RAÍZA DIAS DE FREITAS

# The economic impact of two diagnostic strategies in the management of restorations in primary teeth: a trial-based economic evaluation

São Paulo

2021

**RAÍZA DIAS DE FREITAS**

# The economic impact of two diagnostic strategies in the management of restorations in primary teeth: a trial-based economic evaluation

**Original Version**

Thesis presented to the School of Dentistry, University of São Paulo, by the graduate program in Dental Sciences to obtain the title of Doctor of Science.

Concentration Area: Paediatric Dentistry and Orthodontics

Supervisor: Profa. Dra. Mariana Minatel Braga

Second Supervisor: Prof. Dr. Fausto Medeiros Mendes

São Paulo

2021

Catalogação da Publicação
Serviço de Documentação Odontológica
Faculdade de Odontologia da Universidade de São Paulo

Freitas, Raíza Dias de.
The economic impact of two diagnostic strategies in the management of restorations in primary teeth: a trial-based economic evaluation / Raíza Dias de Freitas; supervisor Mariana Minatel Braga, second supervisor Fausto Medeiros Mendes. -- São Paulo, 2021.
115 p. : fig., tab., graf. ; 30 cm.

Thesis (Doctorate degree) -- Graduate Program in Dental Sciences. Concentration Area: Paediatric Dentistry and Orthodontics. – Faculty of Dentistry, University of São Paulo.
Original version.

1. Economic evaluation. 2. Cost-effectiveness analysis. 3. Randomised controlled trial. 4. Dental caries. I. Braga, Mariana Minatel. II. Mendes, Fausto Medeiros. III. Title.

Fábio Jastwebski – librarian - CRB8/5280

Freitas RD. The economic impact of two diagnostic strategies in the management of restorations in primary teeth: a trial-based economic evaluation. [thesis] Presented to the School of Dentistry of the University of São Paulo to obtain the title of Doctor of Science.

Approved in: 03/12/2021

**Examination Board**

Prof(a). Dr(a). Daniela Prócida Raggio
Institution: Universidade de São Paulo Veredict: Approved

Prof(a). Dr(a). Tamara Kerber Tedesco
Institution: Universidade Cruzeiro do Sul Veredict: Approved

Prof(a). Dr(a). Clarissa Araújo Gurgel Rocha
Institution: Universidade Federal da Bahia Veredict: Approved

À minha mãe, Aurízia, minha maior incentivadora nessa caminhada acadêmica.

Obrigada por tanto!

## AGRADECIMENTOS / ACKNOWLEDGEMENTS

À minha mãe, **Aurízia**, a maior incentivadora do meu caminho científico. Desde a graduação, ela apoiou as minhas aventuras e sonhou todos os meus sonhos, inclusive o de fazer o doutorado na USP. Além de todo apoio emocional, também não posso deixar de mencionar o suporte financeiro, essencial para que minha única preocupação durante todos esses anos fosse a de me dedicar aos estudos. Meu sonho é um dia conseguir retribuir tudo que me proporcionou até hoje e acredito que, após a conclusão do doutorado, estarei um pouquinho mais perto disso. Obrigada, mãe. Você é colo, acolhimento e cuidado. Sua vida é um exemplo de fé e persistência. A você dedico essa tese e todas as minhas conquistas.

Ao meu pai, **Aécio**, que também sempre me deu todo o suporte necessário para que eu alcançasse os meus objetivos. Nunca mediu esforços para investir nos meus estudos e apoiar minhas idas e vindas pelo mundo. Estendo esses agradecimentos a **Wesley** e **Inarene**. Deus foi bom demais comigo e me deu mais um pai e mais uma mãe. Vocês também são parte desta conquista.

Ao meu irmão **Adriano**, minha cunhada **Marcela** e meus sobrinhos **Aecinho** e **Pedro**. Apesar da distância e da minha ausência durante todos esses anos, sempre que estamos juntos é muito especial. Obrigada por serem a melhor família que eu poderia ter. Agradeço também a minha irmã **Larissa**, minha Bene, tão única e especial. Obrigada por sempre me apoiar e se colocar à disposição pra me ajudar em tudo que eu precisar. Também espero um dia poder retribuir tudo que você fez e faz por mim.

À toda a minha família, em Vitória da Conquista e Irecê, em especial à tia **Mirinha** e aos meus avós **Nazinha**, **Ireny** e **Sebastião**. A história que estou construindo deve muito a vocês, que abriram os caminhos e batalharam para proporcionar uma vida melhor para as próximas gerações.

Agradeço imensamente aos meus orientadores, **Mari** e **Fausto**. Ter esses dois orientadores foi uma sorte grande e espero que continuemos nossa parceria por muitos anos. Obrigada, **Mari**, por ter me aceitado como aluna mesmo sem me conhecer e por ter acreditado no meu potencial. Obrigada por me ensinar a pensar fora do óbvio e estar sempre disposta a ajudar. Obrigada por todo aprendizado, você

abriu um mundo novo da economia da saúde que eu nunca tinha conhecido. Admiro demais sua inteligência e criatividade, você é um exemplo pra mim. **Fausto**, obrigada por ter aberto as portas da USP para mim e também por ter me proporcionado participar do CARDEC-3, onde aprendi muito sobre pesquisa e fiz amigos maravilhosos. Você me inspira a ser melhor e a me superar. Agradeço demais pela sua disponibilidade e paciência comigo, esses anos de convivência foram incríveis.

À **Dani**, que não foi minha orientadora, mas me ensinou tanto! Dani, você me surpreendeu desde o primeiro dia na USP com seu cuidado e atenção com os alunos. Na clínica, nunca teve tempo ruim para você. Lava material, ajuda os alunos, anota, avalia, enfim, encara o que tiver que encarar. Sou sua fã e admiro muito o lugar que você ocupa como mulher pesquisadora, resistindo às dificuldades com classe, bom-humor e fazendo ciência de qualidade.

Aos professores do departamento de Odontopediatria da USP: **Ana Lídia**, **Ana Estela**, **Imparato**, **Márcia**, **Marcelo** e **Salete**. Aprender com os autores dos melhores livros da Odontopediatria foi uma honra! Cada um com sua expertise, vocês contribuem com a nossa formação sem medir esforços. Tenho muito orgulho de ter sido aluna de vocês. Professora Márcia, obrigada por me dar a primeira oportunidade de orientar alunos no seu corredor no noturno. Com você aprendi muito de Odontopediatria clínica, ensinamentos que irei levar para sempre comigo. Professor Imparato, seu alto astral contagia a clínica. Obrigada pela parceria nos casos clínicos, espero que um dia eu consiga tirar fotos como você.

Às professoras da UFBA que me motivaram a seguir o caminho da Odontopediatria, **Carla Gurgel** e **Andreia**. Também agradeço a professora **Clarissa Gurgel**, um exemplo de pesquisadora e uma mente brilhante que me inspira desde o primeiro dia de aula na patologia durante a graduação.

Aos professores do curso de especialização de Odontopediatria da UNIP, em especial à professora **Anna Carolina** e **Tamara Tedesco**. Babou, você levou nosso curso com o maior cuidado do mundo e me ensinou a ser odontopediatra. Tá, você contribuiu tanto para minha caminhada científica! Sempre presente nas clínicas de quarta reavaliando 1000 pacientes e mesmo assim com altíssimo astral. Você me deu a primeira oportunidade de dar aula em São Paulo, foi minha orientadora na especialização, sentou comigo na clínica quando precisei, enfim, você esteve em muitos pedacinhos da minha formação e serei eternamente grata por isso.

A todos os colegas da pós-graduação. Obrigada por compartilharem comigo as angústias de ser um aluno de pós, deixando esse caminho mais leve. Em especial, agradeço a meus amigos mais próximos **Ana Laura**, **Haline**, **Rafael** e **Rodolfo**, que, além de amigos maravilhosos, foram os melhores dentistas que poderíamos ter no CARDEC-03, sempre dispostos a ajudar. Ana Laura, você foi alegria nos meus dias de pós, sempre com uma piada para descontrair, animando nossas clínicas e trazendo leveza para os dias difíceis. Haline, minha mainha em São Paulo, obrigada por ser minha casa, porto seguro, confidente e tudo mais que uma alma nordestina precisa longe de casa. Admiro sua força, coragem e jeito de encarar a vida, com muita praticidade e garra. Estendo esses agradecimentos também a **Dieggo**, vocês formam uma linda família, **Helena** é muito sortuda por ter esses papais tão especiais. Rafa, meu leonino amado, obrigada por trazer leveza nas clínicas, pelas risadas incontáveis e por me ensinar revisão sistemática. Você é brilhante, estarei sempre torcendo pelo seu sucesso. Rodsu querido, você é um dos melhores corações que já conheci, você foi fundamental nessa trajetória, desde o dia 1 foi braço direito e esquerdo nas clínicas do CARDEC, sempre com sorriso no rosto e jeito descontraído.

Às Faustinhas, **Bruna Moro**, **Bruna Brondani**, **Carol**, **Júlia**, **Laura**, **Nati**, **Renata** e **Vanessa**, e às Marianetes: **Dudu**, **Dai**, **Karina**, **Gabi** e **Bethinha**. Obrigada pela convivência esses anos, por dividirem o trabalho e estarem sempre dispostas a ajudar. Agradeço à querida **Isabel Olegário** pelos ensinamentos, mesmo de longe sempre presente e disposta a ajudar. Bel, você é um exemplo pra mim, te admiro muito.

Agradeço ao Serviço de Documentação Odontológica, em especial à **Glauci Fidélis**, sempre disposta a ajudar e até me tranquilizando nesse momento difícil que é a entrega de uma tese.

Aos secretários do departamento de Odontopediatria, **Anne**, **Júlio**, **Fátima** e **Antônio**, por me ajudarem inúmeras vezes. Também gostaria de agradecer imensamente à **Catia Tiezzi**, por sempre responder prontamente a todas as minhas dúvidas.

Ao **Fernando Nunes**, por toda ajuda com a FAPESP e tudo mais que precisei. Fernando, obrigada por ser tão solícito, por nos ajudar com leveza e sorriso no rosto. Você é incrível!

Ao **Luis Gabriel**, que me aguentou durante a escrita da tese, cuidou de mim e segurou meus surtos. Você é especial.

Aos meus queridíssimos parceiros de vida, **Amanda**, **Gustavo**, **Liz**, **Henrique Castro**, **Henrique Trindade**, **Rafaela** e **Eduardo**, obrigada por tudo, por ouvir minhas lamentações e sempre estarem ao meu lado durante todos os momentos.

À **Manuela**, **Ludmila** e **Vanessa**, queridas amigas de UFBA e Fiocruz. Obrigada por serem ouvido aberto e por compartilharem as angústias da vida acadêmica comigo.

Ao querido **Daniel Morassutti**, por dividir comigo as dificuldades do doutorado, me apoiar e incentivar sempre. Obrigada pela sua amizade e por tudo que fez por mim.

To my supervisor from Sheffield, **Chris Deery**. Chris, thank you for all your efforts for making my Sheffield experience the best.

To **Sarosh** and **Alison**. Thank you for having me at your place, for all the lunches, dinners, and tea times at the garden during the pandemic. I will always be grateful for the nice moments spent together.

To **Charles Gillott** for sharing the Sheffield life with me and for checking the English from Chapter I. Cheers, pal.

À **Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP)** e à **Coordenação de Aperfeiçoamento Pessoal de Nível Superior (CAPES)** pelo suporte financeiro durante o meu curso de Doutorado.

À **Universidade de São Paulo**, universidade que sempre admirei e sonhei um dia estudar. A experiência foi ainda melhor que o sonho.

Obrigada a todos que de forma direta ou indireta me ajudaram a chegar até aqui. E que venham os próximos desafios.

