 – 12) | 0.060 |
| PE | 6.5 (0 – 9) | 4.0 (0 – 10) | **0.008** |
| FC | 0.0 (0 – 1) | 0.0 (0 – 1) | 0.999 |
| FB | 0.0 (0 – 4) | 0.5 (0 – 4) | 0.617 |
| Overall | 11.0 (4 – 19) | 9.5 (3 – 17) | **0.042** |

PA=parental activities; PE=parental emotions; FC=Family conflicts; FB=financial burden Min=minimum; Max=maximum *Friedman test. Significant at<0.05

**Figure 1**. CONSORT flow diagram.

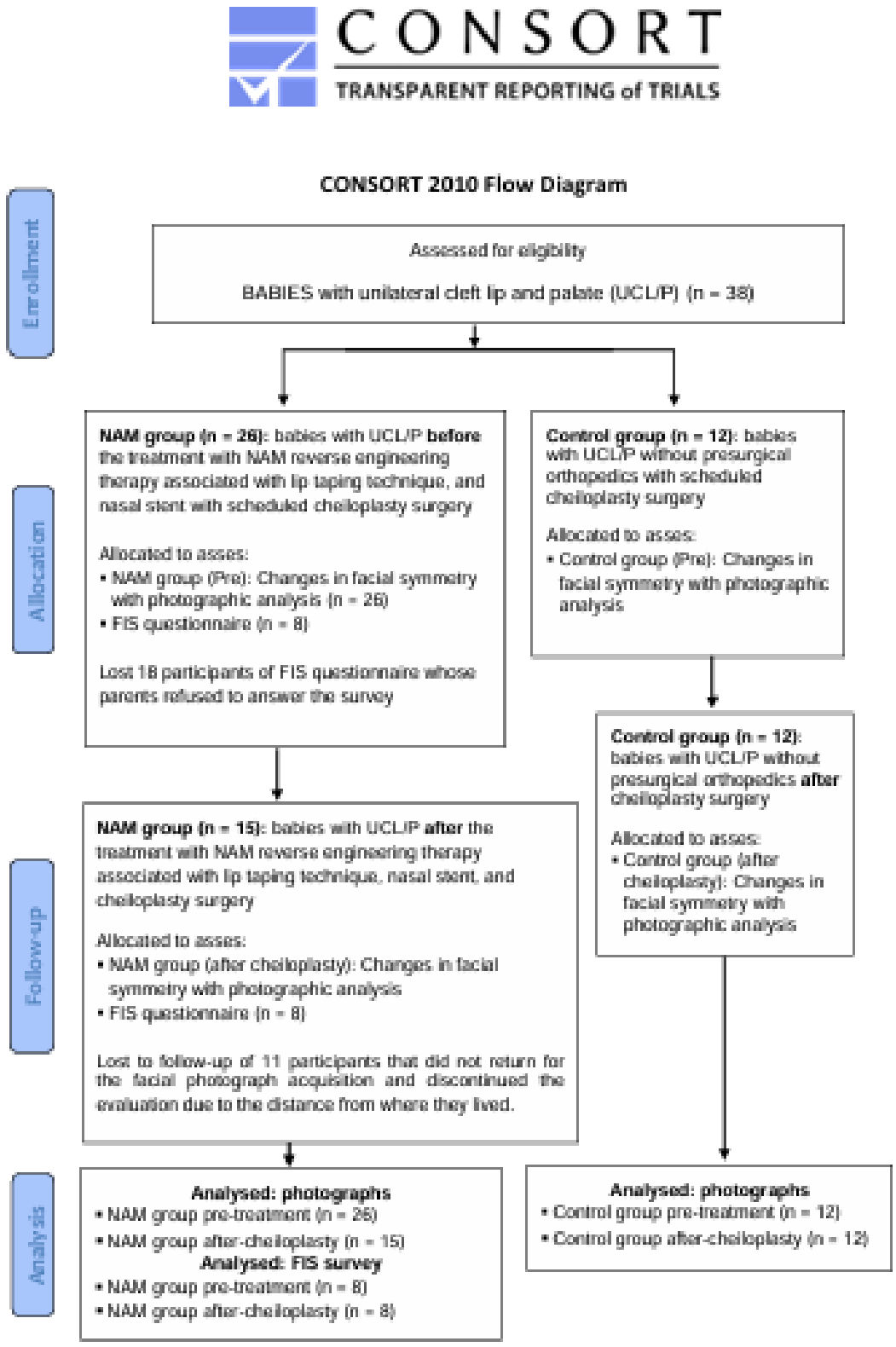


**Figure 2.** Photographic analysis. A and B - Representative images and measurement of the nasal base/intercantal length ratio measure and mouth width/interpupillary distance ratio, respectively. C and D- Representative images and columella angle measurement, respectively. Two-way ANOVA statistical test (P<0.05) with Tukey´s multiple comparison post-test.

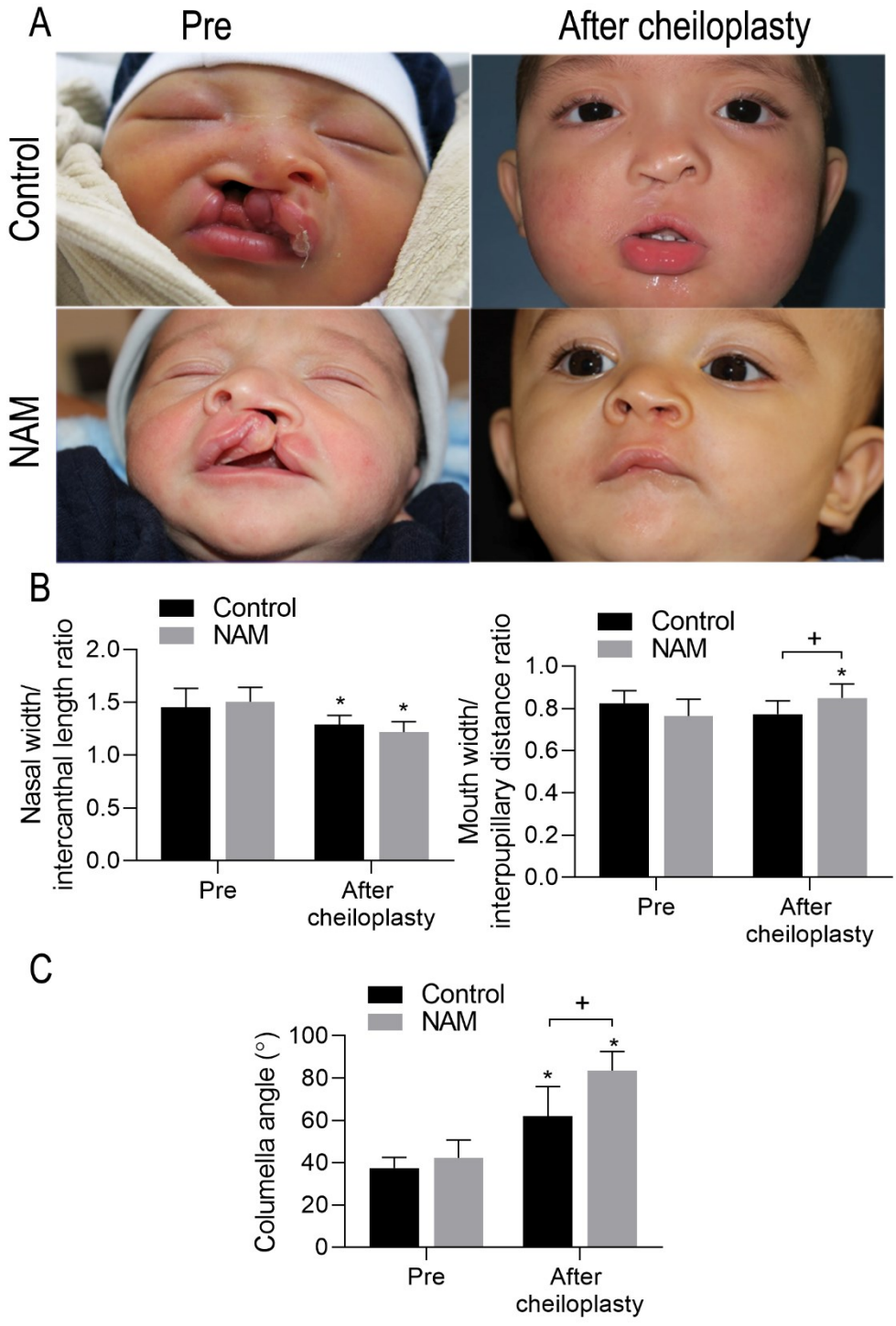
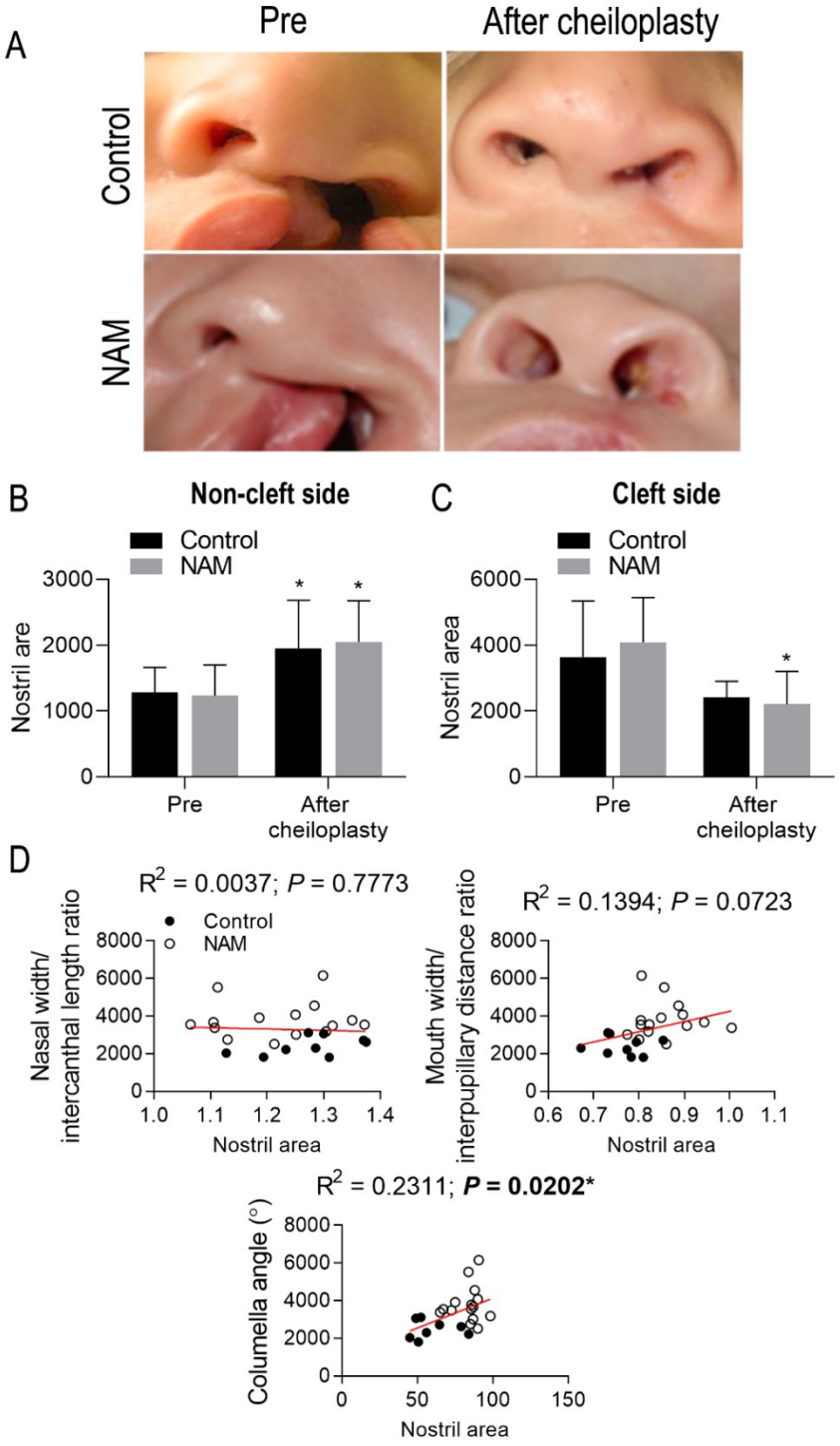


**Figure 3**. A, B and C – Representative images and the analysis of the nostril area of the non-cleft and cleft sides, respectively. Two-way ANOVA statistical test (P<0.05) with Tukey´s multiple comparison post-test. D - Pearson´s correlation of the facial parameters. P<0.05



# 6 ARTIGO 3

Artigo submetido e sob revisão no periódico *International Journal of Oral & Maxillofacial Surgery*

## Effects of nasoalveolar molding associated with cheiloplasty in individuals with cleft lip and palate: a systematic review and meta-analysis.

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## Abstract

Objective: To investigate the impact of nasoalveolar molding (NAM) treatment after cheiloplasty surgery on the results of nasal symmetry in individuals with cleft lip and palate (CLP).

Methods: The reporting of this review follows the Preferred Reporting Items for systematic reviews and MetaAnalyses guidelines (PRISMA). Electronic searches were performed in six databases in October 2023. Studies comparing individuals with CLP undergoing treatment with NAM and cheiloplasty and individuals undergoing cheiloplasty alone, in any language and publication date, were considered. The selection of studies and data extraction were carried out by two calibrated authors. The

ROBINS-I tool was used to assess the risk of bias and meta-analyses were conducted. Standardized mean difference (SMD) and confidence interval (CI) were provided, and strength of evidence was assessed.

Results: 416 articles were retrieved; nine studies were included. In the group treated with NAM following cheiloplasty, there was an increase in nostril height and columellar width and length, in the short and long term ($p$<0.05). Nostril width and bialar width decreased in the short term and increased in the long term, in individuals undergoing treatment with NAM and cheiloplasty ($p$<0.05). Meta-analysis showed that bialar width 5 years after surgery in individuals who had undergone treatment with NAM and cheiloplasty was significantly higher than in individuals who had undergone only cheiloplasty (SMD=0.37, [95% CI=0.04–0.70]). Six studies exhibited a moderate risk of bias; three exhibited a serious risk of bias. Strength of evidence ranged from very low to moderate.

Conclusions. Treatment with NAM generated a positive impact on nasal symmetry with an increase in nostril height, width and length of the columella, in the short and long term. NAM treatment improved nostril width and bialar width only in the short term.

Keywords: Cleft lip and palate; cheiloplasty; nasoalveolar molding; meta-analyses; systematic review.

## Introduction

Pre-surgical orthopedic devices, especially those utilized in nasoalveolar molding (NAM), developed by Grayson (Grayson et al., 1999), in newborn babies with cleft lip and palate (CLP), are applied to reduce distortion of the alveolar arch segments and minimize tension in the site where surgery will take place (Mustafa K et al., 2023; Kinouche et al., 2018), preparing the affected region for the first lip surgery called cheiloplasty (Clark et al., 2011).

In recent years, treatment with NAM has been widely used, through a combination of plates, nasal stents and lip tapes, to improve nasal, labial and alveolar deformities (Fedeles et al., 2012; Gibson E et al., 2021; Haddad R et al., 2023;

Kornbluth et al., 2018) with consequent aesthetic, social and nutritional benefits for the child (Gong et al., 2017; Alqadi S. et al., 2023).

In addition to a reduction in the need for secondary bone grafts in mixed dentition (Santiago PE, et al., 1998), when receiving a baby for cheiloplasty who has undergone treatment with NAM, the surgeon finds the structures affected by the cleft more harmonic and closer together (Rau A et al., 2015). Although there are studies that show changes in facial structures, emphasizing the valuable assistance of this therapy (Maillard S et al., 2017; Nayak T et al., 2020), the success of treatment with NAM depends on the patient's adherence – as well as their parents/guardians – to a strict schedule, which requires periodic visits to monitor the device used (Wlodarczyk JR et al., 2021).

Additionally, restoring the anatomy, symmetry and projection of the nose is important for individuals with CLP, parents and surgeons (Sasaki et al., 2012). At the time of surgical intervention, when considering individual differences and severity, the surgeon is usually faced with challenging aspects in the region affected by the cleft, such as: separated lip segments on the cleft side, widening of the base of the nostril, and collapse of the lower lateral nasal cartilage, displaced laterally and inferiorly (Thakur et al., 2022; Barillas et al., 2008).

Studies have been analyzing the benefits of the various aspects of treatment with NAM (Broder HL et al., 2016; Chang SY et al., 2018; Aihara Y. et al., 2021). However, the heterogeneous nature of the studies limits the availability of robust scientific evidence of its effect on clefts in non-syndromic patients (Rossell-Perry P. et al., 2020).

Therefore, this study is a systematic review and critical examination of the literature on the impact of NAM on the results of nasal symmetry, in the long and/or short term, after cheiloplasty surgery.

## Methods

### Protocol and registration.

This review follows the Preferred Reporting Items for Systematic reviews and MetaAnalyses guidelines (PRISMA) (Page et al., 2021). A protocol was recorded at the

International Prospective Register of Systematic Reviews (PROSPERO, National Institute of Health Research, UK) (CRD42023477752).

**Eligibility Criteria**

The inclusion criteria was based on original observational studies (clinical trials, case-control, cross-sectional and cohort) in which babies treated with NAM were compared to babies not treated with NAM, having nasal symmetry assessed after cheiloplasty surgery intervention, in the immediate and/or long term. Studies in any language and publication date were considered. The exclusion criteria were studies with insufficient data or heterogeneous measurements, narrative reviews, case reports, guidelines, consensus statements, editorials, letters, commentaries, or conference abstracts. The PICO question was prepared as follows: P (population): cleft lip patients; I (intervention): NAM and cheiloplasty; C (Comparison): cheiloplasty only; O (outcome): nasal symmetry.

**Databases consulted and search strategies**

The electronic bibliographic search was carried out in the Pubmed (National Library of Medicine), Web of Science (Clarivate Analytics), Clinical Trials, Scopus (Elsevier), Embase (Elsevier) and Cochrane Library databases in October 2023. For management and verification of duplicates, references were loaded into the EndNote software (EndNote; Clarivate Analytics, Toronto, ON, Canada). The search strategy was a combination of MeSH terms and keywords joined by Boolean operators: (cheiloplasty, OR cleft lip surgery, OR cleft-lip surgery) AND (nasoalveolar molding, OR NAM, OR nasoalveolar molding).

**Study selection**

In Phase 1, after excluding duplicates, two independent authors (T.M.S and N.A.) read the abstracts of all selected references. The complete reading of the chosen articles was carried out by the same authors, in Phase 2. Any disagreement in the

study selection process was resolved through discussion between peers. Articles that met the eligibility criteria were included in this study.

**Data extraction**

Each selected study was allocated in a table and the following information was extracted: last name of the first author, year of publication, country where the study was conducted, study design, number of participants in the experimental group (G1) and the control group (G2), type of cleft lip and palate evaluated, sex and average age of participants at the times evaluated, moments of evaluation of the outcome, objective measurements carried out in the comparison between the two groups and results of the comparisons of outcomes between the two groups. Data extraction was performed by one author (T.M.S.) and checked by a second author (L.G.A.).

**Risk of bias of individual studies**

The risk of bias assessment was carried out in each study individually, using the ROBINS-I tool (Cochrane Methods) (Sterne et al., 2016). This checklist contains seven criteria evaluated in three domains: pre intervention, at intervention and post intervention. The pre intervention domain verified: a) whether there was the presence of confounding factors and whether these factors were listed; b) whether the selection of participants for the study was carried out in the same way for experimental and control groups, and whether monitoring began at the same moment. The intervention domain verified: c) whether the intervention classification was well defined, and whether it was decided retrospectively. In the post intervention domain, the following were checked: d) if the two groups were subjected to the same intervention, or if there was a deviation from the intended intervention; e) if there was a report of lost data or with the potential to be lost; f) if the outcome measurements were carried out in a valid and reliable fashion for both groups; and g) if there was selective reporting of results. Each criterion was rated on the following scale: “low”, “moderate”, “serious”, “critical” or “not informed“. Finally, in each study a general judgment was given, associating the classification of all the previously mentioned criteria, where: “low” - judged the study as being at low risk of bias for all domains; “moderate”- judged the study as being at low or moderate risk of bias for all domains; “serious” - judged the study as being at

serious risk of bias in at least one domain, but not at critical risk of bias in any domain; “critical” - judged the study as being at critical risk of bias in at least one domain; and “not informed” – when there was a lack of information in one or more key domains of bias (a judgment was required for this). This assessment was carried out by two authors (T.M.S and L.G.A) and all disagreements were resolved through discussion between peers.

**Meta-analyses**

Data of studies that were methodologically homogeneous were pooled into meta-analyses of continuous outcomes. The software used was the Review Manager (RevMan) Version 5.4. The Cochrane Collaboration 2020 was used to conduct meta-analyses. Mean, standard deviation (SD) and sample size were used. In articles where median, minimum, and maximum had been provided, the mean and SD were calculated with the following equations below(Wan et al., 2014**):**

$$\boldsymbol{Mean} = \frac{\boldsymbol{minimum} + (\boldsymbol{2\ x\ median}) + \boldsymbol{maximum}}{\boldsymbol{4}}$$

$$\boldsymbol{SD} = \frac{\boldsymbol{maximum} - \boldsymbol{minimum}}{\boldsymbol{4}}$$

The results of meta-analyses were given in standardized mean difference (SMD) and 95% confidence interval (CI) (Higgins et al., 2023). In all meta-analyses, the random effect model was used. Inconsistency was measured with $I^2$.

**Assessment of strength of evidence**

The strength of the evidence was assessed using the GRADE (Grading of Recommendations, Assessments, Development and Evaluation) instrument (Schünemann et al., 2013). GRADEpro software was used.

## Results

### Study selection

The bibliographic search in electronic databases allowed us to retrieve 416 records, of which 116 were removed because they were duplicates. After reading the title and summary of the 300 publications in Phase 1, 274 references were excluded due to lack of suitability for the purpose of the research. In Phase 2, the remaining 26 articles were evaluated in their full text. Finally, 9 articles that met the eligibility criteria for this systematic review were included (Haddad et al., 2023; Nayak et al., 2021; Kurnik et al., 2021; Harrison et al., 2020; Maliha et al., 2020; Bonanthaya et al., 2018; Fedeles et al., 2012;) A flowchart of this selection process is presented in Figure 1 and the list of references excluded in Phase 2 and the reasons for exclusion are available in Supplement 1.

### Characteristics of the included studies

The included studies were published in English between 2008 (Barillas et al., 2008) and 2023 (Haddad et al., 2023). All had an experimental group and control group. Regarding the designs, one study was a cohort study (Haddad et al., 2023), another was a retrospective cross-sectional study (Harrison et al., 2020), 4 were retrospective studies (Nayak et al., 2021; Maliha et al., 2020; Bonanthaya et al., 2018; Barillas et al., 2008) and three publications did not inform the design of the study carried out (Kurnik et al., 2021; Fedeles et al., 2012; Clark et al., 2011 ). Among the nine included studies, one was conducted in Lebanon (Haddad et al., 2023), two were carried out in India (Nayak et al., 2021; Bonanthaya et al., 2018), five in the USA (Kurnik et al., 2021; Harrison et al., 2020; Maliha et al., 2020; Clark et al., 2011; Barillas et al., 2008) and one in Slovakia (Fedeles et al., 2012). A total of 420 babies were evaluated (233 with unilateral cleft and 187 with bilateral cleft), of which 207 were treated with NAM (experimental group) and 213 were not subjected to NAM treatment (control group). Sample sizes in each study ranged from 15 (Fedeles et al., 2012) to 121 individuals (Bonanthaya et al., 2018). The age of patients at the time of assessment ranged from six months (Nayak et al., 2021) to 14 years (Maliha et al., 2020). In five studies, participants were recruited from university and hospital referrals, as well as from care centers (Haddad et al., 2023; Harrison et al., 2020; Bonanthaya

et al., 2018; Clark et al., 2011; Barillas et al., 2008), and in two studies (Kurnik et al., 2021 and Nayak et al., 2021) it was unclear where the patients were recruited from. In the study conducted by Maliha et al., 2020, there is no information about where the individuals in the experimental group were recruited from, the individuals in the control group being admitted from several different institutions. In the study of Fedeles et al., 2012 the individuals treated in the sample were admitted at the time of cheiloplasty surgery, all belonging to the Slovak population (Table 1). Classifying the moments evaluated as T1 = before operation time, T2 = immediate post operation time and T3 = long term post operation time, three studies carried out evaluations at two moments: Nayak et al., 2021 (T2 and T3), Harrison et al., 2020 (T1 and T3) and Fedeles et al., 2012 (T1 and T2). Two studies evaluated the sample at T2 (Haddad et al., 2023 and Bonanthaya et al., 2018). And finally, four publications (Kurnik et al., 2021; Maliha et al., 2020; Clark et al., 2011; Barillas et al., 2008) performed measurements only at T3. Objective assessments of nasal symmetry were performed using two-dimensional photographs, three-dimensional images and impressions with dental materials. Some research studies (Kurnik et al., 2021; Harrison et al., 2020; and Clark et al., 2011), used three-dimensional facial images in their analyses, acquired using a 3dMD Imaging System (3dMD, Atlanta, GA), and virtual models derived from these images were analyzed using 3dMD Vultus (3dMD, Atlanta, GA). Barillas et al., 2008, performed the measurements using polysiloxane vinyl dental impression material. The molding extended from the eyebrow area, including the intercanthal region, to the highest point of the red border of the upper lip. Some authors (Haddad et al., 2023; Nayak et al., 2021; Maliha et al., 2020; Bonanthaya et al., 2018; Fedeles et al., 2012) evaluated nasal symmetry using two-dimensional photographs with the aid of software, such as ImageJ (National Institute of Health, Bethesda, Maryland, USA) or Dolphin Imaging and Management Software (2018 Patterson Dental Supply, Inc.). With the intention of minimizing technical errors, Nayak et al., 2021, Fedeles et al., 2012 and Barillas et al., 2008 calculated the measurements using ratios between the sides affected and not affected by the cleft (Table 1).

**Risk of study bias**

In the pre intervention domain, all nine included studies presented a moderate risk of bias for the “selection of participants for the study” criterion. In the studies, the start of monitoring and the start of the intervention did not coincide for all participants.

This situation seems to be an inherent condition of retrospective studies, which are carried out by retrieving records for evaluation, with a time range for selecting participants, counted in years. It would be unlikely, or even impossible, that all babies in the sample could receive cheiloplasty surgery or NAM treatment at the same time. The studies of Harrison et al., 2020 and Maliha et al., 2020 received a “serious” risk of bias assessment in the “confounders” criterion because these two studies listed factors that could confuse the results, such as the use of a variety of surgical techniques for lip repair in primary surgery, and the fact that patients in the control group came from several institutions, making it impossible to identify the lip repair technique. For this reason, these two studies received a final judgment of “serious” risk of bias. In the intervention domain, all nine studies presented low risk of bias for the “Classifying the intervention” criterion. In the post intervention domain, all nine studies presented low risk of bias for the “deviations from the intended intervention” criterion. For the “missing data” criterion, in most studies (Haddad et al., 2023; Nayak et al., 2021; Harrison et al., 2020; Maliha et al., 2020; Bonanthaya et al., 2018; Fedeles et al., 2012; Barillas et al., 2008), the information was not provided, or the risk of bias was moderate (Kurnik et al., 2021) or serious (Clark et al., 2011). For the “measuring outcomes” criterion, in most studies (Haddad et al., 2023; Nayak et al., 2021; Harrison et al., 2020; Maliha et al., 2020; Bonanthaya et al., 2018; Fedeles et al., 2012), the information was not provided, or the risk of bias was low (Kurnik et al., 2021; Clark et al., 2011; Barillas et al., 2008). For the “selecting reported result” criterion, all studies did not present information.

In the final judgment, six studies (Haddad et al., 2023; Nayak et al., 2021; Kurnik et al., 2021; Bonanthaya et al., 2018; Fedeles et al., 2012; Barillas et al., 2008) presented moderate risk of bias and three (Harrison et al., 2020; Maliha et al., 2020; Clark et al., 2011) had a serious risk of bias (Table 2).