“Caminho se conhece andando, então, vez em quando, é bom se perder. Perdido, fica perguntando, vai só procurando e acha sem saber. Perigo é se encontrar perdido, deixar sem ter sido, não olhar, não ver. Bom mesmo é ter sexto sentido, sair distraído, espalhar bem-querer”.

Chico César

## RESUMO

Freitas RD. O impacto econômico de duas estratégias de diagnóstico no manejo de restaurações em dentes decíduos: avaliação econômica baseada em um ensaio clínico [tese]. São Paulo: Universidade de São Paulo, Faculdade de Odontologia; 2021. Versão Original.

O objetivo desta tese foi avaliar o impacto econômico de utilizar a estratégia Caries Around Restorations and Sealants (CARS) em substituição à estratégia da Federação Dentária Internacional (FDI) para avaliação e manejo de restaurações em dentes decíduos. Este volume apresenta dois capítulos relacionados ao objetivo da tese, sendo o primeiro um plano de avaliação econômica e o segundo uma avaliação econômica com diferentes Análises de Custo-Efetividade (CEAs). O plano de análise econômica propõe uma série de análises baseadas em um ensaio clínico randomizado. O ensaio clínico Caries Detection in Children – 3 (CARDEC-03) incluiu participantes de 3 a 10 anos com pelo menos uma restauração em dente decíduo que foram aleatoriamente alocadas para um dos grupos, de acordo com a estratégia de diagnóstico (FDI ou CARS) a ser utilizada nas restaurações. Os participantes foram acompanhados por 2 anos. Para todas as avaliações, será utilizada a perspectiva da sociedade. Serão realizadas CEAs e Análise de Custo-Utilidade considerando o FDI como estratégia referência. Será realizada análise por intenção de tratar e as diferenças em custos e efeitos entre a estratégia CARS e a FDI serão avaliadas. Análises de sensibilidade determinísticas e probabilísticas serão realizadas e curvas de aceitabilidade serão construídas utilizando diferentes valores de disposição a pagar. Adicionalmente, um modelo de Markov será construído para avaliar um horizonte temporal maior. Além do plano de análises, esta tese também avaliou a custo-efetividade em utilizar a estratégia CARS em substituição à estratégia FDI para avaliação de restaurações em dentes decíduos. Para compreender melhor esta relação, foram avaliados 4 efeitos: número de novas intervenções operatórias, tempo até a necessidade de uma nova intervenção operatória, necessidade de novas intervenções operatórias e o número de novas substituições. Custos e efeitos foram comparados entre os grupos por medidas relativas, conforme a quantidade de restaurações incluídas por grupo. Simulações de Monte-Carlo avaliaram as incertezas ao redor dos parâmetros e curvas de aceitabilidades foram construídas. Dados de 163 pacientes e 650 restaurações foram utilizados para a avaliação econômica. Não houve diferença estatisticamente significante entre o custo e o número de novas intervenções operatórias das duas estratégias após 2 anos de acompanhamento. Através da análise dos dados simulados, o CARS demonstrou-se custo-efetivo nas quatro CEAs. Considerando um limiar de disposição a pagar de 100 dólares, esta estratégia apresentou Net Monetary Benefits (NMB) positivos para os efeitos número de novas intervenções operatórias, tempo até a necessidade de uma nova intervenção operatória e número de novas substituições. As simulações demonstraram que, considerando um limiar de disposição a pagar de 100 doláres, o CARS tem uma probabilidade de aproximadamente 90% de ser custo-efetivo considerando o efeito tempo até a necessidade de uma nova intervenção operatória. O pior cenário foi para o efeito necessidade de novas intervenções operatórias, no qual o CARS apresentou NMB negativo e uma probabilidade de aproximadamente 50% de ser custo-efetivo, considerando um limiar de disposição a pagar de 100 dólares. Em conclusão, o CARS é uma alternativa custo-efetiva ao FDI, sobretudo considerando o adiamento de novas intervenções operatórias em dentes decíduos.

Palavras-chave: Avaliação econômica em saúde. Análise de custo-efetividade. Ensaio clínico controlado randomizado. Cárie dentária.

# ABSTRACT

Freitas RD. The economic impact of two diagnostic strategies in the management of restorations in primary teeth: a trial-based economic evaluation [thesis]. São Paulo: University of São Paulo, School of Dentistry; 2021. Original Version.

The aim of this thesis was to evaluate the economic impact of using the Caries Around Restorations and Sealants (CARS) strategy instead of the World Dental Federation (FDI) strategy for the assessment and management of restorations in primary teeth. The thesis comprises two chapters, related to the aim of the thesis. The first chapter is a health economic analysis plan and the second chapter is an economic evaluation with different Cost-Effectiveness Analyses (CEAs). The first chapter proposes a series of analyses based on a randomised clinical trial. The Caries Detection in Children - 3 (CARDEC-03) trial included children from 3 to 10 years with at least one restoration in a primary tooth. Children were randomly allocated to one of thw two groups, according to the diagnostic strategy (FDI or CARS). Participants were followed up for 2 years. For all economic evaluations, the societal perspective will be used. CEAs and Cost-Utility Analysis will be performed considering FDI as the reference strategy. Intention-to-treat analysis will be performed and differences in costs and effects between the strategies will be evaluated. Deterministic and probabilistic sensitivity analyses will be carried out and acceptability curves will be plotted according to different willingness-to-pay values. Additionally, a Markov model will be used to evaluate a wider time horizon. In addition to the analysis plan, this thesis also assessed the cost-effectiveness of using the CARS strategy instead of the FDI strategy for the assessment of restorations in primary teeth. Four effects were evaluated: number of new operative interventions, time to the first new operative intervention, need for new operative interventions, and the number of new replacements. Costs and effects were compared between groups by relative measures, according to the number of restorations included per group. Monte-Carlo simulations assessed uncertainties around the parameters and acceptability curves were plotted. Data from 163 patients and 650 restorations were used for the economic evaluation. There was no statistically significant difference between costs and number of new operative interventions of the two strategies after

2 years of follow-up. Simulated data demonstrated that CARS was mostly cost-effective for the four CEAs. Considering a willingness-to-pay threshold of 100 dollars, this strategy showed positive Net Monetary Benefits (NMBs) for the effects number of new operative interventions, time to the first new operative intervention, and number of new replacements. Considering a willingness-to-pay threshold of 100 dollars, CARS has a probability of approximately 90% of being cost-effective considering the time to the first new operative intervention. The worst-case scenario was for the effect of need for new operative interventions, in which CARS presented negative NMB and a probability of approximately 50% of being cost-effective, considering a threshold of willingness to pay of 100 dollars. In conclusion, CARS is a cost-effective alternative to FDI, especially considering the postponing new operative interventions in primary teeth.

Keywords: Economic evaluation. Cost-effectiveness analysis. Randomised controlled trial. Dental caries.

## ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| B-ECOHIS | Brazilian version of the Early Childhood Health Impact Scale |
| BLPM | Bruna Lorena Pereira Moro |
| BRL | Brazilian Real |
| CAPES | Coordination for the Improvement of Higher Education Personnel |
| CARDEC | Caries Detection and Management in Children |
| CARS | Caries Around Restorations and Sealants |
| CE | Cost-Effectiveness |
| CEA | Cost-Effectiveness Analysis |
| CHEERS | Consolidated Health Economic Evaluation Reporting Standards |
| CI | Confidence Interval |
| CNPq | Brazilian National Council for Scientific and Technological Development |
| CUA | Cost-Utility Analysis |
| DMFT | Number of Decayed, Restored or Missed permanent Teeth |
| Dmft | Number of Decayed, Restored or Missed primary Teeth |
| ECOHIS | Early Childhood Health Impact Scale |
| FAPESP | São Paulo Research Foundation |
| FDI | World Dental Federation |
| IBGE | Brazilian Institute of Geography and Statistics |
| ICCMS | International Caries Classification and Management System |
| ICDAS | International Caries Detection and Assessment System |
| IPCA | Extended National Consumer Price Index |
| ISPOR | International Society for Pharmacoeconomics and Outcomes Research |
| ITT | Intention To Treat |
| NA | Not Applicable |
| OHRQoL | Oral Health-Related Quality of Life |

| | |
|---|---|
| PP | Per Protocol |
| QALYs | Quality-Adjusted Life Years |
| RCT | Randomised Controlled Trial |
| SD | Standard Deviation |
| SG | Standard Gamble |
| TKT | Tamara Kerber Tedesco |
| VAS | Visual Analogue Scale |
| WTP | Willingness-To-Pay |

## SYMBOLS

| | |
|---|---|
| Δ | Delta |
| $ | International dollars |

# PREFACE

The present thesis comprises two chapters related to a trial-based economic evaluation aiming to assess the impact of different strategies on caries around the restorations' detection and management in primary teeth. The clinical trial was registered in the clinicaltrials.gov platform in May 9th 2018 (NCT03520309) and approved by the Committee for Ethics in Research of the School of Dentistry, University of São Paulo (registration number 2.291.642) (Annex A). The economic aspects related to the trial and patients' preferences for dental caries health states are deeply explored in the present thesis, which was supported by the São Paulo Research Foundation (FAPESP/ Grants #2017/22897-3, #2018/03199-6, and #2018/20464-5), the Coordination for the Improvement of Higher Education Personnel (CAPES), and the Brazilian National Council for Scientific and Technological Development (CNPq; Grants #141425/2017-2 and #420458/2018-2). The opinions expressed in the present thesis are those of the authors and not necessarily those of FAPESP, CAPES, and CNPq. This thesis is a result of the main author's PhD project developed at the University of São Paulo and the chapters are described, as follows:

The first chapter (I) is the Health Economics Analysis Plan for the trial-based economic evaluation, previously describing all the parameters that will be used in the analysis, corroborating with transparency in research. The article was accepted for publication at the Trials journal in 13th October 2021 (Annex B). The preprint version is already available at researchsquare.com and the accepted version of the manuscript is presented in chapter I.

(I) Raiza Dias Freitas, Bruna Lorena Pereira Moro, Laura Regina Antunes Pontes et al. The economic impact of two diagnostic strategies in the management of restorations in primary teeth: a health economic analysis plan for a trial-based economic evaluation, 02 July 2021, PREPRINT (Version 1) available at Research Square [https://doi.org/10.21203/rs.3.rs-378301/v1].

The second chapter (II) is a trial-based economic evaluation, comprising four different Cost-Effectiveness Analyses of the two diagnostic strategies for the management of restorations in primary teeth.

(II) How can a less interventionist approach benefit children who had their restorations in primary teeth assessed and managed? – an economic evaluation based on different health outcomes.

**SUMMARY**

# 1 INTRODUCTION

Worldwide expenditures with oral diseases were estimated at approximately US$298 billion in the last global economic impact evaluation (1). Thus, efficient allocation of resources is mandatory for healthcare systems maintenance, as money is constitutively scarce in all economies. Identifying the main conditions associated with the economic burden is relevant for the development of public policies aiming to control those diseases and lessen their costs. Untreated caries in primary teeth was the $10^{th}$ most common oral disease in the last Global Burden of Diseases (2), highlighting the relevant impact of dental caries for both children and healthcare systems globally.

A systematic review of economic evaluations child oral health research revealed a trend for an increase of publications in this field in the last years, however there is a lack of high-quality full economic evaluations in paediatric dentistry. A substantial number of studies has demonstrated important methodological deficiencies, such as not properly reporting how uncertainty was handled in the analysis (3). Therefore, conclusions drawn from those studies poorly guide efficiency in resource use.