**Individual study results**

**Nostril height -** *Distance from the highest point of the upper inner edge of the nostril to the alar base line.*

Of the nine studies included, four did not use this measure to assess nasal symmetry (Harrison et al., 2020; Bonanthaya et al., 2018; Clark et al., 2011 and Barillas

et al., 2008). The study by Haddad et al., 2023, evaluating children with bilateral cleft, found in this measurement a significantly greater extension, on the left and right sides, in the group that had been treated with NAM, in relation to the control group, 3 months after the cheiloplasty. This same significant increase in nostril height in individuals who had been treated with NAM was found by Nayak et al., 2021, at both moments evaluated (immediately after and 5 years after surgery). Kurnik et al., 2021 found this measurement to be higher in an evaluation 5 years after surgery. The findings of Maliha et al., 2020, also show significantly greater nostril height in patients treated with NAM when compared to the control group, in an evaluation 14 years after surgery. The publication by Fedeles et al., 2012 showed a greater nostril height, but without statistical difference, in the group that used NAM when compared to the control group. In this study, the authors did not inform the moment evaluated.

**Nostril width -** *distance from the midpoint of the lateral surface of the columellar crest to the midpoint of the inner edge of the lateral ala.*

In the study of Haddad et al., 2023, the nostril width of patients with bilateral clefts in the group that had received NAM was similar to the nostril width of the group that had not received this intervention, on the right side, and smaller, but without statistical difference, on the left side, 3 months after surgery. Evaluating this same measurement, the study by Nayak et al., 2021, showed that the nostril width of patients with unilateral cleft was slightly smaller in the group that had received treatment with NAM, immediately after cheiloplasty, and slightly larger in the group who had received NAM treatment, 5 years after surgery. Kurnik et al., 2021, in their study with patients with unilateral cleft, found the nostril width to be greater in patients who had received treatment with NAM, 5 years after surgery; however, there was no statistically significant difference. Finally, in the study of Fedeles et al., 2012, in patients with unilateral cleft, we noticed the nostril width decreased more in the group that had received treatment with NAM, but with no statistical difference. There is no information about the timing of the assessment.

**Bialar width -** *greatest distance between the most lateral points of the lateral ala.*

Of the nine studies included, only one study (Barillas et al., 2008) did not evaluate nasal symmetry using this measurement. It is important to highlight that the studies presented other nomenclatures for this same measurement. Haddad et al.,

2023 and Bonanthaya et al., 2018 called this measurement “Bialar width”, with the first study finding significantly lower values in the group treated with NAM compared to the control group, 3 months after surgery; and the second study found higher values in the group that had received treatment with NAM compared to the control group, 6 months after surgery. The studies of Nayak et al., 2021, Harrison et al., 2020 and Maliha et al., 2020 called this measure “Alar base width”. The study by Nayak et al., 2021 found this measurement to be slightly lower in the experimental group when compared to the control group, immediately after cheiloplasty, and slightly higher 5 years after surgery. Harrison et al., 2020, found this measurement to be significantly higher in the group that had been treated with NAM, 5 years after surgery. Maliha et al., 2020 found this measurement to be lower in the group that had been treated with NAM, 14 years after surgery; however, with no statistically significant difference. Kurnik et al., 2021 called this measurement “Nasal width” and found it to be greater, but without statistically significant difference, in the group treated with NAM in relation to the control group, 5 years after surgery. Fedeles et al., 2012 called this measurement “Interalar distance” and found it to be significantly lower in the group treated with NAM compared to the control group, although they did not inform the moment evaluated. Clark et al., 2011 called this measurement “alar width” and found it to be greater, but without statistically significant difference, in the group treated with NAM, 5 years after surgery.

**Alar length -** *distance between the facial insertion point of the alar base and the pronasal point.*

Six of the nine studies in this review (Nayak et al., 2021; Kurnik et al., 2021; Harrison et al., 2020; Maliha et al., 2020; Bonanthaya et al., 2018; and Fedeles et al., 2012) did not use this measurement to evaluate nasal symmetry. In their study with patients with bilateral clefts, Haddad et al., 2023, observed that alar length was significantly shorter in the group that had undergone treatment with NAM, on the left and right sides, 3 months after surgery. Clark et al., 2011 evaluated this measurement under the name “Alar base position in superoinferior direction”, finding it to be greater, but without statistically significant difference, in the group that had been treated with NAM, 5 years after surgery. Finally, Barillas et al., 2008 analyzed this measurement under the name “Nasal ala projection length” finding it to be significantly higher in the group that had been treated with NAM, 9 years after surgery.

**Columellar length -** *distance along the crest of the columella between the base of the columella and a horizontal line connecting the most superomedial points of the internal nares.*

In their study with patients with bilateral clefts, Haddad et al., 2023 found significantly greater columellar length in patients undergoing treatment with NAM, 3 months after surgery. Nayak et al., 2021 found significantly greater columellar length in the group that had been treated with NAM immediately after surgery. At 5 years after surgery, the authors found this measurement to be higher, but without a statistically significant difference, in the group of individuals who had been treated with NAM. Harrison et al., 2020 and Fedeles et al., 2012 found the length of the columella to be greater, but without a statistically significant difference, in the experimental group, 5 years after surgery and at an uninformed time, respectively.

**Columellar width –** *greatest laterolateral distance from the midpoint of the columella.*

Only the research studies by Kurnik et al., 2021 and Harrison et al., 2020 evaluated this measurement and both found higher values in the group of patients who had undergone treatment with NAM compared to the control group, 5 years after surgery. In the study by Kurnik et al., 2021 these findings were not statistically significant and in the study by Harrison et al., 2020 this difference was significant. It is important to highlight some measurements carried out only by Barillas et al., 2008, such as Nasal ala projection length and Nasal dome height to evaluate nasal symmetry. The authors found significantly higher values for the group treated with NAM in both measurements, at 9 years after surgery.

Finally, the study by Clark et al., 2011 was also the only study to use the Alar base projection measure. Lower values, but without statistically significant differences, were found in the group that had been treated with NAM, compared to the control group, at 5 years after surgery (Table 1).

## Meta-analyses

Three meta-analyses were feasible. One meta-analysis with data of three studies (Nayak et al., 2021; Kurnik et al., 2021; Clark et al., 2011) demonstrated that the bialar width 5 years after surgery in individuals who had undergone cheiloplasty

and treatment with NAM was significantly higher than in individuals who had undergone only cheiloplasty (SMD = 0.37, [95% CI = 0.04 – 0.70], $I^2$ = 0%) (Figure 2).

One meta-analysis with data of two studies (Nayak et al., 2021; Kurnik et al., 2021) showed no significant difference in the nostril height 5 years after surgery between individuals who had undergone cheiloplasty and treatment with NAM and individuals who had undergone only cheiloplasty (SMD = 0.51, [95% CI = -0.32 – 1.34], $I^2$ = 78%) (Figure 3).

One meta-analysis with data of two studies showed no significant difference in the nostril width 5 years after surgery between individuals who had undergone cheiloplasty and treatment with NAM and individuals who had undergone only cheiloplasty (SMD = 0.22, [95% CI = -0.13 – 0.58], $I^2$ = 0%) (Figure 4).

**Assessment of strength of evidence**

In the meta-analysis evaluation of the Bialar width measurement, a moderate strength of evidence was obtained, while in the meta-analyses for the Nostril height and Nostril width measurements, the strength of evidence was very low (Supplementary file 3).

**Discussion**

The effectiveness of NAM treatment has been the subject of discussion for a long time, despite its regular presence in many centers treating patients with cleft lip and palate (Abbott et al., 2012, Maillard et al., 2017). In search of evidence, studies have investigated the results of surgical procedures in individuals treated and not treated with NAM, using two- and three-dimensional images, as well as other forms such as facial and intraoral impressions (Cai et al., 2020, Nur Yilmaz et al. , 2018). The plates, nasal stents and lip taping that make up NAM treatment aim to improve the shape of the jaw and the symmetry of a nose with collapsed architecture (Kinouchi et al., 2018, Peanchitlertkajorn et al., 2018 ). The nasal asymmetry that may persist after cheiloplasty challenges surgeons and the entire team caring for a patient with a cleft lip palate (Ruíz-Escolano et al., 2016, Shetty et al., 2016). The expectation for patients undergoing cheiloplasty and treatment with NAM is a less wide and longer nostril, a

smaller bialar width, a greater alar length and a longer and wider columella, when compared to babies who have undergone surgery but who have not been subjected to NAM treatment. Several studies included in this systematic review and meta-analysis showed that individuals undergoing cheiloplasty and treated with NAM, in the short term (Haddad et al., 2023, Nayak et al., 2021) and in the long term (Nayak et al. , 2021, Kurnik et al., 2021, Maliha et al., 2020), showed a significantly greater increase in nostril height than individuals operated but not treated with NAM. While the plate used in NAM treatment brings the alveolar segments closer together (Saad et al., 2020), the nasal stent inserted into the slit nostril opening corrects nasal deformity and asymmetry (Jahanbin et al., 2020), through the application of light forces in immature alar cartilage (Matsuo et al., 1984). This mechanism can, as shown in the results of this systematic review and meta-analysis, increase the height of the nostril and benefit patients undergoing cheiloplasty and treatment with NAM. This greater nasal harmony, measurable in the short and long term, has great clinical importance (Yilmaz et al., 2018; Kinouchi et al., 2018) and a strong impact on aesthetics (Broder et al., 2016).

For nostril width, a measurement that, when reduced, positively affects nasal harmony, some studies included in this systematic review and meta-analysis showed that, in the short term, there is a slightly greater decrease in this measurement among individuals undergoing cheiloplasty and treated with NAM (Haddad et al., 2023; Nayak et al., 2021). However, in the long term, results show that individuals operated and treated with NAM had wider nostrils than those operated but not treated with NAM (Nayak et al., 2021; Kurnik et al., 2021). Comparing the nostril width with what occurs in the bialar width, we see that there is a decrease in the bialar width in the short term (Haddad et al., 2023; Nayak et al., 2021) and an increase in this width in the group of individuals subjected to cheiloplasty and who underwent long-term NAM treatment (Bonanthaya et al., 2018; Nayak et al., 2021; Kurnik et al., 2021; Harrison et al., 2020; Clark et al., 2011). These two measurements show results in the horizontal (latero-lateral) direction of the slit, where the first measurement measures the width of the nostril and the second measurements the width of the two nostrils, at their base. The expectation for these measurements with the use of the nasal stent – elevating the lowered nostril due to the presence of the cleft, associated with lip tapes applied to the upper lip region, bringing its cleft segments closer together – is a decrease in nostril width and bialar width ( Jahanbin et al., 2020). Based on the results of the studies

included, it is notable that the rehabilitation of this nasolabial region is still not clear, as in the short term we see a small favorable change and in the long term, the group treated with NAM presents greater values in these widths than the group that was not treated with NAM. Therefore, we conclude that the increase in laterolateral width was not favorably affected by NAM treatment.

One of the biggest challenges for the aesthetic reconstruction of patients with cleft lip and palate, especially bilateral, is a deficient columella (Grayson, et al., 2004). An increase in this structure, making it longer and wider, is beneficial for nasal harmony. Haddad et al., 2023, Nayak et al., 2021, Harrison et al., 2020 and Fedeles et al., 2012 found greater columellar length in patients undergoing cheiloplasty and NAM treatment, in the short and long term of follow-up. The columellar width, in the studies of Kurnik et al., 2021 and Harrison et al., 2020, was also greater in patients with cleft lip and palate undergoing treatment with NAM, showing a positive impact of this treatment in the two evaluations of this structure. NAM treatment can enlarge columella tissues through tissue expansion and development (Mancini et al., 2019), giving surgeons the chance to achieve columella lengthening in addition to good healing under less tension, good projection of the nasal tip and some symmetry of the nostrils (Cai et al., 2020; Kirbschus et al., 2006; Grayson et al., 2001).

Some limitations should be examined in this systematic review and meta-analysis of the included studies, such as the moderate to serious risk of bias. These limitations arise from the fact that these studies were retrospective and non-randomized (Euser et al., 2009). Such studies also present different times for starting monitoring and the loss of data during the research (Howe et al., 2016). Another point to be considered is the presence of different methodologies and the heterogeneity of the outcomes evaluated (Fletcher et al., 2007). Standardizing the methodology would allow meta-analyses to be carried out with a greater number of studies and with more outcomes evaluated, helping to show more clearly the effects of treatment with NAM on nasal symmetry.

## Conclusion

The results obtained for nostril height and columellar width/length were favored by cheiloplasty followed by NAM treatment, showing an increase in the size of these

measurements, in the short and long term, bringing benefits to nasal harmony. Alar length was also positively impacted by treatment with NAM, shortly after the labrum repair surgery. Treatment with NAM decreases nostril width and bialar width measurements when evaluated in the short term. In the long term, these measurements were higher in individuals who underwent treatment with NAM, when compared to the group that did not undergo treatment with NAM.

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# Table 1: Data extraction of the included articles

| Authors, year, Country, Study design | Groups and characteristics | Outcomes assessed and times evaluated | Results of comparisons between groups |
|---|---|---|---|
| Haddad et al., 2023, Lebanon, Cohort study | **G1** = (NAM + cheiloplasty)<br>**N =** 15<br>**Type**: BCLP<br>**Mean age:** 1.1 months +/- 0.2 at T1 (before cheiloplasty) (gender distribution not informed)<br><br>**G2** = (cheiloplasty only)<br>**N =** 15<br>**Type:** BCLP<br>**Mean age:** 5 months +/- 0.2 at T1 (before cheiloplasty) (gender distribution not informed) | The following outcomes were assessed 3 months post-cheiloplasty **(T2=Immediate time)**:<br><br>-Nostril height R, mm<br><br>-Nostril height L, mm<br><br>-Nostril width R, mm<br><br>-Nostril width L, mm<br><br>-Alar lenght R, mm<br><br>-Alar lenght L, mm<br><br>-Bialar width, mm<br><br>-Columella lenght, mm | Outcomes / G1 at T2 Mean (SD) / G2 at T2 Mean (SD) / G1 x G2 Mean (SD) / *p* value<br>Nostril height R, mm: 6.47 (0.64) / 4.75 (0.83) / 1.72 (0.74) / < 0.001<br>Nostril height L, mm: 6.17 (0.68) / 3.86 (0.83) / 2.31 (0.75) / < 0.001<br>Nostril width R, mm: 7.12 (0.65) / 7.12 (1.3) / 0.00 (1.02) / 0.984<br>Nostril width L, mm: 6.82 (0.72) / 7.57 (1.11) / -0.75 (0.93) / 0.062<br>Alar lenght R, mm: 13.69 (1.14) / 14.34 (1.25) / -0.65 (1.19) / 0.197<br>Alar lenght L, mm: 13.99 (1.39) / 14.55 (1.55) / -0.56 (1.47) / 0.361<br>Bialar width, mm: 24.84 (1.71) / 26.98 (1.93) / -2.14 (1.82) / 0.009<br>Collumelar length, mm: 5.21 (0.57) / 3.58 (0.78) / 1.63 (0.68) / < 0.001 |
| Nayak et al., 2021, India, Retrospective study | **G1** = (NAM + Cheiloplasty)<br>**N** = 38<br>**Type**: UCLP<br>**Mean age**: 6.0 +/- 1.9 months at T1 (19 males, 19 females)<br><br>**G2 =** (Cheiloplasty only)<br>**N** = 48<br>**Type**: UCLP<br>**Mean age:** 6.4 +/- 3.3 months at T1 (16 males, 32 females) | The outcomes were assessed immediately after cheiloplasty **(T2 = immediate time)** and approximately 5 years after cheiloplasty **(T3 = long term time):**<br><br>-Nostril height, ratio<br><br>-Nostril width, ratio<br><br>-Alar base width, ratio<br><br>-Columella lenght, ratio | Outcomes / G1 at T2 Mean (SD) / G2 at T2 Mean (SD) / G1xG2 Mean (SD) / *p* value<br>Nostril height, ratio: 0.96 (0.25) / 0.82 (0.15) / 0.14 (0.20) / -<br>Nostril width, ratio: 1.04 (0.39) / 1.09 (0.27) / -0.05 (0.33) / -<br>Alar base width, ratio: 0.98 (0.16) / 1.03 (0.16) / -0.05 (0.16) / -<br>Columella length, ratio: 1.00 (0.14) / 0.90 (0.12) / 0.10 (0.13) / -<br><br>Outcomes / G1 at T3 Mean (SD) / G2 at T3 Mean (SD) / G1xG2 Mean (SD) / *p* value<br>Nostril height, ratio: 0.81 (0.16) / 0.79 (0.16) / 0.02 (0.16) / -<br>Nostril width, ratio: 1.33 (0.29) / 1.26 (0.23) / 0.07 (0.26) / -<br>Alar base width, ratio: 1.25 (0.23) / 1.17 (0.14) / 0.08 (0.19) / -<br>Columella length, ratio: 0.85 (0.12) / 0.82 (0.10) / 0.03 (0.11) / - |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Kurnik et al., 2021, USA, Study design not reported. | **G1** = (NAM + Cheiloplasty)<br>**N** = 16<br>**Type**: UCLP<br>**Mean age**: = 4.7 +/- 1.4 months at T0 (before NAM); (7 males, 9 females)<br><br>**G2** = (cheiloplasty only)<br>**N** = 25<br>**Type**: UCLP<br>**Mean age**: = 5.0 +/- 1.4 months at T0 (before NAM); (16 males, 9 females) | The outcomes were assessed at 5 years of age **(T3=long term time):**<br><br>-Nostril height cleft, mm<br>-Nostril width cleft, mm<br>-Nostril height, ratio<br>-Nostril width, ratio<br>-Nasal width, mm<br>-Columellar width, mm | Outcomes | G1 at T3 Mean (SD) | G2 at T3 Mean (SD) | G1xG2 Mean (SD) | *p* value |
| | | | Nostril height cleft, mm | 9.33 (1.43) | 8.00 (1.27) | 1.33 (1.35) | 0.041 |
| | | | Nostril width Cleft, mm | 12.11 (0.71) | 11.93 (1.75) | 0.18 (1.33) | 0.311 |
| | | | Nostril height, ratio | 0.97 (0.12) | 0.89 (0.08) | 0.08 (0.10) | 0.070 |
| | | | Nostril width, ratio | 1.26 (0.12) | 1.30 (0.25) | -0.04 (0.19) | 0.849 |
| | | | Nasal width, mm | 33.91 (1.55) | 32.95 (3.01) | 0.96 (2.39) | 0.216 |
| | | | Columellar width, mm | 5.19 (0.58) | 4.92 (0.91) | 0.27 (0.76) | 0.531 |
| Harrison et al., 2020, USA, Retrospective comparative cross-sectional study | **G1** = (NAM + Cheiloplasty)<br>**N** = 18<br>**Type**: BCLP<br>**Mean age**: = not informed (10 males, 8 females)<br><br>**G2** = (cheiloplasty only)<br>**N** = 18<br>**Type**: BCLP<br>**Mean age**: =not informed (10 males, 8 females) | The outcomes were assessed at post NAM **(T1=before operation)** and at 5 years post operation **(T3=long term time):**<br><br>-Alar base width, mm<br><br>-Columella length, mm<br><br>-Columella width, mm | Outcomes | G1 (T3 – T1) Mean (SD) | G2 (T3 – T1) Mean (SD) | G1xG2 Mean (SD) | *p* value |
| | | | Alar base width, mm | 3.20 (3.11) | 3.09 (2.47) | 0.11 (2.80) | - |
| | | | Columella length, mm | 3.09 (1.58) | 2.20 (1.10) | 0.89 (1.36) | - |
| | | | Columella width, mm | 1.81 (1.81) | 0.55 (0.82) | 1.26 (1.40) | - |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Maliha et al., 2020, USA, Retrospective single institution review. | **G1** = (NAM + Cheiloplasty)<br>**N** = 20<br>**Type**: UCLP<br>**Age (range):** = 18-25 years (10 males, 10 females)<br><br>**G2** = (cheiloplasty only)<br>**N** = 21<br>**Type**: UCLP<br>**Age (range):** = 17-29 years (16 males, 5 females) | The outcomes were assessed at or past 14 years of age **(T3=long term time):**<br><br>-Nostril height, ratio<br><br>-Alar base width, ratio | Outcomes | G1 at T3 Mean (SD) | G2 at T3 Mean (SD) | G1xG2 Mean (SD) | *p* value |
| | | | Nostril height, ratio | 0.88 (0.09) | 0.73 (0.17) | 0.15 (0.13) | 0.002 |
| | | | Alar base width, ratio | 0.99 (0.08) | 1.04 (0.13) | -0.05(0.10) | 0.115 |
| Bonanthaya et al., 2018, India, Retrospective study. | **G1** = (NAM + Cheiloplasty)<br>**N** = 59<br>**Type**: BCLP<br>**Mean age**: = not informed (42 males, 17 females)<br><br>**G2** = (cheiloplasty only)<br>**N** = 62<br>**Type**: BCLP<br>**Mean age**: = not informed (47 males, 15 females) | The outcomes were assessed 6 months after cheiloplasty **(T2 = immediate time):**<br><br>-Columella height<br><br>-Bialar width | Outcomes | G1 at T2 Mean (SD) | G2 at T2 Mean (SD) | G1xG2 Mean (SD) | *p* value |
| | | | Columella height, mm | 0.79 (0.40) | 0.43 (0.40) | 0.36 (0.40) | < 0.001 |
| | | | Bialar width, mm | 0.33 (0.40) | 0.17 (0.30) | 0.16 (0.35) | 0.013 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Fedeles et al., 2012, Slovakia, Study design not reported. | **G1 =** (NAM + Cheiloplasty)<br>**N = 6**<br>**Type**: UCLP (6)<br>**Mean age:** Mean age and gender distribution not informed.<br><br>**G2 =** (Cheiloplasty only)<br>**N = 9**<br>**Type**: UCLP<br>**Mean age:** Mean age and gender distribution not informed. | The outcomes were assessed before cheiloplasty **(T1=not informed)** and after cheiloplasty **(T2=not informed):**<br><br>-Nostril height, ratio<br>-Nostril width, ratio<br>-Interalar distance, ratio<br>-Columella lenght, ratio | Outcomes | G1 (T2-T1) Mean (SD) | G2 (T2-T1) Mean (SD) | G1xG2 Mean (SD) | *p* value |
| | | | Nostril height, ratio | 1.00 (3.01) | 0.11 (1.04) | 0.89 (2.25) | - |
| | | | Nostril width, ratio | -4.58 (2.46) | -4.27 (2.29) | -0.31 (2.37) | - |
| | | | Interalar distance, ratio | -3.33 (2.93) | -4.67 (2.38) | 1.34 (2.66) | - |
| | | | Columella lenght, ratio | 1.08 (1.92) | 0.77(1.66) | 0.31 (1.79) | - |
| Clark et al., 2011, USA, Study design not reported. | **G1** = (NAM + Cheiloplasty)<br>**N** = 20<br>**Type**: UCLP<br>**Mean age** = 5,1 years (2.6-10.0 range); Gender distribution not informed<br><br>**G2** = (cheiloplasty only)<br>**N** = 5<br>**Type**: UCLP<br>**Mean age**: = 6.0 years (4.9-7.6 range) Gender distribution not informed | The outcomes were assessed at 5-6 years on average after cheiloplasty **(T3 = long term time):**<br><br>-Alar width, mm<br>- Alar base projection, mm<br>-Alar base position in Superoinferior direction, mm | Outcomes | G1 at T3 Median (Min-Max) | G2 at T3 Median (Min-Max) | G1xG2 Median (Min-Max) | |
| | | | Alar width, mm | 0.40 (-4.8 - 2.8) | 0.30 (-3.6 - 1.3) | 0.10 | |
| | | | Alar base projection, mm | 0.00 (-4.6 - 3.8) | 0.60 (-0.7 - 1.5) | -0.60 | |
| | | | Alar base position in Superoinferior direction, mm | -0.70 (-3.4 - 2.7) | -0.50 (-1.3 - -0.1) | -0.20 | |
| Barillas et al., 2008, USA, Retrospective review. | **G1** = (NAM + Cheiloplasty)<br>**N** = 15<br>**Type**: UCLP<br>**Age (range)**: = 7-11 years; Gender distribution not informed<br><br>**G2** = (cheiloplasty only)<br>**N** = 10<br>**Type**: UCLP<br>**Mean age**: = 7-11 years Gender distribution not informed | The outcomes were assessed at 9 years on average after cheiloplasty **(T3 = long term time):**<br><br>-Nasal ala projection length<br><br>-Nasal dome height | Outcomes | G1 at T3 Mean (SD) | G2 at T3 Mean (SD) | G1xG2 Mean (SD) | *p* value |
| | | | Nasal ala projection length, mm | 96.50 (2.30) | 93.00 (1.70) | 3.50 (2.02) | - |
| | | | Nasal dome height, mm | 96.40 (5.90) | 86.80 (7.50) | 9.60 (6.74) | - |

**Table 2:** Evaluation of risk of bias of the included studies using ROBINS-I

| Included studies | Domain | | | | | | | Overall risk of bias judgment |
|---|---|---|---|---|---|---|---|---|
| | Pre intervention | | At intervention | Post intervention | | | | |
| | Confounding | Selecting participants for the study | Classifying the interventions | Deviations from intended intervention | Missing data | Measuring outcomes | Selecting reported result | |
| Haddad et al., 2023 | Low | Moderate | Low | Low | Not informed | Not informed | Not informed | **Moderate** |
| Nayak et al., 2021 | Low | Moderate | Low | Low | Not informed | Not informed | Not informed | **Moderate** |
| Kurnik et al., 2021 | Low | Moderate | Low | Low | Moderate | Low | Not informed | **Moderate** |
| Harrison et al., 2020 | Serious | Moderate | Low | Low | Not informed | Not informed | Not informed | **Serious** |
| Maliha et al., 2020 | Serious | Moderate | Low | Low | Not informed | Not informed | Not informed | **Serious** |
| Bonanthaya et al., 2018 | Low | Moderate | Low | Low | Not informed | Not informed | Not informed | **Moderate** |
| Fedeles et al., 2012 | Low | Moderate | Low | Low | Not informed | Not informed | Not informed | **Moderate** |
| Clark et al., 2011 | Low | Moderate | Low | Low | Serious | Low | Not informed | **Serious** |
| Barillas et al., 2008 | Low | Moderate | Low | Low | Not informed | Low | Not informed | **Moderate** |