Economic evaluations might answer different types of questions, depending on the methodology applied and the effects assessed in the study. Technical efficiency questions can be guided by Cost-Effectiveness Analysis (CEA) when interventions for the same outcome are compared (4). CEA is a type of full economic evaluation assessing costs in monetary units and effects in natural units (5). Depending on the economic question guiding the economic evaluation, a Randomised Controlled Trial (RCT) may be an interesting source of data. Despite their limitations in generalizability, as they are usually conducted with a specific sample, trial-based economic evaluations conducted from clinical studies with a random sample from the target population will have a high internal validity and potential generalizability (5), as rigorous methodological aspects have been considered for that. In this sense, previously establishing an analysis plan for the economic evaluation is an important first step to achieving this final goal.

Our group has been conducting pioneer studies evaluating caries diagnosis in children. The Caries Detection and Management in Children (CARDEC) research group has demonstrated that the visual examination is the best method for caries detection in primary teeth, avoiding overdiagnosis and overtreatment (6,7). The most recent trial (CARDEC-03) assessed two diagnostic strategies for caries detection around the restorations in primary teeth, the Caries Around Restorations and Sealants (CARS), which is focused on caries detection, and the World Dental Federation (FDI), with an aesthetics approach. The protocol for the trial has been already published as well as results from nested studies (8,9).

The research reported in the present thesis comprises economic evaluations based on the CARDEC-03 trial. This is the first economic study comparing two diagnostic strategies for caries detection around the restorations and its results will provide relevant information for technical efficiency when the assessment of restorations needs to be performed in paediatric dentistry.

# 2 PROPOSITION

The present study aims to assess whether the CARS strategy is more efficient for resource allocation than the FDI strategy for the assessment and management of restorations in primary teeth.

# 3 CHAPTER I: HEALTH ECONOMICS ANALYSIS PLAN

**The economic impact of two diagnostic strategies in the management of restorations in primary teeth: a health economic analysis plan for a trial-based economic evaluation**

Raíza Dias Freitas[1], Bruna Lorena Pereira Moro[2], Laura Regina Antunes Pontes[3], Haline Cunha Medeiros Maia[4], Ana Laura Passaro[5], Rodolfo Carvalho Oliveira[6], Jonathan Rafael Garbim[7], Maria Eduarda Franco Vigano[8], Tamara Kerber Tedesco[9], Christopher Deery[10], Daniela Prócida Raggio[11], Maximiliano Sergio Cenci [12], Fausto Medeiros Mendes[13], Mariana Minatel Braga[14,*], CARDEC collaborative group[15]

[1] Department of Pediatric Dentistry, School of Dentistry, University of São Paulo, São Paulo, Brazil. raizafreitas@usp.br
[2] Department of Pediatric Dentistry, School of Dentistry, University of São Paulo, São Paulo, Brazil. bruna.moro@usp.br
[3] Department of Pediatric Dentistry, School of Dentistry, University of São Paulo, São Paulo, Brazil. laura.pontes@usp.br
[4] Department of Pediatric Dentistry, School of Dentistry, University of São Paulo, São Paulo, Brazil. halinemaia@usp.br
[5] Department of Pediatric Dentistry, School of Dentistry, University of São Paulo, São Paulo, Brazil. ana.passaro@usp.br
[6] Department of Pediatric Dentistry, School of Dentistry, University of São Paulo, São Paulo, Brazil. rodolfoco@usp.br
[7] Department of Pediatric Dentistry, School of Dentistry, University of São Paulo, São Paulo, Brazil. jonathan.rafael@usp.br
[8] Department of Pediatric Dentistry, School of Dentistry, University of São Paulo, São Paulo, Brazil. maria.vigano@usp.br
[9] Graduate Program in Dentistry, Ibirapuera University, São Paulo, Brazil. tamara.tedesco@ibirapuera.edu.br
[10] School of Clinical Dentistry, University of Sheffield, Sheffield, UK. c.deery@sheffield.ac.uk

[11] Department of Pediatric Dentistry, School of Dentistry, University of São Paulo, São Paulo, Brazil. danielar@usp.br.
[12] Graduate Program in Dentistry, Federal University of Pelotas, Pelotas, Rio Grande do Sul, Brazil. cencims@gmail.com
[13] Department of Pediatric Dentistry, School of Dentistry, University of São Paulo, São Paulo, Brazil. fmmendes@usp.br.
[14] Department of Pediatric Dentistry, School of Dentistry, University of São Paulo, São Paulo, Brazil. mmbraga@usp.br.
[15] Corporate author. cardec.fo@usp.br

*Corresponding author:
Mariana Minatel Braga
University of São Paulo, School of Dentistry
Address: Lineu Prestes Avenue, 2227
05508000, São Paulo-SP, Brazil
Phone/Fax: +55 11 3091-7835 Fax: 55 11 3091-7854
E-mail: mmbraga@usp.br

**Abstract**

**Background:** Different approaches have been used by dentists to base their decision. Among them, there are the aesthetical issues that may lead to more interventionist approaches. Indeed, using a more interventionist strategy (the World Dental Federation - FDI), more replacements tend to be indicated than using a minimally invasive one (based on the Caries Around Restorations and Sealants - CARS). Since the resources related to the long-term health effects of these strategies have not been explored, the economic impact of using the less invasive strategy is still uncertain. Thus, this health economic analysis plan aims: to describe methodologic approaches for conducting a trial-based economic evaluation that aims to assess whether a minimally invasive strategy is more efficient in allocating resources than the conventional strategy for managing restorations in primary teeth and extrapolating these findings to a longer time horizon.

**Methods:** A trial-based economic evaluation will be conducted, including three cost-effectiveness analyses (CEA) and one cost-utility analysis (CUA). These analyses will

be based on the main trial (CARDEC-03/NCT03520309), in which children aged 3 to 10 were included and randomized to one of the diagnostic strategies (based on FDI or CARS). An examiner will assess children's restorations using the randomized strategy, and treatment will be recommended according to the same criteria. The time horizon for this study is two years, and we will adopt the societal perspective. The average costs per child for 24 months will be calculated. Three different cost-effectiveness analyses (CEA) will be performed. For CEAs, the effects will be the number of operative interventions (primary CEA analysis), the time to these new interventions, the percentage of patients who did not need new interventions in the follow-up, and changes in children's oral health-related quality of life (secondary analyses). For CUA, the effect will be tooth-related quality-adjusted life-years (QALYs). Intention-to-treat analyses will be conducted. Finally, we will assess the difference when using the minimally invasive strategy for each health effect (∆effect) compared to the conventional strategy (based on FDI) as the reference strategy. The same will be calculated for related costs (∆cost). The discount rate of 5% will be applied for costs and effects. We will perform deterministic and probabilistic sensitivity analyses to handle uncertainties. The net benefit will be calculated, and acceptability curves plotted using different willingness-to-pay thresholds. Using Markov models, a longer-term economic evaluation will be carried out with trial results extrapolated over a primary tooth lifetime horizon.

**Discussion:** The main trial is ongoing, and data collection is still not finished. Therefore, economic evaluation has not commenced. We hypothesize that conventional strategy will be associated with more need for replacements of restorations in primary molars. These replacements may lead to more reinterventions, leading to higher costs after two years. The health effects will be a crucial aspect to take into account when deciding whether the minimally invasive strategy will be more efficient in allocating resources than the conventional strategy when considering the management of restorations in primary teeth. Finally, patients/parents preferences and consequent utility values may also influence this final conclusion about the economic aspects of implementing the minimally invasive approach for managing restorations in clinical practice. Therefore, these trial-based economic evaluations may bring actual evidence of the economic impact of such interventions.

**Trial registration:** NCT03520309. Registered May 9th, 2018. Economic evaluations (the focus of this plan) are not initiated at the moment.
**Keywords:** Cost-effectiveness analysis, cost-utility analysis, dental caries

**Background**

Reinterventions in restored teeth are common procedures in Dentistry. Caries lesions around restorations, frequently denominated as "secondary caries", have been identified as the main reason for repairing or replacing the restorations in primary teeth [1]. The detection of these lesions and other aspects related to defective restorations in primary teeth is challenging as it involves a clinical inspection of the dental surface and the restorative material as well as their interface. The visual-tactile method is commonly used for this purpose. Some clinical strategies based on this method have been proposed to standardize the clinical assessment of restorations and support treatment decisions [2].

In general, dentists base their decision on different parameters, including aesthetical ones. This option tends to result in a more interventionist approach. In 2007, the World Dental Federation (FDI) proposed a strategy to evaluate restorations comprising aesthetic, functional, and biological parameters, including the presence of caries and related aspects [3]. The FDI criteria were proposed for research and clinical practice and used to decide reintervention in restored teeth [4]. Due to the several aesthetic parameters evaluated, the diagnostic strategy based on FDI embraces a cosmetic dentistry perspective, relating to a more interventionist approach for the clinical practice.

On the other hand, the Caries Associated with Restorations and Sealants (CARS) strategy is a more recently minimally invasive strategy proposed as part of the International Caries Classification and Management System (ICCMS) [5] and exclusively focused on detecting caries lesions around the restorations [6]. The CARS strategy is based on the International Caries Detection and Assessment System (ICDAS) scores. It is more consistent with a Cariology background, leaning on a less interventionist approach, based solely on the occurrence of caries lesions and their characteristics.

To date, there is no consensus on the best strategy to adopt in clinical practice, and most studies do not explore the clinical relevance of the accuracy tests nor patient-centered outcomes [2]. An ongoing clinical trial (CARies DEtection in Children

- CARDEC-03) aims to assess the impact of using the FDI and CARS criteria in the assessment of restorations in primary teeth [7]. At first glance, when using a more interventionist strategy (using the FDI criteria), the indication of replacements of restorations in the baseline was more frequent than using the strategy based on CARS [8]. Nevertheless, the resources related to the long-term health effects have not been explored yet.

When defective restorations in primary teeth need to be assessed to guide their management, it is not known if this minimally invasive strategy is efficient for allocating resources compared to the conventional strategy, based on FDI criteria. Even if the diagnostic method benefits patients, the subsequent financial impact should be assessed, featuring phase 5 studies for diagnostic methods [9]. As dental expenditure was $298 billion in 2010, representing 4.6% of global healthcare costs [10], economic evaluations to direct resources to the best diagnostic strategies are critical for clinical practice to be financially viable. On the other hand, economic evaluations assessing diagnostic strategies are scarce and, in several cases, are not standardized and present low quality [11].

We are presenting a health economic analysis plan to guide a trial-based economic evaluation. The publication of the health economic analysis plan has been becoming the best practice for trial-based economic assessments. Publishing an economic analysis plan is currently relevant since it increases the reproducibility, dissemination to other research groups and transparency of the analyses. Indeed, this process intends to guarantee that the process avoids selection bias related to data sources and valuation methods, selective reporting in results and the use of unplanned analyses to satisfy a specific hypothesis [12, 13]. The present health economic analysis plan aims: 1- to describe methodologic strategies for conducting a transparent trial-based economic evaluation that aims to assess whether a minimally invasive strategy is more efficient in allocating resources than the conventional strategy for managing restorations in primary teeth; 2- to construct a decision analytic modelling framework to extrapolate these findings considering a primary molar lifetime horizon.

**Methods**

This manuscript is a health economic analysis plan following the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Good Research

Practices Task Force Report recommendations [14] and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) [15] checklist.

*Study Design*

A trial-based economic evaluation will be conducted (piggyback approach), including three cost-effectiveness analyses (CEA) - different health effects- and a cost-utility analysis (CUA). The clinical trial investigating the diagnostic strategy for restorations assessment is the third diagnostic study conducted by the CARDEC collaborative group at the School of Dentistry of the University of São Paulo (São Paulo, Brazil). The CARDEC-03 trial is a two-arm, parallel-group, patient-randomized controlled trial aiming to assess which diagnostic strategies (based on FDI criteria or CARS) leads to fewer new interventions in restored primary teeth during two years of follow-up. Further details regarding the trial have been published in the study protocol [7].

The strategy based on the FDI criteria will be acknowledged as the reference strategy for assessing the restorations. However, recognize there is no robust evidence supporting this assumption. Despite this, a reference strategy for economic evaluation must be assumed. Considering that the CARS strategy is associated with a less interventionist approach, we will consider it as the new strategy. Moreover, FDI criteria were first proposed and appointed by experts as the standard criteria for restorations' assessment [16, 17].

*Target population and Eligibility Criteria*

Children's participation was voluntary. Our sample includes 3-to-10-year-old children seeking dental care at the Pediatric Dentistry clinic from our school, with at least one dental restoration in a primary tooth. The exclusion criteria were children whose parents did not consent to their participation, children who did not assent participating in this study, and children with limited ability to co-operate even when behavior management was used [18].

*Comparators - Interventions and Follow-up*

Aiming to compare a more interventionist strategy to a supposedly less interventionist approach when assessing dental restorations and guiding clinical decision-making, children were allocated to one of the two diagnostic strategies for the assessment of restorations. To simplify, we will refer to them, from that point, as FDI and CARS strategies. A trained and calibrated examiner (BLPM) performed the assessments, and treatment decisions were based on the criteria. The FDI criteria [16] can be adapted depending on the purpose of the study. Therefore, since dental caries is the most common reported reason for reinterventions in primary teeth, we chose to evaluate related parameters as marginal staining and adaptation, besides the recurrence of caries. The CARS strategy will be used as originally proposed [5] (Table 1). Details regarding clinical criteria, sample size, randomization, allocation, blinding, and treatment of the restorations have been previously described in a clinical trial protocol [7].

Children will be followed for 24 months after the baseline interventions. Clinical assessments are being scheduled at 6-month intervals. In the baseline and at each follow-up visit, children are being instructed about diet and oral hygiene. The same examiner responsible for baseline evaluation will reassess the restorations at each appointment and propose a new treatment plan for each child based on the randomized strategy.

*Time horizon, study perspective and discount rate*

The time horizon for the main evaluations was set as 24 months (time of study enrollment). Secondary longer-term economic evaluation with trial results will be performed to extrapolate the results over a primary tooth lifetime horizon. We will adopt the societal perspective, accounting for direct and indirect costs. A discount rate of 5% will be applied for costs and effects as the trial is being conducted in Brazil, a lower-middle-income country [19]. Further sensitivity analyses will test the influence of this assumption by considering different discount rates (0-10%).

*Costs and resources*

The costs of each strategy will be estimated using a micro-costing approach. The direct and indirect costs per tooth and child will be calculated over 24 months (Supplemental Material 1). Direct costs will comprise the expenses related to the dental office accommodation, dental instruments and equipment and their respective maintenance, materials used to implement the strategies and staff expenses (based on working hours and time spent on patient's care). Firstly, direct costs will be estimated per tooth included in the trial. Then, we will sum up all child's eligible teeth for calculating direct costs with each child.

We will calculate the accommodation costs using rental costs and municipal taxes per $m^2$ of the area used by each dental unit. Subsequently, the accommodation costs per hour will be calculated. The same calculation will be used for dental instruments and equipment, estimating a life span of 3 years for instruments [20] and 5 years for equipment [21], with a monthly usage of 160 hours. The staff salary (dentists and dental auxiliaries) will be calculated based on the Brazilian Federal Law's monthly wage, allowing 40 hours per week (8 hours/day) for each dentist and dental nurse. For dental material, we will calculate the mean value of each item in three different dental stores and quantities used during clinical appointments.

Indirect costs will include out-of-pocket expenditures, such as transportation (public or private), any opportunity costs of accompanying a person's absence from the workplace, and the patient's time accessing care. These costs will be estimated per child, considering the time spent during appointments and waiting or travelling to/from the dental clinic. For indirect costs per tooth, time spent performing procedures related to each specific tooth will be first considered. For the child's general appointments (e.g., instructions, fluoride applications) and the child's and accompanying person's waiting/travelling, the time spent will be fully considered for each tooth, as if only one tooth had been included per child. Possible dental interventions received externally to the research, but related to the assessed teeth, will also be considered indirect costs.

Transportation costs will be calculated using the municipality’s fares for public transportation. For private transport, we will consider the distance from the family's house to the University and an average price for fuel obtained from the Brazilian National Agency, assuming an 8 km per litre efficiency. The patient's and accompanying person's time will be valued, respectively, based on the Brazilian minimum wage and mean Brazilian salary. Suppose the accompanying person reports any earning loss due to being present at the child's appointments; an additional cost of a working day will be added for each appointment the child attends. The accompanying person's working absence time will also be calculated based on the mean Brazilian salary. In this case, the working days and hours will be considered to estimate this person's value per working hour.

To estimate the costs, we have registered in a specific form the number of appointments, the time spent at each one and materials used during patient care (Supplemental Material 2). This form has also been used to collect information about transportation and absence from work. Details about the cost estimation of each of the resources mentioned above can be found in Supplemental Material 1.

Costs will be calculated in Brazilian Real (BRL) considering the base year for the analysis and converted to international dollars using Purchasing Power Parities (PPP) measured for the same period (or the most recent indicator available at the time of the analyses).

*Health Outcomes*

Three health effects will be considered for different CEAs to bring different perspectives when decision-making. The primary health effect considered will be the number of new operative interventions per child after the baseline assessment. Other endpoints were set as secondary health effects: the time to the new operative interventions (survival), the percentage of children who did not need new operative interventions and the relevant change in the Oral Health-Related Quality of Life (OHRQoL) scores (Table 2).

For the first health outcomes (related to new operative interventions), we will assess the children for 24 months, following them each six months. The cumulative result will be accumulated for 24 months when computing the number of events (new interventions) and the time to an event during this period. The restorations will be evaluated by an examiner (TKT), blinded to the diagnostic strategy. At this assessment, surfaces were scored according to the restoration integrity and occurrence of caries, determining the need (or not) of repair, replacement or other possible new interventions [22-23] (Table 2). At this stage, the idea was to use an external assessor using a different approach (from those interventions under comparison and randomized) not to bias the outcome assessment. Based on this assessment, new interventions (events) will be considered when any need for restoration repair or replacement is identified, any presence of secondary caries lesion exposing dentin is detected, any need for extension of the existing restoration or endodontic treatment is required (due to caries or tooth fracture) and/or any episode of pain is reported (Table 2).

The OHRQoL will be assessed using the Brazilian version of the Early Childhood Health Impact Scale (B-ECOHIS) [24]. This questionnaire is answered by parents as a proxy of the child's OHRQoL and is a valid measure for children [25]. Although the ECOHIS has been proposed for pre-school children [26], it was chosen to measure effectiveness in the entire sample, comprising children from 3-to-9 years old. The questionnaire was answered in the baseline and will be answered at 24-month follow-up completion. The difference between the ECOHIS final and baseline scores will be calculated. The change in ECOHIS scores will be classified according to the minimal important difference calculated [25].

For CUA, the effect will be the gain in tooth-related Quality Adjusted Life Years (QALYs). To estimate tooth-related QALYs, we will use the Standard Gamble (SG) approach to calculate weights (utility scores) based on the patient's parent's preferences regarding health states related to dental caries. For that, we anchored the weighs in tooth loss (the worst scenario). The parent preference will be used as a proxy measure for the child's preference regarding different health statuses. More details about the Standard Gamble experiment may be found in the next section.

*Standard Gamble*

We will conduct an SG experiment to measure different oral health states' preferences related to dental caries in primary teeth. As parents' answers will be considered a proxy measurement, a representative sample of those parents seeking dental treatment in a reference center will be selected. A minimum sample size of 50 parents was calculated to permit an absolute difference of 0.05 units and guarantee the power of 80% and a significance level of 5%. To compensate for possible non-normal distribution and possible non-response or lost participants, we added up, respectively, 10% and 20% to this calculated sample, totalizing 63 participants to be recruited.

The recruited sample will be stratified by the child's caries experience and opportunity for dental treatment (children firstly seeking the treatment vs those already enrolled in treatment) to contribute to the sample representativeness. Part of this sample will be selected among children's parents from the main clinical trial (CARDEC-3). The other will be recruited among parents whose children are seeking treatment in the school's dental clinics. Adults will be asked about their preference between two courses of action resulting in different outcomes regarding their child's oral condition.

The health states will be illustrated on cards, and the SG will be conducted using a chance board. The health states considered are 1) a primary molar with dentin caries lesion; 2) a restored primary molar; 3) a restored primary molar needing repair/replacement. Children's parents will choose between alternatives A and B. Alternative A offers a probability "p" of achieving the best possible health state, which is a sound tooth that will last like that until it exfoliates. Then, a probability "1 – p" of having the worst possible condition is assumed (early tooth loss) (Figure 1). Alternative B will be a particular health state of a restored primary molar. The probability "p" will be changed in the chance board until the parent is indifferent to the two options [27]. This probability will be considered the parent's preference (utility weight) for their child's health state (utility value). We will then calculate the tooth-related QALYs, also considering the time for which the child presented such a state. The same experiment with the other health states will be conducted, as demonstrated in Figure 1.

*Analytical methods*

The economic evaluations will be considered intention-to-treat analyses using data collected after two years, as previously described. In the case of missing data, we will investigate their nature and choose the most appropriate method to handle the missing data, e.g., multiple imputations. Imputations will consider health and economic outcomes and the possible relationship between them and other pertinent covariates. When new operative treatments have been performed externally to the research, the same strategy used for missing data will be used for cost estimation.

Cox regression model with shared frailty will be used to compare the need for a new intervention. The health effects listed above will be compared between groups using the most appropriate statistical test, depending on data distribution. Given the usual right-skewed distribution of cost data, we will use the bootstrapping quantile regression to compare the total costs of the diagnostic strategies [28]. Bootstrapping replications will be set at 1,000, and a fixed seed will be determined. We will use the software Stata13 (StataCorp LP, Texas, USA) and set a 5% significance level for these analyses.

We will work with the difference between the strategies both regarding the inputs (∆costs: $CARS\ costs - FDI\ costs$) and outputs (∆effects: $CARS\ effects - FDI\ effects$) since the focus of this series of economic evaluations is the economic impact of using the minimally invasive strategy (based on CARS) instead of the conventional strategy (based on FDI criteria) for managing dental restorations. Bootstrap confidence intervals will be calculated for each parameter considering the costs, effects, incremental costs and incremental effects[29].

Deterministic one-way sensitivity analysis will be conducted for CEAs and CUA to assess the quantitative relationship among estimates in parameters that could perform differently in a distinct scenario, such as costs, discount rate, and effects. In these analyses, we will also test the influence of different baseline conditions as covariates associated with the effects and costs [30], checking the possibility of extrapolating data from this single trial to a broader population. The results will be demonstrated in a tornado diagram.

Additionally, a Bayesian approach will be used to explore uncertainties on the same parameters. By adopting this approach, we will describe the probabilities around the actual values obtained in this study [31–33]. The data distribution of costs and effects will be checked using XLSTAT Premium 2021.3.1 (Addinsoft, Paris, France), and, based on that distribution, Monte-Carlo simulations (x10,000) will be generated to be plotted in a cost-effectiveness plane (CE plane). The proportion of points in each quadrant of the CE plane will be calculated, and the location of points will also be assessed visually. We will calculate the incremental net benefit using the following equation:

$$Incremental\ Net\ Benefit = Incremental\ Effect\ \times Ceiling\ Ratio\ - Incremental\ Cost,$$

being value 1 for a positive coefficient and 0 for a negative coefficient value. Thus, for the interpretation, if the difference is higher than zero (the value 1), it means that for one additional unit of effectiveness, the incremental cost is below the Ceiling Ratio (the maximum value that decision-makers are willing to pay). If the difference is less than zero (the value 0), the incremental cost of each additional unit of effectiveness is above the Ceiling Ratio [34]. Finally, acceptability curves will be plotted for each effect using the incremental net benefit framework and assuming different ceiling ratios to check the uncertainties around threshold points.