Figure 1 – Flowchart of the selection process

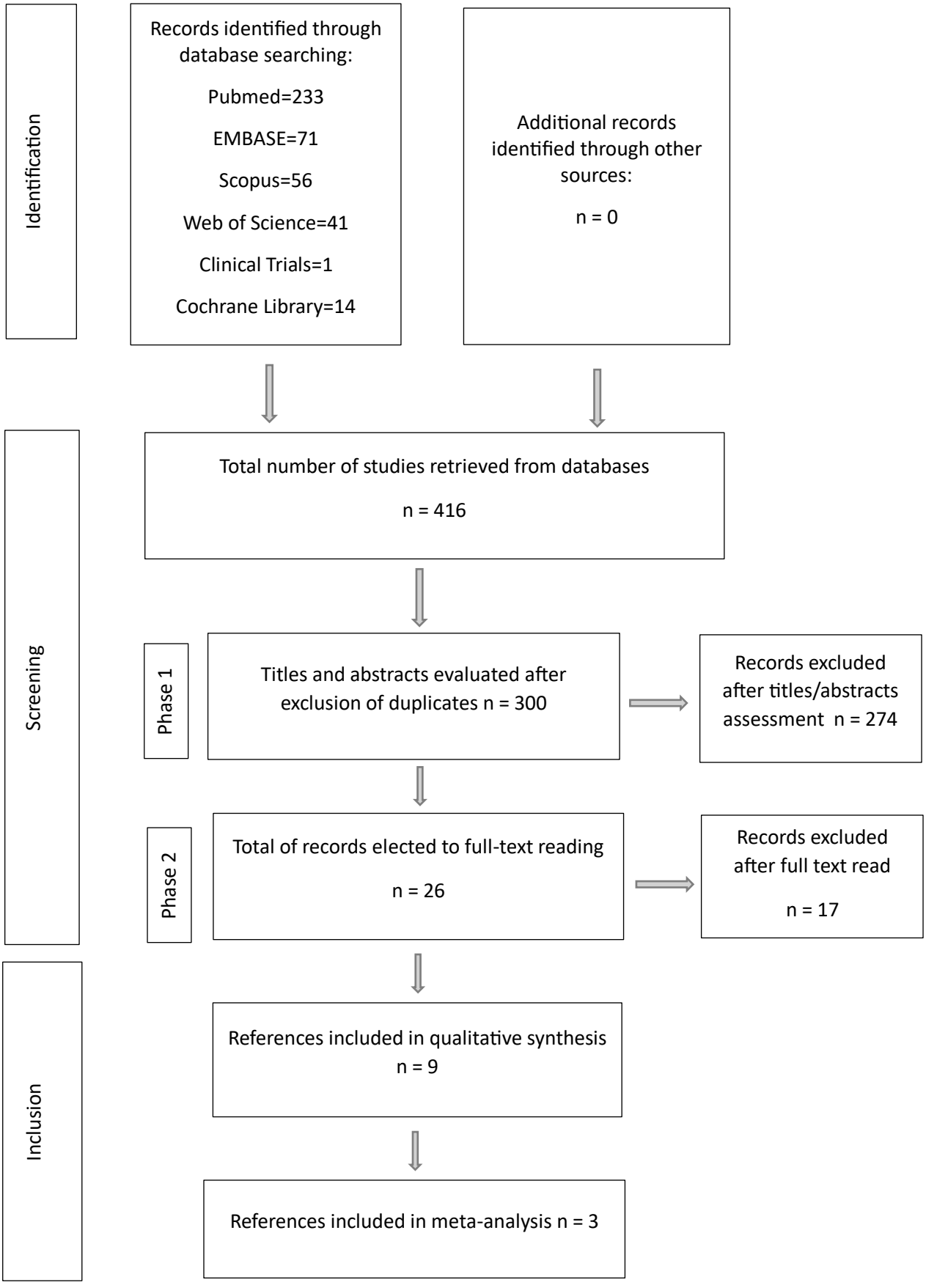


Figure 2 - Meta-analysis of the measure Bialar Width

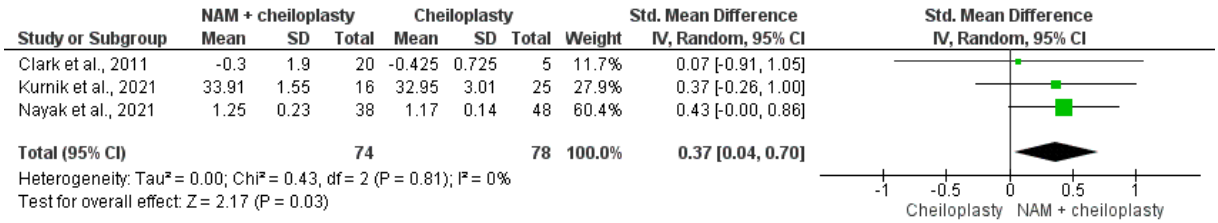



Figure 3 – Meta-analysis of the measure Nostril Height

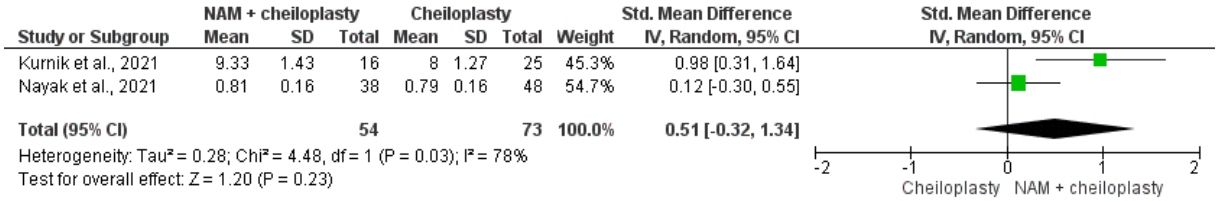
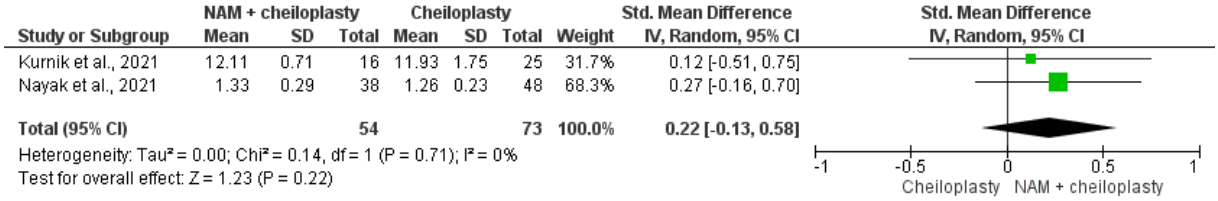



Figure 4 - Meta-analysis of the measure Nostril Width

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**Supplementary File 1: References excluded after assessment of the full text:**

Kondra K, Stanton E, Jimenez C, Ngo K, Wlodarczyk J, Jacob L et al. Rethinking the Rule of 10s: Early Cleft Lip Repair Improves Weight Gain. 2023; 20211206(3):306-312.

Reason: There is no outcome of nasal symmetry.

Lenz JH, Akota I, Zaleckas L, Soots M, Bagante I, Rogovska I et al. Lips and noses in 10-year-old patients with repaired complete unilateral clefts of lip, alveolus, and palate. A prospective three-centre study of the Baltic Cleft Network. 2022; 20211218(3):246-253.

Reason: It presents a subjective assessment of surgical results with heterogeneous evaluations. And it also evaluates primary nasal surgery and not just cheiloplasty.

Meazzini MC, Parravicini F, Cohen N, Rossetti G, Autelitano L. Nasoalveolar molding and skeletal development in patients with bilateral cleft lip and palate: A retrospective cephalometric study at the completion of growth. 2022; 20220303(5):400-405.

Reason: It presents assessments of skeletal development using cephalometric points, without evaluating nasal symmetry.

Wang F, Liu T, Wang C, Song Q. Variational Characteristics of Nasolabial Appearance and Its Influencing Factors for the Unilateral Cleft Lip Repair with Modified Huaxi Technique. 2021; 32(3):1094-1098.

Reason: It cannot be included because it does not have nasal symmetry as an outcome.

Bhutiani N, Tripathi T, Verma M, Bhandari PS, Rai P. Assessment of Treatment Outcome of Presurgical Nasoalveolar Molding in Patients with Cleft Lip and Palate and Its Postsurgical Stability. 2020; 20200301(6):700-706.

Reason: There is no control group, and the experimental group presents UCLP and BCLP patients evaluated in a single group.

Rachwalski M, Najak T, Bitra S, Shetty PN, Bonanthaya K. Nasolabial aesthetics in bilateral cleft lip and palate: nasoalveolar molding vs. no nasoalveolar molding. 2019; 48:22-23.

Reason: Excluded due to being meeting abstract.

Nayak T, Bonanthaya K, Parmar R, Shetty PN, Rao DD. A Comparative Cephalometric Study of Nasoalveolar Molding- and Non-Nasoalveolar Molding-Treated Bilateral Cleft Patients at Early Mixed Dentition Period. 2019; 20180927(5):569-575.

Reason: Excluded for using cephalometric measurements in assessments.

Liang ZG, Yao JF, Chen PKT, Zheng CS, Yang JY. Effect of Presurgical Nasoalveolar Molding on Nasal Symmetry in Unilateral Complete Cleft Lip/Palate Patients After Primary Cheiloplasty Without Concomitant Nasal Cartilage Dissection: Early Childhood Evaluation. 2018; 55(7):935-940.

Reason: It presents a subjective assessment of surgical results, without objective measurements of nasal symmetry.

Kornbluth M, Campbell RE, Daskalogiannakis J, Ross EJ, Glick PH, Russell KA et al. Active Presurgical Infant Orthopedics for Unilateral Cleft Lip and Palate: Intercenter Outcome Comparison of Latham, Modified McNeil, and Nasoalveolar Molding. 2018; 20180220(5):639-648.

Reason: It presents heterogeneous measurements and cephalometric points to obtain them.

Shetty V, Agrawal RK, Sailer HF. Long-term effect of presurgical nasoalveolar molding on growth of maxillary arch in unilateral cleft lip and palate: randomized controlled trial. 2017; 20170414(8):977-987

Reason: It cannot be included because it does not have nasal symmetry as an outcome.

Broder HL, Flores RL, Clouston S, Kirschner RE, Garfinkle JS, Sischo L et al. Surgeon's and Caregivers' Appraisals of Primary Cleft Lip Treatment with and without Nasoalveolar Molding: A Prospective Multicenter Pilot Study. 2016; 137(3):938-945.

Reason: It presents a subjective assessment of surgical results without objective measurements of nasal symmetry.

Laverde BLB, Silva Freitas R, Nasser IJG. Assessment of labionasal structures in patients with unilateral cleft lip. 2016; 27(1):78-81.

Reason: Article excluded for not presenting measurements after cheiloplasty intervention, only presenting measurements before and during surgery.

Bonanthaya K, Parmar R, Shetty PN. Naso-Alveolar Molding and primary cleft lip surgery. 2015; 44:e2.

Reason: Excluded due to being meeting abstract.

Liang Z, Yao J, Philip KTC, Zheng C, Yang J. The effect of presurgical nasoalveolar molding (PNAM) on nasal symmetry in unilateral complete cleft lip/palate after primary cheiloplasty. 2015; 44:e101-e102.

Reason: Excluded due to being meeting abstract.

Rubin MS, Clouston S, Ahmed MM, Lowe M, Shetye PR, Broder HL et al. Assessment of presurgical clefts and predicted surgical outcome in patients treated with and without nasoalveolar molding. 2015; 26(1):71-75.

Reason: It cannot be included because it does not have nasal symmetry as an outcome.

Patel PA, Rubin MS, Clouston S, Lalezaradeh F, Brecht LE, Cutting CB et al. Comparative Study of Early Secondary Nasal Revisions and Costs in Patients with Clefts Treated with and Without Nasoalveolar Molding. 2015; 26(4):1229-1233.

Reason: It cannot be included because it does not have nasal symmetry as an outcome.

Lee CTH, Garfinkle JS, Warren SM, Brecht LE, Cutting CB, Grayson BH. Nasoalveolar molding improves appearance of children with bilateral cleft lip-cleft palate. 2008; 122(4):1131-1137.

Reason: Excluded because the intervention is not cheiloplasty but “Fork flaps” surgery.

## Supplementary File 2: Description of assessment of risk of bias

### Haddad et al., 2023:

**Pré Intervention:**

Confounding: There are no confounders such as rhinoplasty or gingivoperiosteoplasty or any variation in the surgical technique. All the patients were recruited from the same Department of Orthodontics and Dentofacial Orthopaedics (a tertiary care paediatric hospital). All patients were operated by the same surgeon who has an experience in treating cleft lip and palate patients for more than 20 years.

Selecting participants for the study: : All selected patients were eligible for the study. The start of follow-up and the start of intervention did not coincide for all participants.

**At Intervention:**

Classifying Intervention: The intervention was well defined (cheiloplasty + NAM or cheiloplasty Only) and was decided retrospectively.

**Post Intervention**:

Deviation from intended Intervention: There was no deviation from the intended intervention, as everyone underwent the same intervention (cheiloplasty).

Missing data: No information is reported about missing data or the potential for data to be missing.

Measuring outcomes: No information is reported about the methods of outcome assessment.

Selecting reported result: There is too little information to make a judgement.

Reason of overall judgment: **MODERATE.** The study is judged to be at low or moderate risk of bias for all domains.

### Kurnik et al., 2021:

**Pre-Intervention:**

Confounding: There are no confounders like surgical revisions or secondary alveolar bone grafting. (We focused on patients at 5 years of age, as that would provide the longest-term outcome without including confounding changes from revisions or secondary alveolar bone grafting.)

Selecting participants for the study: All selected patients were eligible for the study. The start of follow-up and the start of intervention did not coincide for all participants.

**At Intervention:**

Classifying Intervention: The intervention was well defined (cheiloplasty + NAM or cheiloplasty Only) evaluate at 5 years of age (T3=long term time) and was performed retrospectively.

**Post Intervention**:

Deviations from intended intervention: There was no deviation from the intended intervention, as everyone underwent the same intervention (cheiloplasty).

Missing data: The analysis addressed missing data and is likely to have removed any risk of bias. (All patients with unilateral cleft lip who underwent primary cheiloplasty performed by a single surgeon over a 7-year period (n = 195) were reviewed. Patients with complete unilateral cleft lip and palate, in which the cleft extended through the entirety of lip and palate, were considered candidates for nasoalveolar molding and eligible for this study. Any patient with a soft-tissue band (also known as a Simonart band) was excluded, as were patients with cleft lip and alveolus or incomplete cleft lip, regardless of the severity of nose deformity. Patients with inadequate follow-up images were also excluded. Sixty-seven patients had complete cleft lip and palate and 41 patients had adequate follow-up and images at each time point. Sixteen patients completed nasoalveolar molding treatment, and 25 patients did not.)

Measuring outcomes: The outcome measure was unlikely to be influenced by knowledge of the intervention received by study participants or the outcome assessors were unaware of the intervention received by study participants. (To verify that the nasoalveolar molding and no–nasoalveolar molding groups were similar at presentation, two blinded cleft surgeons independently assessed images captured at T0 and arranged them according to “surgical severity.” To verify that subjects who successfully completed nasoalveolar molding had significant nasolabial changes, the two blinded cleft surgeons again ranked subject images obtained before and after nasoalveolar molding (at T1). Raters assessed image sets at least 3 weeks apart to avoid recall bias. The mean rank score was used to define severity at T0 and T1Photographs in frontal, submental, and right and left lateral views were cropped in a trapezoidal fashion to limit observer’s attention to the nasolabial region and assembled in a single slide for each patient at each time point, in which raters were asked to arrange slides in the order from best to worst nasal appearance. The image order was used as a rank score. Molding appliances and tape were removed during image capture and patient facial features that could reveal that a patient was undergoing nasoalveolar molding (i.e., skin changes on cheeks from chronic taping) were cropped or removed. Images of children with right side clefts were flipped horizontally so that the appearance of all subjects involved a left-side cleft.)