Subgroup analyses considering age (3 to 6 vs 7 to 10 years) and patients' caries experience (≤3 vs>3 restorations) will also be conducted.

*Modelling for* primary tooth lifetime horizon

We will construct a decision analytic modelling framework to extrapolate the findings considering a longer time horizon (the primary molar lifetime) (Supplemental File 3). As the base case, we will consider a child as those enrolled in the trial. Then, based on the mean age of children enrolled on the main trial, we will establish the number of cycles of the Markov model.

Probabilities and costs will be extracted from the main trial. If necessary, any additional reference value will be identified from the literature. The SG experiment will generate utility values. We will assume that probabilities will maintain the same at each cycle during the time horizon. The half-cycle correction will be used to account for the fact that events and transitions can occur at any point during the cycle, not necessarily at the start or end of each cycle.

We will adopt the same strategies adopted in the trial-based analyses for deterministic and probabilistic analyses using the model framework. The final interpretation of uncertainties will be considered for this longer time horizon. Data will be modelled and analyzed using a Markov simulation model. Tree Age Pro 2017 (TreeAge Software, Williamstown, MA, USA).

**Discussion**

The results from this study will provide necessary evidence regarding the economic impact of the possible implementation of potentially less interventionist diagnostic strategies, such as that based on CARS, when managing restorations in primary teeth. Owing to the lack of high-quality economic evaluation studies in the pediatric dentistry field [11], our study will strengthen the evidence and guide an evidence-informed decision-making process concerning diagnosing dental caries adjacent to restorations in primary teeth. To the best of our knowledge, no study has evaluated the economic impact of diagnostic strategies focused on such a clinical condition.

The strategy based on FDI may lead to a greater number of operative interventions [8], probably due to merge the assessment of the presence of recurrent caries and the restoration staining and adaptation. At first glance, the need for more interventions in the first treatment plan may lead to additional costs since the baseline. However, in a complete economic evaluation, not only costs are considered. Health outcomes are also important in determining the cost-effectiveness of a strategy [35]. Assuming a longer time horizon, we can expect as more interventionist; more re-interventions may be needed, as demonstrated in a previous clinical trial from our group [36]. Then, much higher expenses could have resulted. On the other hand, eventually, depending on how the non-intervened restorations behave during the follow-up, a different scenario may be observed, impacting on effects or not. Since it is an ongoing trial, the long-term health effects (at two years) will be crucial to decide, for assessment and management of restorations in primary teeth, whether a minimally invasive strategy (as that based on CARS) will be more efficient in allocating resources than the conventional one (based on FDI criteria).

CEA is one of the most widely used economic evaluations in healthcare, as the effects are clinical measures [35, 37]. We opted to use different parallel economic evaluations at this protocol to bring different perspectives and additional subsidies to decision-makers. In this sense, we considered the primary health effect as the number of new operative interventions. This outcome represents the effect magnitude explored when comparing the diagnostic strategies in the trial. Although other endpoints (effects) have been set as secondary ones, they may show additional views to decision-makers. They offer perspectives regarding the time to the effect, demand for treatment and patient-centred opinions that may also be helpful when implementing one or another in the health system.

On the other hand, patients/parents' preferences and consequent utility values may also influence the final impression about the economic aspects of implementing the minimally invasive strategy, like CARS, in clinical practice. In this sense, CUA would be a valuable tool since it integrates patient-centred care philosophy and should be used when the quality of life is an important outcome [27]. CUA evaluates the effects on qualitative and quantitative health gains, often measured through QALYs. These are the product of time and utility obtained through the patient's preferences for different health states [27]. As dental caries in children has a relevant impact on quality of life [38], studies involving the economic implications of caries diagnosis and management would benefit from CUA.

Utilities related to health states related to dental caries in primary teeth have been assessed through pre-scored multi-attribute health status classification systems, such as the CHU-9D, or through the Visual Analogue Scale (VAS) [39, 40]. One of the main concerns about pre-scored measures is that they may not identify the impact of oral diseases, such as dental caries [41]. Besides, the scaling methods will not necessarily express participants' sacrifice is willing to take to achieve the health states, and they are more prone to contextual bias [42]. Conversely, the SG is a choice-based method of obtaining 'patients' preferences for health states under uncertainty. Although it is time-consuming, the SG is conceptually based on the expected utility theory [43], and it involves the highest sacrifice the participants are willing to take. Finally, in this SG experiment, we could anchor the utility weights in tooth loss, considering it is our worst scenario planned and called the measure derived from it as tooth-related QALY. Although its questionable interchangeability to general QALYs, tooth-related QALY may be a relevant measure for decision-makers in Dentistry, especially considering primary teeth, the type of injuries and their health consequences in children.

Given the SG experiment inherent complexity, we decided to adopt the parents' valuation of utility as a proxy measurement from the child's preferences related to their oral health states. This approach has been widely used in studies of children's preferences [44]. Although these proxy answers have some limitations, it would be a reasonable and feasible approach to a first attempt in determining utility scores related to dental caries, independently of the child's age. Due to the broader age range in the base clinical trial, we opted for this approach.

Therefore, the results of these trial-based economic evaluations may bring actual evidence about the economic impact of such implementation and contribute to the decision-making process pertaining to the assessment and management of restorations in children. Analytical strategies adopted (e.g. probabilistic sensitivity analyses (scenario) and modelling for primary molars lifespan) may be alternatives to minimize possible limitations in results extrapolation derived from single-studies economic evaluations [45]. In this sense, they may permit that the results are broadly generalized to children seeking dental treatment, who will demand decision and management of their previously placed restorations.

**Trial Status**

CARDEC-03 trial recruitment took place from November 2017 to November 2018. Each patient will be followed for 24 months. Due to the COVID-19 pandemic situation, our goal is to complete the follow-up by May 2021.

**List of abbreviations**

FDI: World Dental Federation; CARS: Caries Around Restorations and Sealants; CEA: Cost-effectiveness analysis; ECOHIS: Early Childhood Oral Health Impact Scale; CUA: Cost-utility analysis; QALYs: quality-adjusted life years; ICER: Incremental Cost-Effectiveness Ratio; ICCMS: International Caries Classification and Management System; ICDAS: International Caries Detection and Assessment System; HEAP: Health Economic Analysis Plan; RCT: Randomized Controlled Trial; ISPOR: International Society for Pharmacoeconomics and Outcomes Research; CARDEC: Caries Detection in Children; OHRQoL: Oral Health-Related Quality of Life; SG: Standard Gamble.

**Declarations**

*Ethics approval and consent to participate*

The clinical trial was approved by the Ethical Committee of the School of Dentistry (registration nº 2.291.642), University of São Paulo (São Paulo, Brazil), on 22nd September 2017, and was registered on Clinicaltrials.gov (registration NCT03520309). All parents or guardians will sign a written informed consent form before the child participates in the study, and literate children will sign an assent form. Parents and guardians are free to withdraw their children from the clinical trial at any time, without losing any rights regard treatments they would receive during the trial.

*Consent for publication*

Not applicable.

*Availability of data and materials*

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

*Competing interests*

The authors declare they have no competing interests.

*Funding*

The São Paulo Research Foundation (FAPESP; Grants #2017/22897-3, # 2018/03199-6, and #2018/20464-5), Coordination for the Improvement of Higher Education Personnel (CAPES), and the Brazilian National Council for Scientific and Technological Development (CNPq; Grant #420458/2018-2) financially supported the CARDEC-03 clinical trial. The financial grant was given for protocol accomplishment and PhD scholarships to students involved in the project. The protocol, including a preview of these economic evaluations, was peer-reviewed by these governmental institutions. However, they have no intellectual role or responsibility in study protocol design or execution. DPR, FMM, MSC and MMB are granted for research productivity with scholarship awards by CNPq.

*Author's contributions*

MMB, FMM, DPR, and MSC contributed to the conception of the clinical trial. MMB and RDF were responsible for the idealization of the economic evaluation and drafted the manuscript. BLPM and LRAP are in charge of patients' recruitment and treatment plans. HCMM, ALP, RCO, and JRG are responsible for treating patients and collecting costs data. TKT and DPR will be responsible for the follow-up assessments. MEFV and RDF will develop and execute the SG. MMB and FMM will perform statistical analyses. CD contributed to the methodology, writing, reviewing, and editing. The CARDEC collaborative group staff members are responsible for the study's organization and conduction, performing treatments, and oral hygiene orientation for the participants. All authors critically reviewed and approved the final manuscript as submitted.

*Acknowledgements*

The authors thank all members of the collaborative group described in the next section of this manuscript. Also, we wish to acknowledge the participants of the Scientific Writing course and the post-graduation students from the Pediatric Dentistry Seminar (School of Dentistry, University of São Paulo) for contributing to the improvement of this manuscript and Mr Charles Joseph Gillott for language revision.

*Author's information*

The CARDEC collaborative group investigates caries diagnosis in primary teeth. This group involves researchers, dentists, technicians, graduate and undergraduate students. The list of the participants can be found at the following link (https://sites.usp.br/cardec/grupo_de_pesquisa/cardec-03/grupo-de-colaboradores-2/).

## References

1. Chisini LA, Collares K, Cademartori MG, de Oliveira LJC, Conde MCM, Demarco FF, et al. Restorations in primary teeth: a systematic review on survival and reasons for failures. Int J Paediatr Dent. 2018;28:123–39.

2. Signori C, Gimenez T, Mendes FM, Huysmans MCDNJM, Opdam NJM, Cenci MS. Clinical relevance of studies on the visual and radiographic methods for detecting secondary caries lesions – A systematic review. J Dent. 2018;75 May:22–33. doi:10.1016/j.jdent.2018.05.018.

3. Hickel R, Roulet JF, Bayne S, Heintze SD, Mjör IA, Peters M, et al. Recommendations for conducting controlled clinical studies of dental restorative materials. Clin Oral Investig. 2007;11:5–33.

4. Marquillier T, Doméjean S, Le Clerc J, Chemla F, Gritsch K, Maurin J-C, et al. The use of FDI criteria in clinical trials on direct dental restorations: A scoping review. J Dent. 2018;68:1–9. doi:10.1016/j.jdent.2017.10.007.

5. Pitts NB, Ismail AI, Martignon S, Ekstrand K, Douglas GV V., Longbottom C. ICCMS™ Quick Reference Guide for Practitioners and Educators. ICCMS™ Resour. 2014;:1–84.

6. Pitts N, Ekstrand K. International Caries Detection and Assessment System (ICDAS) and its International Caries Classification and Management System (ICCMS) - methods for staging of the caries process and enabling dentists to manage caries. Community Dent Oral Epidemiol. 2013;41:e41–52. doi:10.1111/cdoe.12025.
7. Moro BLP, Signori C, Freitas RD, Pontes LRA, Lenzi TL, Tedesco TK, et al. The effect of two clinical criteria in the assessment of caries lesions around restorations in children (CARDEC-03): study protocol for a diagnostic randomized clinical trial. F1000Research. 2021;9:650. doi:10.12688/f1000research.23801.3.
8. Moro BLP, Freitas RD, Pontes LRA, Pássaro AL, Lenzi TL, Tedesco TK, et al. Influence of different clinical criteria on the decision to replace restorations in primary teeth. J Dent. 2020;101:103421. doi:10.1016/j.jdent.2020.103421.
9. Haynes RB, You JJ. The architecture of diagnostic research. In: Knottnerus JA, Buntinx F, editors. The Evidence Base of Clinical Diagnosis. Londres: BMJ; 2009. p. 20–41.
10. Rogers HJ, Rodd HD, Vermaire JH, Stevens K, Knapp R, El Yousfi S, et al. A systematic review of the quality and scope of economic evaluations in child oral health research. BMC Oral Health. 2019;19:1–15.
11. Listl S, Galloway J, Mossey PA, Marcenes W. Global Economic Impact of Dental Diseases. J Dent Res. 2015;94:1355–61.
12. Thorn JC, Davies CF, Brookes ST, Noble SM, Dritsaki M, Gray E, et al. Content of Health Economics Analysis Plans (HEAPs) for Trial-Based Economic Evaluations: Expert Delphi Consensus Survey. Value Health. 2021;24(4):539-47.
13. Dritsaki M, Gray A, Petrou S, Dutton S, Lamb SE, Thorn JC. Current UK Practices on Health Economics Analysis Plans (HEAPs): Are We Using Heaps of Them? Pharmacoeconomics. 2018;36:253–7. doi:10.1007/s40273-017-0598-x.
14. Ramsey SD, Willke RJ, Glick H, Reed SD, Augustovski F, Jonsson B, et al. Cost-effectiveness analysis alongside clinical trials II - An ISPOR good research practices task force report. Value Heal. 2015;18:161–72. doi:10.1016/j.jval.2015.02.001.
15. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. Eur J Heal Econ. 2013;14:367–72.

16. Hickel R, Peschke A, Tyas M, Mjör I, Bayne S, Peters M, et al. FDI World Dental Federation: Clinical criteria for the evaluation of direct and indirect restorations-update and clinical examples. Clin Oral Investig. 2010;14:349–66.
17. Hickel R, Peschke A, Tyas M, Mjör I, Bayne S, Peters M, et al. FDI World Dental Federation - clinical criteria for the evaluation of direct and indirect restorations. Update and clinical examples. J Adhes Dent. 2010;12:259–72. doi:10.3290/j.jad.a19262.
18. AAPD. Guideline on Behavior Guidance for the Pediatric Dental Patient: Reference Manual. Am Acad Pediatr Dent. 2011;36:179–91.
19. Haacker M, Hallett TB, Atun R. On discount rates for economic evaluations in global health. Health Policy Plan. 2020;35:107–14.
20. da Mata C, Allen PF, Cronin M, O'Mahony D, McKenna G, Woods N. Cost-effectiveness of ART restorations in elderly adults: a randomized clinical trial. Community Dent Oral Epidemiol. 2014;42:79–87. doi:10.1111/cdoe.12066.
21. Floriano I, Gimenez T, Reyes A, Matos R, Mattos-Silveira J. Análise de custos de diferentes abordagens para avaliação de lesões de cárie em dentes decíduos. Braz Oral Res. 2013;27:41–9.
22. Frencken JE, Makoni F, Sithole WD. Atraumatic Restorative Treatment and Glass-Ionomer Sealants in a School Oral Health Programme in Zimbabwe: Evaluation after 1 Year. Caries Res. 1996;30:428–33. doi:10.1159/000262355.
23. Roeleveld AC, van Amerongen WE, Mandari GJ. Influence of residual caries and cervical gaps on the survival rate of Class II glass ionomer restorations. Eur Arch Paediatr Dent. 2006;7:85–91. doi:10.1007/bf03320820.
24. Martins-Júnior PA, Ramos-Jorge J, Paiva SM, Marques LS, Ramos-Jorge ML. Validations of the Brazilian version of the Early Childhood Oral Health Impact Scale (ECOHIS). Cad Saude Publica. 2012;28:367–74. doi:10.1590/S0102-311X2012000200015.
25. Novaes TF, Pontes LRA, Freitas JG, Acosta CP, Andrade KCE, Guedes RS, et al. Responsiveness of the Early Childhood Oral Health Impact Scale ( ECOHIS ) is related to dental treatment complexity. Health Qual Life Outcomes. 2017;15:1–9.
26. Pahel BT, Rozier RG, Slade GD. Parental perceptions of children's oral health: The Early Childhood Oral Health Impact Scale (ECOHIS). Health Qual Life Outcomes. 2007;5:6. doi:10.1186/1477-7525-5-6.

27. Brazier J, Ratcliffe J, Salomon JA, Tsuchiya A. Measuring and Valuing Health Benefits for Economic Evaluation. 2nd editio. Oxford: Oxford University Press; 2017.

28. Desgagné A. The use of the bootstrap statistical method for the pharmacoeconomic cost analysis of skewed data. Pharmacoeconomics. 1998;13 5 PART I:487–97.

29. Barber JA, Thompson SG. Analysis of cost data in randomized trials: An application of the non-parametric bootstrap. Stat Med. 2000;19:3219–36.

30. Braga M, Machado T, Rocha E, Floriano I, Raggio D, Mendes F. How to extrapolate trial-based economic evaluations to populations? – proposing sensitivity analyses based on national data. In: Caries Research. 2021.

31. Briggs AH, Gray AM. Handling uncertainty when performing economic evaluation of healthcare interventions. Health Technol Assess (Rockv). 1999;3:635–8.

32. Sendi P, Gafni A, Birch S. Opportunity costs and uncertainty in the economic evaluation of health care interventions. Health Econ. 2002;11:23–31.

33. Heitjan DF, Moskowitz AJ, Whang W. Bayesian estimation of cost-effectiveness ratios from clinical trials. Health Econ. 1999;8:191–201.

34. Hounton S, Newlands D. Applying the net-benefit framework for assessing cost-effectiveness of interventions towards universal health coverage. Cost Eff Resour Alloc. 2012;10:8. doi:10.1186/1478-7547-10-8.

35. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. Fourth Edi. Oxford, Uk: Oxford University Press; 2015.

36. Pontes L, Novaes T, Lara J, Gimenez T, Moro B, Camargo L, et al. Impact of visual inspection and radiographs for caries detection in children: a 2-year randomized clinical trial. J Am Dent Assoc. 2020;151:407–15.

37. Rudmik L, Drummond M. Health economic evaluation: Important principles and methodology. Laryngoscope. 2013;123:1341–7.

38. Martins MT, Sardenberg F, Bendo CB, Vale P, Paiva SM, Pordeus IA, et al. Dental caries remains as the main oral condition with the greatest impact on children ' s quality of life. PLoS One. 2017;12:1–8.

39. Tamošiunas V, Kay E, Craven R. A preliminary study applying decision analysis to the treatment of caries in primary teeth. Stomatologija. 2013;15:84–91.

40. Koh R, Pukallus M, Kularatna S, Gordon LG, Barnett AG, Walsh LJ, et al. Relative cost-effectiveness of home visits and telephone contacts in preventing early childhood caries. Community Dent Oral Epidemiol. 2015;43:560–8.
41. Foster Page LA, Beckett DM, Cameron CM, Thomson WM. Can the Child Health Utility 9D measure be useful in oral health research? Int J Paediatr Dent. 2015;25:349–57.
42. Bleichrodt H, Johannesson M. An experimental test of a theoretical foundation for rating-scale valuations. Med Decis Mak. 1997;17:208–16.
43. Sampson C, Devlin N, Parkin D. Drop Dead: Is Anchoring at 'Dead' a Theoretical Requirement in Health State Valuation? OHE Res Pap. 2020.
44. Wolstenholme JL, Bargo D, Wang K, Harnden A, Räisänen U, Abel L. Preference-based measures to obtain health state utility values for use in economic evaluations with child-based populations: a review and UK-based focus group assessment of patient and parent choices. Qual Life Res. 2018;27:1769–80. doi:10.1007/s11136-018-1831-6.
45. Sculpher MJ, Claxton K, Drummond M, McCabe C. Whither trial-based economic evaluation for health care decision making? Health Econ. 2006;15:677–87. doi:10.1002/hec.1093.

**Legends**

Table 1. Clinical strategies for FDI and CARS criteria – adapted from Moro et al. 2021 [7].

Table 2. Summary of health outcomes (health effects) used in economic evaluations. – 95%CI*: bootstrap adjusted confidence interval at 95%

Figure 1. The Standard Gamble experiment to be performed with parents assessing three health states related to dental caries in their child's primary molars.

Supplemental Material 1 – Cost items and valuation methods for direct and indirect costs

Supplemental Material 2 – Form used for resource measurement and subsequent cost estimation.

Supplemental Material 3 – First draft of a theoretical framework to construct an analytic Markov model for modelling strategies for primary tooth lifetime horizon.

EQUATOR network reporting checklist - Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist. Note the items related to Results and Discussion (aspects related to findings) are not addressed since this is a health economic analysis plan.

Table 1 - Clinical strategies for FDI and CARS criteria – adapted from Moro et al. 2021 [7].

| FDI SCORES[1] | Classification | Marginal Staining | Marginal adaptation | Recurrence of caries |
|---|---|---|---|---|
| 1 | Clinically excellent/ very good | No marginal staining. | Harmonious outline, no gaps, no white or discolored lines. | No secondary or primary caries |
| 2 | Clinically good | Minor marginal staining, easily removable by polishing. | Marginal gap (<150 µm), white lines. Small marginal fracture removable by polishing. Slight ditching, slight step/flashes, minor irregularities. | Very small and localized demineralization |
| 3 | Clinically sufficient/ satisfactory | Moderate marginal staining, not esthetically unacceptable. | Gap < 250µm not removable. Several small marginal fractures. Major irregularities, ditching or flash, steps. | Larger areas of demineralization |
| 4 | Clinically unsatisfactory | Pronounced marginal staining; major intervention is necessary. | Gap > 250µm or dentine/ base exposed. Severe ditching or marginal fractures. Larger irregularities or steps. | Caries with cavitation |
| 5 | Clinically poor | Deep marginal staining, not accessible for intervention. | Restoration (complete or partial) is loose but in situ. Generalized major gaps or irregularities. | Deep secondary caries or exposed dentine that is not accessible for repair of restoration |

| CARS SCORES[2] | Classification | Clinical features |
|---|---|---|
| 0 | Sound restored/sealed surface | A sound tooth surface adjacent to a restoration/sealant margin. There should be no evidence of caries (no or questionable change in enamel translucency after air drying for 5 seconds). Surfaces with marginal defects less than 0.5mm in width, developmental defects; fluorosis; tooth wear, and extrinsic or intrinsic stains will be recorded as sound. Stained margins consistent with non-carious habits without signs of demineralization should be scored as sound. |
| 1 | First visual change in enamel | When seen wet there is no changes in color due to carious activity, but after prolonged air drying (approximately 5 seconds) an opacity or discoloration consistent with demineralization is visible that is not consistent with the clinical appearance of sound enamel. |
| 2 | Distinct visual change in enamel/dentin adjacent to a restoration margin | If the restoration margin is placed on enamel, the tooth must be viewed wet. When wet there is an opacity consistent with demineralization or discoloration that is not consistent with the clinical appearance of sound enamel (the lesion is still visible when dry). If the restoration margin is placed on dentin: Code 2 applies to discoloration that is not consistent with the clinical appearance of sound dentin or cementum. |
| 3 | Carious defects of <0.5 mm with the signs of code 2 | Cavitation at the margin of the restoration/sealant less than 0.5mm, in addition to either an opacity or discoloration consistent with demineralization that is not consistent with the clinical appearance of sound enamel or with a shadow of discolored dentin. |
| 4 | Marginal caries in enamel/ dentin/ cementum adjacent to restoration with underlying dark shadow from dentin | The tooth surface may have characteristics of code 2 with a shadow of discolored dentin visible through an apparently intact enamel surface or with localized breakdown in enamel but no visible dentin. This appearance is often seen more easily when the tooth is wet and is a darkening and intrinsic shadow which may be grey, blue, orange, or brown in color. Note: view tooth wet and then dry. This lesion should be distinguished from amalgam shadows. |
| 5 | Distinct cavity adjacent to restoration | Distinct cavity adjacent to restoration/sealant with visible dentin in the interfacial space with signs of caries as described in code 4, in addition to a gap > 0.5mm in width. OR<br>In those instances where margins are not visible, there is evidence of discontinuity at the margin of the restoration/sealant and tooth substance of the dentin as detected by 0.5mm ball-ended probe run along the restoration/sealant margin. |
| 6 | Extensive distinct cavity with visible dentin | Obvious loss of tooth structure, the extensive cavity may be deep or wide and dentin is clearly visible on both the walls and at the base. |

[1] Based on Hickel et al. 2010 [16]; [2] Based on Pitts et al. 2014 [4].