Selecting reported result: There is too little information to make a judgement.

Reason of overall judgment: **MODERATE.** The study is judged to be at low or moderate risk of bias for all domains.

**Nayak et al., 2021:**

**Pré Intervention:**

Confounding: There are no confounders such as rhinoplasty or gingivoperiosteoplasty or any variation in the surgical technique. All patients were recruited from the same treatment center, all UCLP, non-syndromic. All 38 patients in group G1 treated with NAM device and 48 patients in group G2 did not receive NAM. All operated by 2 surgeons, using the same technique.

Selecting participants for the study: All selected patients were eligible for the study. The start of follow-up and the start of intervention did not coincide for all participants.

**At Intervention:**

Classifying Intervention: The intervention was well defined (cheiloplasty + NAM or cheiloplasty Only) evaluated in time 1 (immediately after cheiloplasty) and time 2 (5 years after cheiloplasty) and was performed retrospectively.

**Post Intervention**:

Deviations from intended intervention: There was no deviation from the intended intervention, as everyone underwent the same intervention (cheiloplasty).

Missing data: No information is reported about missing data or the potential for data to be missing.

Measuring outcomes: No information is reported about the methods of outcome assessment.

Selecting reported result: There is too little information to make a judgement.

Reason of overall judgment: **MODERATE.** The study is judged to be at low or moderate risk of bias for all domains.

**Harrison et al., 2020:**

**Pre-Intervention:**

Confounding: Reliability or validity of measurement of an important domain was low enough that we expect serious residual confounding. (Primary cleft lip repair was performed at the average age of 5.00 months (range: 2.60-8.86) using a variety of techniques previously described by Noordhoff's (1986), Byrd et al. (2008), and cutting and Kamdar (2008). Palatoplasty of the hard palate was performed at the average age of 1.16 years (range: 0.77- 1.59) and of the soft palate at the age of 1.64 years (range: 0.98- 2.10) using techniques described by Furlow (1986), Bardach (1995), and Sommerlad (2003). Autogenous iliac alveolar bone graft was performed at an average of 10.15 years (range: 7.98- 11.33). In 54% of patients in the 10 and 15 years of age groups, columellar lengthening surgery was performed at the average age of 1.57 years (range: 1.4-1.71).)

Selecting participants for the study: All selected patients were eligible for the study. The start of follow-up and the start of intervention did not coincide for all participants. (All patients included were diagnosed with BCLP and underwent primary bilateral cleft lip repair and primary cleft rhinoplasty at Children's Health Medical Center in Dallas

between 2004 and 2019. . No patients with syndromic BCLP were included in this study. An equal number of age and sex-matched control patients' 3-dimensional images were analyzed for comparison.)

**At Intervention:**

Classifying Intervention: The intervention was well defined (cheiloplasty + NAM or cheiloplasty Only). The outcomes were assessed at post NAM (T1=before operation) and at 5 years post operation (T3=long term time) and was performed retrospectively.

**Post Intervention**:

Deviations from intended intervention: There was no deviation from the intended intervention, as everyone underwent the same intervention (cheiloplasty).

Missing data: No information is reported about missing data or the potential for data to be missing.

Measuring outcomes: No information is reported about the methods of outcome assessment.

Selecting reported result: There is too little information to make a judgement.

Reason of overall judgment: **SERIOUS**. The study is judged to be at serious risk of bias in at least one domain, but not at critical risk of bias in any domain.

**Maliha et al., 2020:**

**Pre-Intervention:**

Confounding: At least one known important domain was not appropriately measured, or not controlled for. (Patients in the NAM group underwent cleft lip repair with primary rhinoplasty by 2 surgeons using the modified Millard's type rotational and advancement cleft lip repair technique. Patients in the non-NAM cohort had cleft lip repairs performed at several different institutions, precluding the identification of primary cleft lip and nasal repair techniques.) (Additionally, our NAM and non-NAM patients were operated on by different surgeons.)

Selecting participants for the study: All selected patients were eligible for the study. The start of follow-up and the start of intervention did not coincide for all participants.

**At Intervention:**

Classifying Intervention: : The intervention was well defined (cheiloplasty + NAM or cheiloplasty Only). The outcomes were assessed at or past 14 years of age (T3=long term time) and was performed retrospectively.

**Post Intervention**:

Deviations from intended intervention: There was no deviation from the intended intervention, as everyone underwent the same intervention (cheiloplasty).

Missing data: No information is reported about missing data or the potential for data to be missing.

Measuring outcomes: No information is reported about the methods of outcome assessment.

Selecting reported result: There is too little information to make a judgement.

Reason of overall judgment: **SERIOUS**. The study is judged to be at serious risk of bias in at least one domain, but not at critical risk of bias in any domain.

**Bonanthaya et al., 2018:**

**Pre-Intervention:**

Confounding: No confounding expected. (This study included only those patients who underwent a modified Millard's cheiloplasty before 1 year of age. The cheiloplasty was done by the same two surgeons without primary rhinoplasty or gingivoperiosteoplasty.)

Selecting participants for the study: All selected patients were eligible for the study. The start of follow-up and the start of intervention did not coincide for all participants. (Patients with incomplete clefts and those with craniofacial anomalies were excluded.)

**At Intervention:**

Classifying Intervention: : The intervention was well defined (cheiloplasty + NAM or cheiloplasty Only). The outcomes were assessed 6 months after cheiloplasty (T2 = immediate time) and was performed retrospectively.

**Post Intervention**:

Deviations from intended intervention: There was no deviation from the intended intervention, as everyone underwent the same intervention (cheiloplasty).

Missing data: No information is reported about missing data or the potential for data to be missing.

Measuring outcomes: No information is reported about the methods of outcome assessment.

Selecting reported result: There is too little information to make a judgement.

Reason of overall judgment: **MODERATE.** The study is judged to be at low or moderate risk of bias for all domains.

**Fedeles et al., 2012:**

**Pre-Intervention:**

Confounding: There are no confounders or any variation in the surgical technique. All patients were recruited from the same treatment center (National cleft centre in Bratislava, Slovakia). The patients used in this systematic review were UCLP. The G1

group had 6 patients UCLP, treated with NAM device and in G2 group had 9 patients UCLP did not receive NAM. All operated using the same surgical protocol.

Selecting participants for the study: All selected patients were eligible for the study. The start of follow-up and the start of intervention did not coincide for all participants.

**At Intervention:**

Classifying Intervention: The intervention was well defined (cheiloplasty + NAM or cheiloplasty Only) evaluated in time 1 (before cheiloplasty) and time 2 (after cheiloplasty) and was performed retrospectively.

**Post Intervention**:

Deviations from intended intervention: There was no deviation from the intended intervention, as everyone underwent the same intervention (cheiloplasty).

Missing data: No information is reported about missing data or the potential for data to be missing.

Measuring outcomes: No information is reported about the methods of outcome assessment.

Selecting reported result: There is too little information to make a judgement.

Reason of overall judgment: **MODERATE.** The study is judged to be at low or moderate risk of bias for all domains.

**Clark et al., 2011:**

**Pre-Intervention:**

Confounding: No confounding expected. (All the operations were performed by 1 surgeon. Both sexes and all races were included.)

Selecting participants for the study: All selected patients were eligible for the study. The start of follow-up and the start of intervention did not coincide for all participants.

**At Intervention:**

Classifying Intervention: : The intervention was well defined (cheiloplasty + NAM or cheiloplasty Only). The outcomes were assessed at 5-6 years on average after cheiloplasty (T3 = long term time) and was performed retrospectively.

**Post Intervention**:

Deviations from intended intervention: There was no deviation from the intended intervention, as everyone underwent the same intervention (cheiloplasty).

Missing data: The analysis addressed missing data and is likely to have removed any risk of bias. (Forty-eight patients met the inclusion criteria and were invited to participate in the study. The patients who did not respond were followed up with telephone calls until they were either contacted or confirmed lost to follow-up. Fifteen

patients were contacted but declined to come back to the clinic. Eight patients were lost to follow-up because they either moved out of state or changed their address and telephone numbers.) The final sample was 25 patients.

Measuring outcomes: The outcome measure was unlikely to be influenced by knowledge of the intervention received by study participants. (The examiners were completely blinded to the patient's treatment record during the assessment and analysis.)

Selecting reported result: There is too little information to make a judgement.

Reason of overall judgment: **SERIOUS**. The study is judged to be at serious risk of bias in at least one domain, but not at critical risk of bias in any domain.

**Barillas et al., 2008:**

**Pre-Intervention:**

Confounding: No confounding expected. All patients, nasoalveolar molding and control, were treated with extended Mohler-type lip repair, Millard-type gingivoperiosteoplasty, and Cutting-type primary nasal surgery. All operations were performed by the same surgeon.

Selecting participants for the study: All selected patients were eligible for the study. The start of follow-up and the start of intervention did not coincide for all participants.

**At Intervention:**

Classifying Intervention: : The intervention was well defined (cheiloplasty + NAM or cheiloplasty Only). The outcomes were assessed at 9 years on average after cheiloplasty (T3 = long term time) and was performed retrospectively.

**Post Intervention**:

Deviations from intended intervention: There was no deviation from the intended intervention, as everyone underwent the same intervention (cheiloplasty).

Missing data: No information is reported about missing data or the potential for data to be missing.

Measuring outcomes: The outcome measure was unlikely to be influenced by knowledge of the intervention received by study participants. (All measurements were obtained three times by two independent blinded investigators).

Selecting reported result: There is too little information to make a judgement.

Reason of overall judgment: **MODERATE.** The study is judged to be at low or moderate risk of bias for all domains.

## Supplementary File 3. Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis

| Avaliação de certeza | | | | | | | Nº de pacientes | | Efeito | | Certeza | Importância |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nº de estudos | Desenho do estudo | Risco de viés | Inconsistencia | Evidência indireta | Imprecisão | Outras considerações | Queiloplastia + NAM | Somente queiloplastia | Relativo (95%CI) | Absoluto (95%CI) | | |
| Largura bialar (acompanhamento: média de 5 anos) | | | | | | | | | | | | |
| 3 | Estudos não randomizados | Não grave | Não grave | Grave (a) | Grave (b) | toda confusão residual plausível reduziria o efeito demonstrado | 74 | 78 | - | SMD **0.37 SD more** (0.04 more to 0.7 more) | ⊕⊕⊕◯ Moderada | As evidências são suficientes para apoiar uma conclusão; no entanto, pesquisas futuras ainda podem influenciar a confiança na estimativa |
| Altura da narina (acompanhamento: média de 5 anos) | | | | | | | | | | | | |
| 2 | Estudo não randomizados | Não grave | Muito grave (c) | Grave (d) | Muito grave (e) | toda confusão residual plausível reduziria o efeito demonstrado | 54 | 73 | - | SMD **0.51 SD more** (0.32 fewer to 1.34 more) | ⊕◯◯◯ muito baixa | O verdadeiro efeito é desconhecido e pesquisas adicionais podem ter uma influência significativa na confiança na estimativa |
| Largura da narina (acompanhamento: média de 5 anos) | | | | | | | | | | | | |
| 2 | Estudos não randomizados | Não grave | Grave (f) | Grave (g) | Muito grave (h) | toda confusão residual plausível reduziria o efeito demonstrado | 54 | 73 | - | SMD **0.22 SD more** (0.13 fewer to 0.58 more) | ⊕◯◯◯ muito baixa | O verdadeiro efeito é desconhecido e pesquisas adicionais podem ter uma influência significativa na confiança na estimativa |

CI: confidence interval; SMD: standardized mean difference

Explanations
a. I cannot extrapolate the evidence to other populations.
b. This imprecision criterion was downgraded by one level because the minimum sample size is not sufficient for a quantitative outcome. Although the effect estimate favors the intervention and does not cross the center line, it is in a range that does not provide important clinical benefits to the patient.
c. The inconsistency criterion was downgraded as it presented $I^2$ with a value of 78%.
d. I cannot extrapolate the evidence to other populations.
e. This imprecision criterion was downgraded by one level because the minimum sample size is not sufficient for a quantitative outcome. There was a further downgrade because the effect estimate favors the intervention but crosses the central line.
f. The inconsistency criterion was downgraded.
g. I cannot extrapolate the evidence to other populations.
h. This imprecision criterion was downgraded by one level because the minimum sample size is not sufficient for a quantitative outcome. There was a further downgrade because the effect estimate favors the intervention but crosses the central line.

# 7 CONSIDERAÇÕES FINAIS

A fissura labiopalatina é uma má formação congênita comum que pode apresentar variações em sua extensão e gravidade e requer um prolongado tratamento e reabilitação, que se inicia ao nascimento indo até a idade adulta (Wang *et al*., 2021). Enquanto a fissura que acomete lábio e rebordo alveolar está associada a problemas estéticos, má oclusões e conflitos psicológicos, a fissura que se estende ao palato, atinge a musculatura da região velofaringeana trazendo complicações como dificuldades na alimentação, fala anasalada e inflamações no ouvido médio (Berryhill *et al*., 2016). É uma adversidade desafiadora para todas as especialidades da equipe de atendimento.

A abordagem cirúrgica inicial do bebê com fissura labiopalatina é a queiloplastia, cirurgia de reparo labial, realizada por volta do 6° mês de vida (Laverde *et al*., 2015). É um momento especial na vida da criança com fissura e da família, pois esta cirurgia vai alterar de modo definitivo e positivo a face média da criança. A inserção de tratamentos ortopédicos anteriores a essa primeira cirurgia, têm os seguintes propósitos: aproveitar a oportunidade da plasticidade da cartilagem nasal dos primeiros meses de vida para uma melhor conformação desta estrutura (Lee *et al*., 2008), aproximar os segmentos de lábio evitando tensões exageradas na sutura cirúrgica e aproximar os segmentos dos rebordos sem perder a forma adequada do arco maxilar (Ayhara *et al*., 2021)

O tratamento com modelador nasoalveolar (NAM) no grupo de pacientes fissurados desta pesquisa, comparado a um grupo que não recebeu nenhuma intervenção pré-cirúrgica, mostrou melhoras significativas nas estruturas faciais e nasais, nos momentos antes da queiloplastia e após a queiloplastia. As placas de acetato do modelador nasoalveolar (NAM) engenharia reversa, como visto nesta pesquisa, aproximaram os segmentos do rebordo, diminuindo a largura da fissura sem interferir nas dimensões do arco maxilar. As fitas e os acessórios nasais impactaram positivamente a largura nasal e bucal, altura e largura das narinas. E, considerando o peso do estigma desta adversidade, pudemos ver, mediante aplicação do instrumento FIS, uma melhora nas emoções familiares após o tratamento com NAM e queiloplastia.

Adicionalmente, investigando a produção científica atual, em busca de evidências para relacionar a intervenção tratamento NAM com o desfecho

queiloplastia, na simetria nasal, percebemos que os resultados obtidos para altura da narina e largura/comprimento columelar, foram favorecidos pela queiloplastia seguida do tratamento com NAM, mostrando um aumento no tamanho dessas medidas, trazendo benefícios para a harmonia nasal. O comprimento alar e a largura bialar também foram impactadas de forma positiva pelo tratamento com o NAM. Isso confirma e complementa os resultados encontrados nos capítulos 1 e 2 desta pesquisa.

O aprofundamento na pesquisa da melhor abordagem para estes pacientes é de grande relevância para as famílias dessas crianças e para as equipes que lidam com esta má formação, pois poderá conciliar procedimentos reabilitadores com a conquista de uma melhor qualidade de vida para todos os envolvidos.

Após este estudo, algumas ponderações sobre padronização de protocolos de avaliações faciais com imagens digitais tridimensionais e unificação dos centros de referência para realização de pesquisas com comparação de grupos maiores, apresentaram-se como medidas factíveis e necessárias que tendem a valorizar os resultados nesta área. Porém, em contrapartida, aspectos específicos inerentes a esta adversidade, como largura da fissura, anatomia e textura nasal/facial e a origem étnica do paciente, e ainda a habilidade do cirurgião plástico, parecem permanecer como importantes dificultadores para que os pesquisadores que se debruçam sobre os resultados das intervenções possam vislumbrar evidências concretas na pesquisa do que melhor poderia ajudar estes pacientes.

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## APÊNDICE A – TCLE (Termo de Consentimento Livre e Esclarecido)

(Destinados aos participantes para avaliação do efeitos dos manejo precoces em participantes fissurados – NAM engenharia reversa)

*Rubrica do pesquisador:* _____

*Rubrica do participante:*_____

O menor de idade pelo qual o(a) senhor(a) é responsável está sendo convidado(a) a participar da pesquisa “ESTUDO DA ABRODAGEM PRECOCE DE PACIENTES COM FISSURAS LABIOPALATINAS TRATADOS COM MODELADOR NASO ALVEOLAR (NAM)”. O objetivo do presente estudo é mostrar o progresso do tratamento pré-operatório e pós-operatório com o uso do modelador naso alveolar (NAM), bem como sua contribuição para avaliação dos efeitos da cirurgia de correção de lábio e cirurgia de correção do palato por meio de moldagem. O NAM é um aparelho usado para aproximar as partes das fissuras e melhorar o formato do arco maxilar. Dois grupos de participantes serão comparados de acordo com o tipo de modelador usado no tratamento e os participantes serão aleatoriamente distribuídos entre os grupos. Além disso, avaliaremos sua percepção na evolução do tratamento e o impacto em sua família por meio de questionários. Sua participação no estudo consistirá em seguir as orientações do uso do aparelho NAM no recém-nascido 24 horas por dia, 07 dias por semana durante todo o período que precede a cirurgia para correção labial e responder os questionários nos seguintes tempos: (1) antes do uso do NAM, (2) após uso do NAM, mas antes da cirurgia de lábio, (3) 3 meses após a cirurgia do lábio e (4) 3 meses após a cirurgia do palato de seu filho (a).

A pesquisa será realizada nas clínicas odontológicas da Faculdade de Odontologia da Universidade Federal de Minas Gerais (UFMG). Há o risco de um desconforto no bebê ocasionado pelas moldagens para a confecção do aparelho e da própria presença do aparelho, além de algum constrangimento no momento de responder o questionário. Para minimizar estes acontecimentos a moldagem será sempre realizada pelo professor orientador da clínica e a adaptação e ajuste do aparelho serão feitos por pessoa capacitada e treinada, utilizando material adequado. Mas, caso o desconforto ocorra, você deverá entrar em contato com algum dos pesquisadores para que este

seja averiguado e tratado. O NAM engenharia reversa será confeccionado com placas de polietileno que é um material já disponível no mercado e muito utilizada por ortodontistas. Todas as medidas serão tomadas para minimizar as possibilidades de risco, como a padronização dos procedimentos e utilização de um material confiável. Adicionalmente os questionários serão aplicados em local isolado, livre do trânsito de pessoas e em sala reservada com sua presença e do pesquisador responsável. Caso você se sinta constrangido não há necessidade de responder as questões. A duração de tempo média prevista para responder os questionários será de 10 minutos.

Com esta pesquisa o menor sob sua responsabilidade terá o benefício de ter um melhor acompanhamento do tratamento da correção das fissuras. Em nenhum momento você ou o participante o qual você é responsável terão o nome divulgado, e mesmo com a publicação dos resultados a sua identidade será preservada. Você não terá qualquer ônus ou ganho financeiro por participar da pesquisa, porém será beneficiado recebendo o tratamento. Eventuais despesas decorrentes da participação na pesquisa, como transporte, serão ressarcidas integralmente. O ressarcimento inclui apenas as despesas que o voluntário terá com a participação na pesquisa e que não teria se não participasse.

O material da pesquisa será arquivado pelo pesquisador responsável pela pesquisa em sua sala na Faculdade de Odontologia da UFMG sendo o período de arquivamento em torno de 4 anos, tempo previsto para o término da pesquisa. Após este período e tendo sido o trabalho publicado, o material será destruído.

Você poderá recusar e/ou deixar de participar deste estudo a qualquer momento, sem nenhum constrangimento ou prejuízo na sua relação com os pesquisadores e a UFMG. Os pesquisadores responsáveis por este projeto podem decidir sobre a exclusão do menor sob sua responsabilidade do estudo por razões científicas, a respeito das quais você deverá ser devidamente informados. Em caso de qualquer dúvida deverá e/ou poderá entrar em contato a qualquer hora com os pesquisadores responsáveis

Soraia Macari ou Nathália Viegas de Oliveira (31) 34092426.

*Rubrica do pesquisador:* _____

*Rubrica do participante:*_____

TERMO DE LIVRE CONSENTIMENTO

Declaro que li e entendi as informações fornecidas nesse termo. Tive a oportunidade de realizar perguntas e todas minhas dúvidas foram respondidas de forma satisfatória. Permito a utilização dos dados e resultados da pesquisa para divulgação e ensino, respeitando meu direito de não ser identificado. Este formulário está sendo assinado por mim em duas vias de igual teor e forma. Recebi uma via deste documento e outra via permaneceu com os pesquisadores.

Local:_____ Data___/___/_____

_____

Assinatura do responsável

_____

Nome do participante

Documento apresentado: _____ N°:_____

Pesquisadores: Soraia Macari / Nathália Viegas de Oliveira Tel.:(31) 3409-2426

E-mail: soraiamacari@gmail.com

_____ _____

Assinatura do pesquisador responsável Assinatura do pesquisador auxiliar

Endereço: Av. Antônio Carlos, 6627. Faculdade de Odontologia. Campus Pampulha. Sala 3204.

Em caso de dúvidas éticas o Comitê de Ética em Pesquisa (COEP – UFMG) poderá ser contactado.

Av. Presidente Antônio Carlos, 6627 – Unidade Administrativa II – 2º andar – Sala 2005 – Telefax:3409 4592 – Belo Horizonte – MG.

## APÊNDICE B – Questionário FIS (Family Impact Scale)

### Questionário FIS - ESCALA DE IMPACTO FAMILIAR

As perguntas seguintes tratam dos efeitos que a condição bucal de sua criança pode ter nos seus pais ou outros membros da família

Nos últimos 3 meses, por causa dos dentes, lábios, boca ou maxilares, com que frequência você ou outro membro da família:

1.Ficou chateada (o)?

( ) Nunca ( ) Uma ou duas vezes ( ) Algumas vezes ( ) Frequentemente ( ) Todos os dias ou quase todos os dias ( ) Não sei

2. Teve seu sono interrompido?

( ) Nunca ( ) Uma ou duas vezes ( ) Algumas vezes ( ) Frequentemente ( ) Todos os dias ou quase todos os dias ( ) Não sei

3.Sentiu-se culpada (o)?

( ) Nunca ( ) Uma ou duas vezes ( ) Algumas vezes ( ) Frequentemente ( ) Todos os dias ou quase todos os dias ( ) Não sei

4.Teve que se ausentar do trabalho (por ex.: dor, consulta com o dentista, cirurgia)?

( ) Nunca ( ) Uma ou duas vezes ( ) Algumas vezes ( ) Frequentemente ( ) Todos os dias ou quase todos os dias ( ) Não sei

5.Teve menos tempo para você ou para sua família?

( ) Nunca ( ) Uma ou duas vezes ( ) Algumas vezes ( ) Frequentemente ( ) Todos os dias ou quase todos os dias ( ) Não sei

6.Ficou preocupada (o) com a possibilidade de sua criança ter menos oportunidades na vida (por ex.: para namorar, casar, ter filhos, conseguir um emprego de que ela goste)?

( ) Nunca ( ) Uma ou duas vezes ( ) Algumas vezes ( ) Frequentemente ( ) Todos os dias ou quase todos os dias ( ) Não sei

7.Ficou pouco à vontade em lugares públicos (por ex.: lojas, restaurantes) na companhia de sua criança?

( ) Nunca ( ) Uma ou duas vezes ( ) Algumas vezes ( ) Frequentemente ( ) Todos os dias ou quase todos os dias ( ) Não sei

Nos últimos 3 meses, por causa dos dentes, lábios, boca ou maxilares, com que frequência sua criança:

8.Teve ciúmes de você ou de outros membros da família?

( ) Nunca ( ) Uma ou duas vezes ( ) Algumas vezes ( ) Frequentemente ( ) Todos os dias ou quase todos os dias ( ) Não sei

9.Culpou você ou outro membro da família?

( ) Nunca ( ) Uma ou duas vezes ( ) Algumas vezes ( ) Frequentemente ( ) Todos os dias ou quase todos os dias ( ) Não sei

10.Discutiu com você ou outros membros da família?

( ) Nunca ( ) Uma ou duas vezes ( ) Algumas vezes ( ) Frequentemente ( ) Todos os dias ou quase todos os dias ( ) Não sei

11.Exigiu mais atenção de você ou de outros membros da família?

( ) Nunca ( ) Uma ou duas vezes ( ) Algumas vezes ( ) Frequentemente ( ) Todos os dias ou quase todos os dias ( ) Não sei

Nos últimos 3 meses, por causa dos dentes, lábios, boca ou maxilares, com que frequência sua criança:

12.Interferiu nas atividades da família em casa ou em outro lugar?

( ) Nunca ( ) Uma ou duas vezes ( ) Algumas vezes ( ) Frequentemente ( ) Todos os dias ou quase todos os dias ( ) Não sei

13.Causou discordância ou conflito em sua família?

( ) Nunca ( ) Uma ou duas vezes ( ) Algumas vezes ( ) Frequentemente ( ) Todos os dias ou quase todos os dias ( ) Não sei

14.Causou dificuldades financeiras para sua família?

( ) Nunca ( ) Uma ou duas vezes ( ) Algumas vezes ( ) Frequentemente ( ) Todos os dias ou quase todos os dias ( ) Não sei

OBRIGADO (A) POR SUA PARTICIPAÇÃO.

## APÊNDICE C – Produção intelectual durante o doutorado

- Participação no 52° Encontro do Grupo Brasileiro de Professores de Ortodontia e Odontopediatria, realizado de 11 a 13 de novembro de 2021, com o trabalho "Efeitos do protocolo com placas modeladoras Naso alveolares (NAM) na maxila de pacientes com fissuras labiopalatinas", com carga horária de 15 hs.
- Participação no 1° Congresso do CENTRARE – Centro de Tratamento e Reabilitação de Fissuras Labiopalatais e Deformidades Craniofaciais – como palestrante, cujo tema central foi "Os desafios dos tratamentos reabilitadores nas deformidades craniofaciais", ocorrido dias 14 e 15 de outubro, com carga horária de 9,5 hs.
- Participação na 38° Reunião-SBPqO 2021 – Apresentação Oral-AO0206 "Efeitos do protocolo com placas Modeladoras Naso Alveolares (NAM) na maxila de pacientes.
- Coautoria de trabalho apresentado na SBPqO 2021: Análise fotográfica da simetria facial provocada pelo tratamento NAM (Modelador Naso Alveolar) em bebês com fissura lábio palatais.
- Coautoria de trabalho apresentado na SBPqO 2021: O impacto da pandemia na saúde mental e formação acadêmica dos alunos do curso de graduação e pós-graduação de odontologia e fonoaudiologia.
- Colaboração com Trabalho de Conclusão de Curso da aluna de graduação em Odontologia Vitória Ferreira Leite.
- Participação na equipe de avaliação dos resumos do *XV Encontro Científico da Faculdade de Odontologia da UFMG*
- Participação SLIM – Simpósio do Laboratório de Imunofarmacologia UFMG de 18 a 19 de agosto de 2022 apresentando o poster "The effects of NAM in the symmetry of the face and maxillary arch in babies with unilateral cleft."
- Participação no XV Encontro científico da Faculdade de Odontologia da Universidade Federal de Minas Gerais, no período de 17 a 19 de junho de 2021 com o trabalho intitulado "Efeitos do protocolo com placas modeladores Nasoalveolares (NAM) na maxila de pacientes com fissuras labiopalatinas".
- Participação como monitora no Projeto Atendimento a bebês NAM – Nasoalveolar Molding em 01/2021, 02/2021 e 01/2022