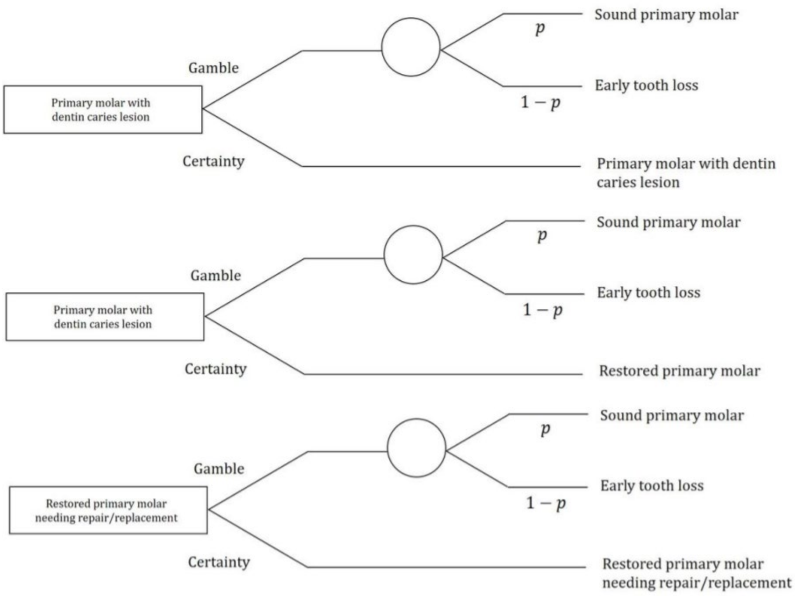
Source: Author

Table 2 - Summary of health outcomes (health effects) used in economic evaluations – 95%CI*: bootstrap adjusted confidence interval at 95%.

| Health Outcome | Outcome assessment | Analysis Metric | Method of aggregation | Follow-up assessments |
|---|---|---|---|---|
| **Percentage of children who did not need new operative interventions** | Frencken et al., 1996 [22] | Restoration success Scores 0, 1, or 7 | Proportion (95% CI*) | 6, 12, 18, and 24 months |
| | Roeleveld et al., 2006 [23] | Restoration success Scores 00 or 10 | Proportion (95% CI*) | 6, 12, 18, and 24 months |
| **Number of new operative interventions** | Frencken et al., 1996 [22] | Restoration failure Scores 2, 3, 4 or 8 | Mean (95% C*I) | 6, 12, 18, and 24 months |
| | Roeleveld et al., 2006 [23] | Restoration failure Scores 11, 12, 13, 20, 21, 30, or 40 | Mean (95% CI) | 6, 12, 18, and 24 months |
| **Oral Health Related Quality of Life** | Early Childhood Oral Health Impact Scale (ECOHIS) | Changes in ECOHIS scores | Median (95% CI*) | Baseline and 24 months |
| **Quality Adjusted Life Years** | Health state: dentin caries lesion Frencken et al., 1996 [22] - Score 4 Roeleveld et al., 2006 [23] - Score 30 (Restoration is not present – new restoration is needed) | Changes in QALYs | Median (95% CI*) | 6, 12, 18, and 24 months |
| | Health state: restored tooth Frencken et al., 1996 [22] Scores: 0, 1, or 7 Roeleveld et al., 2006 [23] Scores: 00 or 10 | | | |
| | Health state: restored tooth needing repair/replacement: Frencken et al., 1996 [22] Scores: 2, 3 or 8 Roeleveld et al., 2006 [23] Scores: 11, 12, 13, 20 or 21 | | | |

Source: Author

Figure 1 - The Standard Gamble experiment to be performed with parents assessing three health states related to dental caries in their child's primary molars.




Source: Author

Supplemental Material 1 - Cost items and valuation methods for direct and indirect costs

| Nature of cost | | Cost items | Estimation of resource quantities | Time-frame for resource measurement | Valuation method | Data Analysis |
|---|---|---|---|---|---|---|
| Direct costs | Cost of intervention | **Accommodation** | Time (h) of usage measured per included tooth | 0, 6, 12, 18, 24 months + urgencies<br>All appointments† required during 24 months and performed in the research dental unit/office.<br>† for diagnosis or treatment | Building: Cost per m² of the area used by a dental unit*, rental cost + municipalities taxes of São Paulo, Brazil (https://www.prefeitura.sp.gov.br/cidade/secretarias/fazenda/servicos/iptu/index.php?p=2456)<br>Electricity costs: 2.3 kw/h, monthly use of 160 hours (8 hours per day and 20 days per month). (https://www.eneldistribuicaosp.com.br/para-sua-casa/tarifa-de-energia-eletrica)<br>* Area assumed: 13.5 m² (based on a mobile dental unit area). | The COST PER RESTOR TOOTH will be calculated. Th costs related to all included te per children will be summed and the COST PER TREAT CHILD will be obtained. |
| | | **Instruments and equipment** | Time (h) of usage measured per included tooth | | Monthly use of 160 hours/ Life span of instruments (3 years) and equipment (5 years) [22,23] | |
| | | **Staff (dentists and auxiliaries)** | Time (h) of active work measured per included tooth | | Monthly wage, determined by the Brazilian Federal Law (3999/61), considering 20 working hours/week. https://www.planalto.gov.br/ccivil_03/leis/1950-1969/l3999.htm | |
| | | **Dental Materials** | Quantities (portions) of each material measured per included tooth | | Mean cost of each item in three different Brazilian dental stores assumed as reference.<br>http://www.dentalcremer.com.br<br>https://www.suryadental.com.br/<br>https://www.dentalgutierre.com.br/ | |
| Indirect costs | Commute costs | **Transportation** | Question answered by child's accompanying person | 0, 6, 12, 18, 24 months + urgencies<br>All appointments† required during 24 months and performed in the research dental unit/office.<br>† for diagnosis or treatment | Child and parent round-trip:<br>- Public transportation: local fare (São Paulo, Brazil - https://www.sptrans.com.br/tarifas/)<br>- Car: distance from the house to the clinic was considered and the average price of fuel will be collected from a National Agency (http://www.anp.gov.br/preco/index.asp) with a fixed ratio of 8.5 km/L. | |
| | | **Patient's time (transportation + waiting + treatment time)** | Time (h) spent per child**<br>** irrespective of the number of teeth included.<br>Transportation: estimated in GoogleMaps using child's address.<br>Waiting time: 0.25h (assumed)<br>Treatment: sum of time spent in appointments | | Minimum wage rate for São Paulo, Brazil, according to the state Law 19.953 (https://www.al.sp.gov.br/repositorio/legislacao/lei/2019/lei-16953-18.03.2019.html)<br>Assumptions: the mean number of working days in the same period, 8 working hours per day | COST PER TREATED CHILD be calculated and will be f considered for each tooth, a: only one tooth had been incluc per child. |
| | | **Accompanying person's time** | Time (h) spent per child**<br>** irrespective of the number of teeth included.<br>Transportation: estimated in GoogleMaps using child's address.<br>Waiting time: 0.25h (assumed)<br>Treatment: sum of time spent in appointments | | Average monthly income for Brazilian population will be estimated using the mean Brazilian income from 2018-2021 (https://www.ibge.gov.br/).<br>Assumptions: the mean number of working days in the same period, 8 working hours per day | |
| | Productivity costs | Days of work missed | work missed (n of days) reported by accompanying person. | | Average monthly income for Brazilian population will be estimated using the mean Brazilian income from 2018-2021 (https://www.ibge.gov.br/).<br>Assumptions: the mean number of working days in the same period, 8 working hours per day | |
| | Health care costs | Related interventions to included tooth receieved in primary care | Interventions (n/type) reported to be received | Any moment during the follow-up | Imputation of value related to type of procedure considering the research database of procedures performed. | The COST PER RESTORED TOC will be calculated. Then, costs rela to all included teeth per children be summed up and the COST F TREATED CHILD will be obtained. |

Source: Author

Supplemental Material 2 - Form used for resource measurement and subsequent cost estimation.

**Patient:** ______________________________________________

**Dentist/Dental auxilliary:** ________________________________

CARDEC - 3

| Date | Procedure | Time |
|---|---|---|
| | | |
| | | |

| DISPOSABLES | |
|---|---|
| 70% Alcohol **(50 ml)** | |
| Bibs **(unit)** | |
| Straw **(1/3 unit)** | |
| Coffee cup **(unit)** | |
| Wooden tongue depressor **(unit)** | |
| Cling Film **(30 cm)** | |
| Autoclave tape **(1 cm)** | |
| Gloves **(1 pair)** | |
| Mask **(unit)** | |
| Protectice eyewear **(unit)** | |
| Cotton Rolls **(unit)** | |
| Syringe sleeve **(unit)** | |
| Plastic clear gloves **(1 pair)** | |
| Saliva ejector **(unit)** | |
| Cap **(unit)** | |

| PROPHY & EXAMINATION | |
|---|---|
| Mouth prop **(unit)** | |
| Cheek retractor **(unit)** | |
| Toothbrush **(unit)** | |
| Prophy brush **(unit)** | |
| Mirror **(unit)** | |
| Disclosing dye - Replak **(drop)** | |
| Floss **(10 cm)** | |
| Examination kit (mouth mirror, probe, tweezers) | |
| Prophy paste **(1 cm)** | |
| Pumice powder **(1 portion)** | |
| Dappen dish **(unit)** | |
| Periodontal curettes **(unit)** | |
| Prophy cup **(unit)** | |

**Dentist**, how was the child's behavior during the procedure?

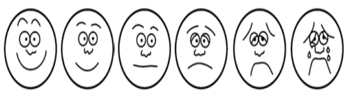
( ) A lot of difficulties
( ) Some difficulty
( ) Indifferent
( ) Cooperated reasonably
( ) Cooperated well

| ANESTHETICS & ISOLATION | |
|---|---|
| Short needle **(unit)** | |
| Ultra-short needle **(unit)** | |
| Ainsworth rubber dam punch **(unit)** | |
| Anesthethic cartridge **(unit)** | |
| Topical anesthetic **(1 cm)** | |
| Otsby dam frame **(unit)** | |
| Dam clamp **(unit)** | |
| Dental dam **(unit)** | |
| Rubber dam fórceps **(unit)** | |
| Cartridge syringe **(unit)** | |

| SURGERY | |
|---|---|
| Elevator **(unit)** | |
| Blade **(unit)** | |
| Scalpel Handle **(unit)** | |
| Molt periosteal **(unit)** | |
| 7 wax spatula **(unit)** | |
| Suture **(unit)** | |
| Forceps **(unit)** | |
| Gauze **(1 swab)** | |
| Carver Hollenbach **(unit)** | |
| Needle holder **(unit)** | |
| Saline water **(ml)** | |
| Seringa descartável **(unit)** | |
| Scissors **(unit)** | |

| TOPICAL FLUORIDE APPLICATION | |
|---|---|
| Duraphat **(1 cm)** | |
| Wooden tongue depressor **(unit)** | |
| Fluoride gel **(portion)** | |
| Micro applicators **(unit)** | |
| Fluoride tray **(unit)** | |

WONG-BAKER FACIAL SCALE
"How did you feel when treating your toothy?".