- Participação como monitora no Projeto Atendimento a bebês com Trissomia 21 no 1° semestre 2022
- Participação como monitora no Projeto Atendimento a pacientes fissurados no 2° semestre de 2022.
- Participação como monitora no Projeto atendimento a bebês NAM – Nasoalveolar molding no 1° semestre de 2024.
- Participação em doutorado sanduíche no Canadá, pelo programa CapesPrint, em parceria com a University of Saskatchewan, na cidade de Saskatoon, no período de março a agosto de 2023, com aprendizado de técnicas laboratoriais na área de análise proteômica.
- Cursos realizados na University of Saskatchewan, no Salivary Proteomics Research Laboratory, College of Dentistry, como Visiting Research:
    - Biosafety Training
    - Biowaste Training
    - Laboratory Safety
    - Safety Orientation for Employees
    - USask WHMIS
    - Microbalance training
    - Methods for quantifying protein concentration in saliva, BCA Protein Assay e Micro-BCA Protein Assay.
- **Artigo publicado:** de Souza TM, Batista ST, de Souza RXS, Rezende SE, Alessi MS, Almeida TFA, Frazão DC, Pretti H, Freitas RDS, Macari S. The Effects of NAM on the Symmetry of the Face and Maxillary Arch in Babies with Unilateral Cleft. J Craniofac Surg. 2023 Sep 1;34(6):1618-1624. Doi: 10.1097/SCS.0000000000009469. Epub 2023 Jun 12. PMID: 37307242.
- **Artigo publicado:** Ianni, TMS; Silva, RR; Montalvany-Antonucci, CC; Pretti, H; Macari, S; *A necessidade de novo planejamento ortodôntico em casos transferidos – caso clínico"* Revista da APCD, 2023.
- **Artigo publicado:** Souza RXS, Souza GAS, Colares JP, Ianni TMS, Magalhães CS, Guerrero-Vargas JA, Montalvany-Antonucci CC, Macari S. A new way of analyzing tooth movement using universal coordinate system geometry single point superposition in a 3D model. Dental Press J Orthod. 2023 Oct

9;28(4):e232333. Doi: 10.1590/2177-6709.28.4.e232333.oar. PMID: 37820226; PMCID: PMC10564451

- Co-autora em artigo que está em processo de submissão na Revista Angle in Orthodontics entitulado: Accuracy of the Invisalign G8 protocol: a preliminary study.
- Co-autora em artigo que está em processo de submissão na Revista Journal Craniofacial Surgery entitulado: Effect of NAM for facial symmetry after cheiloplasty in babies with unilateral cleft and the psychosocial impact on the family
- 1° lugar durante o 55° Encontro do Grupo Brasileiro de Professores de Ortodontia e Odontopediatria, realizado em junho de 2024, com o trabalho intitulado: *Impacto psicossocial na família de bebês com fissura labiopalatina unilateral após uso de NAM e queiloplastia,* apresentado pela aluna de mestrado da UFMG-Kamila Rodrigues Junqueira Carvalho, na sessão de FÓRUM CIENTÍFICO DE ORTODONTIA, Prêmio DENTALCLEAN/Prof. Carlos Alberto Mundstock.

# ANEXO A – Aprovação do COEP (Comitê de Ética e Pesquisa)

UNIVERSIDADE FEDERAL DE MINAS GERAIS

Plataforma Brasil

## PARECER CONSUBSTANCIADO DO CEP

**DADOS DO PROJETO DE PESQUISA**

**Título da Pesquisa:** Estudo da abordagem precoce de pacientes com fissuras labiopalatinas tratados com modelador naso alveolar (NAM)

**Pesquisador:** SORAIA MACARI

**Área Temática:**

**Versão:** 2

**CAAE:** 10111619.1.0000.5149

**Instituição Proponente:** UNIVERSIDADE FEDERAL DE MINAS GERAIS

**Patrocinador Principal:** Financiamento Próprio

**DADOS DO PARECER**

**Número do Parecer:** 3.293.101

**Apresentação do Projeto:**

A ortopedia pré-cirúrgica em pacientes com fissura de lábio e palato tem como objetivo reduzir a amplitude das fissuras, melhorar o alinhamento dos segmentos alveolares e reposicionar a pré-maxila previamente à labioplastia. A pesquisa corresponde a um estudo clínico longitudinal prospectivo, simples cego, quali e quantitativo, in vivo, para a avaliação dos efeitos da abordagem precoce (ortopedia maxilar, labioplastia e palatoplastia) em pacientes com fissura lábiopalatinas transforame incisivo bilaterais. A população do estudo será selecionada na clínica do Projeto de Extensão "NAM Nasoalveolar Modelador" da Faculdade de Odontologia da UFMG através de triagem. Serão realizados exame clínico, anamnese e solicitação de autorização dos pais (TCLE). Os pacientes serão alocados de forma aleatória para tratamento com NAM convencional ou NAM Engenharia Reversa (ER). Todos os procedimentos serão executados no mesmo local e por apenas um operador previamente treinado e calibrado. Serão selecionados bebês de até 1 mês de idade, independentemente do sexo, cuja necessidade de tratamento se enquadrar nos critérios de inclusão; os pais/responsáveis serão convidados a participarem da pesquisa e receberão devidos esclarecimentos e explicação sobre os objetivos do estudo. Os bebês utilizarão o aparelho ortopédico (NAM convencional ou NAM ER) por período de três meses e posteriormente serão encaminhados para labioplastia. Quando o bebê estiver próximo de completar um ano de idade será encaminhado para a palatoplastia. O acompanhamento do sucesso do tratamento do NAM, labioplastia e palatoplastia para centralização da prémaxila será feito por meio de moldagens

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**Telefone:** (31)3409-4592 **E-mail:** coep@prpq.ufmg.br

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Continuação do Parecer: 3.393.101

realizadas nos seguintes tempos experimentais: inicial (T0), após 3 de uso do NAM porém antes da labioplastia (T1), 3 meses pós-labioplastia (T2) e 3 meses pós-palatoplastia (T3). Serão realizadas comparações estatísticas entre os tipos de NAM utilizados e entre os diferentes tempos experimentais com o mesmo aparelho. As impressões intraorais da maxila serão feitas com silicone de adição (Express XT ESPE, Unitek / 3M, CA, EUA). O paciente será posicionado no colo de sua mãe, totalmente acordado, com o rosto em um nível superior ao resto do corpo e em direção ao dentista. O tempo de impressão será de 1 minuto. Para avaliação da percepção dos pais na evolução do tratamento de seus filhos e o impacto do mesmo na família será será aplicada a versão brasileira dodos questionários Parental-Caregiver Perceptions Questionnaire (P–CPQ) e Family Impact Scale (FIS), respectivamente. Os dados registrados poderão ser úteis para a melhor entendimento e tratamento de pacientes com fissuras labiopalatinas e o impacto em suas famílias no primeiro ano de vida destes bebês.

**Objetivo da Pesquisa:**

Objetivo Primário:

O objetivo deste estudo será avaliar os efeitos da abordagem precoce em pacientes com fissura lábiopalatinas transforame incisivo bilaterais.

Objetivo Secundário (Objetivos específicos):

Os objetivos específicos consistirão:

1. Avaliar os efeitos do uso do NAM convencional e engenharia reversa (ER) na fissura labiopalatina e forma do arco maxilar em pacientes com fissuras transforame incisivo;
2. Avaliar os efeitos da labioplastia na fissura labiopalatina e forma do arco maxilar em pacientes com fissuras transforame incisivo;
3. Avaliar os efeitos da palatoplastia na fissura labiopalatina e forma do arco maxilar em pacientes com fissuras transforame incisivo;
4. Avaliar a percepção dos pais na evolução do tratamento de seus filhos e o impacto das diferentes etapas do tratamento na família por meio dos questionários Parental Caregiver Perceptions Questionnaire (P–CPQ) e Family Impact Scale (FIS), respectivamente.

**Avaliação dos Riscos e Benefícios:**

Riscos:

NAM convencional: Há o risco de um desconforto no bebê ocasionado pelas moldagens para a confecção do aparelho e da própria presença do aparelho. Para minimizar estes acontecimentos a moldagem será sempre realizada pelo professor orientador da clínica e a adaptação e ajuste do

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Continuação do Parecer: 3.293.101

aparelho serão feitos por pessoa capacitada e treinada, utilizando material adequado. Mas, caso o desconforto ocorra, você deverá entrar em contato com algum dos pesquisadores para que este seja averiguado e tratado. O NAM convencional será confeccionado com resina acrílica que é um material inerte já disponível no mercado e muito utilizada por ortodontistas. Todas as medidas serão tomadas para minimizar as possibilidades de risco, como a padronização dos procedimentos e utilização de um material confiável. NAM ER: A pesquisa será realizada nas clínicas odontológicas da Faculdade de Odontologia da Universidade Federal de Minas Gerais (UFMG). Há o risco de um desconforto no bebê ocasionado pelas moldagens para a confecção do aparelho e da própria presença do aparelho. Para minimizar estes acontecimentos a moldagem será sempre realizada pelo professor orientador da clínica e a adaptação e ajuste do aparelho serão feitos por pessoa capacitada e treinada, utilizando material adequado. Mas, caso o desconforto ocorra, o paciente deverá entrar em contato com algum dos pesquisadores para que este seja averiguado e tratado. O NAM engenharia reversa será confeccionado com placas de polietileno que é um material já disponível no mercado e muito utilizada por ortodontistas. Questionários: o responsável pelo paciente poderá ficar constrangido de responder o questionário. Para que não ocorra tal situação os questionários serão aplicados em local isolado de trânsito de pessoas, estando o pesquisador responsável pela pesquisa e o entrevistado sozinhos em sala reservada. Os responsáveis poderão desistir de responder o questionário a qualquer momento.

Benefícios:
Com esta pesquisa os bebês terão o benefício de poder ter um melhor acompanhamento do sucesso tratamento da correção das fissuras labio-palatinas.

**Comentários e Considerações sobre a Pesquisa:**
Pesquisa relevante para a Odontologia, em especial para a área de Ortodontia. Término previsto para 02/02/2021. O projeto de pesquisa foi aprovado pelo Departamento. Projeto de pesquisa bem delineado, exequível, e respeita as recomendações éticas na abordagem com os pacientes e seus responsáveis.
As recomendações do CEP formam atendidas:
- os critérios de inclusão foram esclarecidos, serão incluídas apenas mães maiores de 18 anos;
- o TCLE foi adequadamente alterado.

**Considerações sobre os Termos de apresentação obrigatória:**
Este parecer foi elaborado com base nos seguintes documentos anexados à Plataforma Brasil:
- Informações Básicas do Projeto;

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Continuação do Parecer: 3.293.101

- Carta-resposta às diligências;
- Folha de Rosto;
- Parecer consubstanciado aprovado em reunião departamental;
- TCLE para participantes que utilizarão o NAM por engenharia reversa;
- TCLE para participantes que utilizarão o NAM convencional;
- Projeto Detalhado / Brochura Investigador.

**Recomendações:**

Recomenda-se a aprovação do projeto de pesquisa "Estudo da abordagem precoce de pacientes com fissuras labiopalatinas tratados com modelador naso alveolar (NAM)" da pesquisadora responsável Profa. Dra. Soraia Macari.

**Conclusões ou Pendências e Lista de Inadequações:**

Projeto de pesquisa aprovado.

**Considerações Finais a critério do CEP:**

Tendo em vista a legislação vigente (Resolução CNS 466/12), o CEP-UFMG recomenda aos Pesquisadores: comunicar toda e qualquer alteração do projeto e do termo de consentimento via emenda na Plataforma Brasil, informar imediatamente qualquer evento adverso ocorrido durante o desenvolvimento da pesquisa (via documental encaminhada em papel), apresentar na forma de notificação relatórios parciais do andamento do mesmo a cada 06 (seis) meses e ao término da pesquisa encaminhar a este Comitê um sumário dos resultados do projeto (relatório final).

**Este parecer foi elaborado baseado nos documentos abaixo relacionados:**

| Tipo Documento | Arquivo | Postagem | Autor | Situação |
|---|---|---|---|---|
| Informações Básicas do Projeto | PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1307944.pdf | 16/04/2019 13:27:36 | | Aceito |
| Outros | Carta_resposta.docx | 16/04/2019 13:25:33 | SORAIA MACARI | Aceito |
| Projeto Detalhado / Brochura Investigador | Projeto_final_2.docx | 16/04/2019 13:25:08 | SORAIA MACARI | Aceito |
| TCLE / Termos de Assentimento / Justificativa de Ausência | Termo_de_Consentimento_Livre_e_Esclarecido_NAM_ER.docx | 16/04/2019 13:24:22 | SORAIA MACARI | Aceito |
| TCLE / Termos de Assentimento / | Termo_de_Consentimento_Livre_e_Esclarecido_NAM_convencional.docx | 16/04/2019 13:16:34 | SORAIA MACARI | Aceito |

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Continuação do Parecer: 3.393.101

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|---|---|---|---|---|
| Justificativa de Ausência | Termo_de_Consentimento_Livre_e_Esclarecido_NAM_convencional.docx | 16/04/2019 13:16:34 | SORAIA MACARI | Aceito |
| Folha de Rosto | folha_de_rosto.pdf | 12/03/2019 22:55:24 | SORAIA MACARI | Aceito |
| Outros | scan_PARECER_DEPARTAMENTO.pdf | 08/03/2019 19:40:48 | SORAIA MACARI | Aceito |

**Situação do Parecer:**
Aprovado

**Necessita Apreciação da CONEP:**
Não

BELO HORIZONTE, 29 de Abril de 2019

**Assinado por:**
**Eliane Cristina de Freitas Rocha**
**(Coordenador(a))**

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# ANEXO B - Registro da revisão sistemática no PROSPERO



**PROSPERO**

**International prospective register of systematic reviews**

**Effects of nasoalveolar molding associated with primary cleft lip surgery – a systematic review.**

| From | To | Date | Subject |
|---|---|---|---|
| CRD-REGISTER | "iannitms@gmail.com" | Mon, 30 Oct 2023 13:50:19 +0000 | PROSPERO acknowledgement of receipt [477752] |