1 2 3 4 5 6

| X-RAY MATERIALS | |
|---|---|
| Film hanger **(unit)** | |
| Fixer **(50 ml)** | |
| Periapical X-ray film **(unit)** | |
| Child X-ray film **(unit)** | |
| Film holders **(set)** | |
| Developer **(50 ml)** | |

| RESTORATIVES | |
|---|---|
| Polyacrilic acid **(drop)** | |
| Phosphoric acid **(1 cm)** | |
| Single Bond Universal Adhesive **(drop)** | |
| Round bur **(unit)** | |
| Excavator **(unit)** | |
| Wooden wedges **(unit)** | |
| Spatula no. 1 **(unity)** | |
| Carver Hollenbach **(unit)** | |
| Matrix strip - 5mm **(1 cm)** | |
| Matrix strip - 7 mm **(1 cm)** | |
| Micro applicators **(unit)** | |
| Dappen dish **(unit)** | |
| Bulk Fill Restorative **(increment)** | |
| Bulk Fill Flow **(increment)** | |
| Z350 XT restorative **(increment)** | |
| Riva Self Cure encaps. **(unit)** | |
| Tira de poliéster **(1/2 unit)** | |
| Petroleum jelly **(1cm)** | |

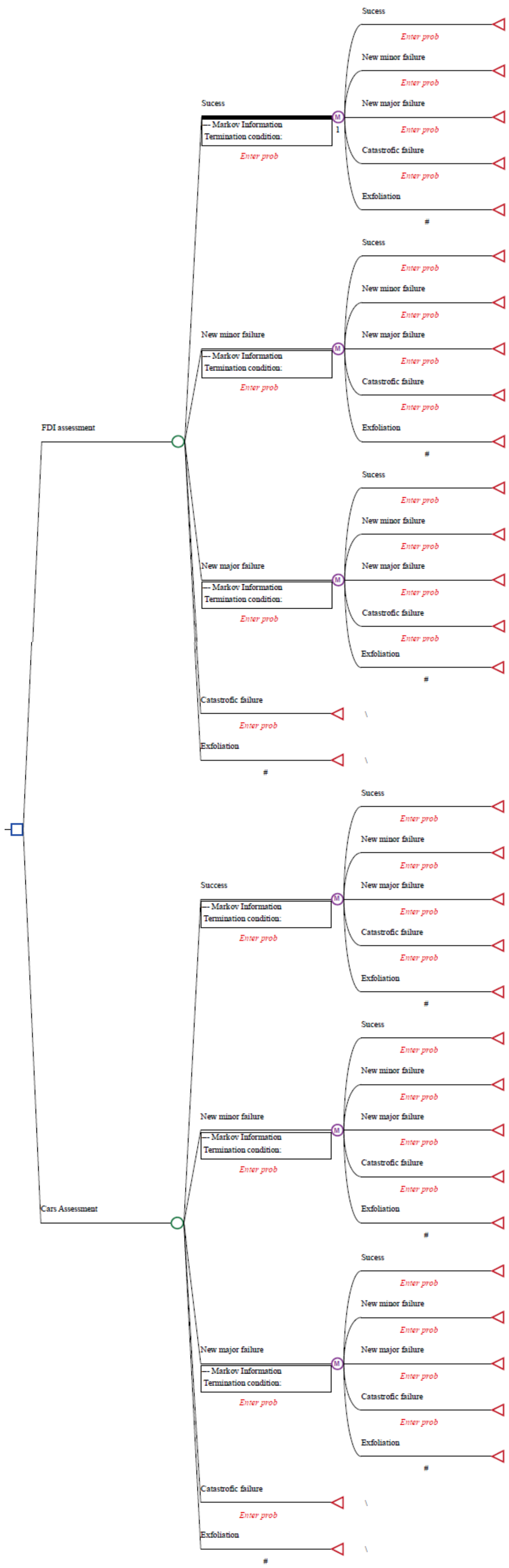
| FINISHING & POLISHING | |
|---|---|
| Diamond bur **(unit)** | |
| Polishing discs **(unit)** | |
| Carbon film paper **(1/3 unit)** | |
| Polishing strips **(unit)** | |
| Abbrasive polishing strips **(1/2 unit)** | |

**Decayed tissue**
Tooth: ________
☐ None
☐ Soft
☐ Hard

**Restoration replacement:**
Decayed tissue underneath the old restoration:
☐ None
☐ Soft
☐ Hard

| Indirect costs |
|---|
| Transportation: ( ) Walk ( ) Bus ( ) Car ( ) Motorcycle ( ) Subway |
| Relatives' absenteeism in the workplace ( ) No ( ) Yes. Earnings loss during the appointment? __________ |

Supplemental Material 3 – First draft of a theoretical framework to construct an analytic Markov model for modelling strategies for primary tooth lifetime horizon.



EQUATOR network reporting checklist - Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist. Note the items related to Results and Discussion (aspects related to findings) are not addressed since this is a health economic analysis plan.

**Table 1 CHEERS checklist—Items to include when reporting economic evaluations of health interventions**

| Section/item | Item No | Recommendation | Reported on page No/ line No |
|---|---|---|---|
| **Title and abstract** | | | |
| Title | 1 | Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared. | 1 |
| Abstract | 2 | Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions. | 3 |
| **Introduction** | | | |
| Background and objectives | 3 | Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions. | 5 |
| **Methods** | | | |
| Target population and subgroups | 4 | Describe characteristics of the base case population and subgroups analysed, including why they were chosen. | 8 |
| Setting and location | 5 | State relevant aspects of the system(s) in which the decision(s) need(s) to be made. | 7 |
| Study perspective | 6 | Describe the perspective of the study and relate this to the costs being evaluated. | 9 |
| Comparators | 7 | Describe the interventions or strategies being compared and state why they were chosen. | 8 |
| Time horizon | 8 | State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate. | 9 |
| Discount rate | 9 | Report the choice of discount rate(s) used for costs and outcomes and say why appropriate. | 9 |
| Choice of health outcomes | 10 | Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed. | 12 |
| Measurement of effectiveness | 11a | *Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data. | 12 |
| | 11b | *Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data. | N/A |
| Measurement and valuation of preference based outcomes | 12 | If applicable, describe the population and methods used to elicit preferences for outcomes. | 13-14 |
| Estimating resources and costs | 13a | *Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs. | 10-12 |
| | 13b | *Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs. | N/A |
| Currency, price date, and conversion | 14 | Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate. | 10-12 |
| Choice of model | 15 | Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended. | 16-17 |
| Assumptions | 16 | Describe all structural or other assumptions underpinning the decision-analytical model. | 16-17 |
| Analytical methods | 17 | Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty. | 14 |

**Table 1 CHEERS checklist—Items to include when reporting economic evaluations of health interventions** *(Continued)*

| | | | |
|---|---|---|---|
| **Results** | | | |
| Study parameters | 18 | Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended. | N/A |
| Incremental costs and outcomes | 19 | For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios. | N/A |
| Characterising uncertainty | 20a | *Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective). | N/A |
| | 20b | *Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions. | N/A |
| Characterising heterogeneity | 21 | If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information. | N/A |
| **Discussion** | | | |
| Study findings, limitations, generalisability, and current knowledge | 22 | Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge. | 17-20 |
| **Other** | | | |
| Source of funding | 23 | Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support. | 21 |
| Conflicts of interest | 24 | Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations. | 21 |

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist.

# 4 CHAPTER II: COST-EFFECTIVENESS ANALYSIS

**How can a less interventionist approach benefit children who had their restorations in primary teeth assessed and managed? – an economic evaluation based on different health outcomes**

## 4.1 INTRODUCTION

Visual inspection is the most accurate method for caries detection for the majority of patients in clinical practice (1). Results from clinical studies have demonstrated that the use of this method avoids overdiagnosis and, consequently, overtreatment in primary teeth (2,3). The inspection of restored teeth, however, remains a difficult task, as the presence of different materials and textures may challenge the diagnostic process, which is based on the physical characteristics observed by the dentist. To aid in the clinical practice, different strategies for the inspection of restorations were proposed, however, high-quality clinical studies in this field are still scarce.

Considering that dental caries is the most prevalent reported reason for reinterventions in restorations in primary teeth (4), the Caries Around Restorations and Sealants (CARS) strategy may be an interesting approach for restorations inspection in paediatric dentistry, as it was proposed for caries lesions detection only (5). However, other characteristics of the restorations may also be a concern for dentists and patients, therefore strategies such as the World Dental Federation (FDI) (6), which evaluates different aspects of the restorations, such as staining and adaptation, could also be a suiting option.

Our group has conducted a clinical trial assessing restorations' survival in primary teeth when using CARS and FDI as diagnostic strategies. Results from a cross-sectional study nested in the main trial demonstrated that the FDI strategy was associated with more replacements of the restorations, representing a more invasive approach when compared to the CARS strategy (7). The Caries Detection in Children 3 (CARDEC-03) trial protocol is currently available (8) and no difference between the two strategies was observed in the restorations' survival and the number of new operative interventions after 24 months (unpublished data).

Preventing unnecessary invasive procedures in Dentistry not only benefits patients, but may also lessen health care systems expenditures. Oral health conditions are a relevant burden for economies worldwide, representing 4.6% of the resources spent with health care (9). Therefore, it is crucial to assess whether the minimally invasive approach observed in the CARS strategy also reflects the efficient use of resources in child oral health care. Economic Evaluations in health care have been used for this purpose, and Cost-Effectiveness Analysis (CEA) is one of the most commonly applied in this field, as it measures costs in monetary units and effects in health effects (10).

Although CEAs are not capable of answering allocative efficiency questions, they may guide technical efficiency questions, determining which strategy is associated with a better output for a budget (11). In this specific situation, differences when combining health effects and expenditures may bring out relevant differences between the strategies. Thus, this study aims to assess the cost-effectiveness of using the CARS strategy instead of the FDI strategy for the assessment and management of restorations in primary teeth. To comprise different perspectives of using these strategies, different health effects were evaluated to provide additional subsides for decision-makers.

## 4.2 METHODS

### 4.2.1 Study design

This is a trial-based full economic evaluation comprising CEAs following the recommendations of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Good Research Practices Task Force Report (12) and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (13) (Appendix A). The clinical trial investigates two diagnostic strategies (CARS and FDI) for the assessment and management of restorations in primary teeth. The

CARDEC-03 trial has finished its final assessments and is currently in the data analysis phase. More information about the main trial is available in a previous publication (8) and at the platform clinicaltrials.gov (NCT03520309).

As previously described in the health economic analysis plan (14), the FDI strategy will be considered as the reference for the EE, as it is considered by experts the standard criteria for restorations' assessment (15,16); moreover, it is related to a more interventionist approach when compared to the CARS strategy.

This chapter focused on the health effects based on the trial, assessing the performance of the two diagnostic strategies on a CEA.

#### 4.2.2 Target population and subgroups

Parents and children who sought dental care at our university were invited to consent and assent to participate in the main trial, respectively. Participants comprised children from 3 to 10 years old with at least one restoration in a primary tooth. Children were excluded from the trial if they did not assent to enrol on the study, if their parents did not consent with their participation, or if they presented severe behaviour limitations in the first appointment, compromising clinical examination.

Based on the main trial and considering relevant risk factors for dental caries disease, subgroups were based on age (3 to 6 vs 7 to 10 years) and caries experience (≤3 vs>3 restorations).

#### 4.2.3 Setting and location

The CARDEC-03 trial was conducted at the School of Dentistry, University of São Paulo (São Paulo, Brazil). São Paulo is the largest city in Brazil and the leading economic national metropolis with a 58,691.90 BRL Gross Domestic Product per capita. The estimated population for 2021 in São Paulo is 12,396,372, according to the Brazilian Institute of Geography and Statistics (IBGE) (17). The School of Dentistry of the University of São Paulo is located in the West Zone of São Paulo and it is a reference for oral health care in that area. Thus, patients usually seek treatment at our dental clinic.

For the main trial, a team of 5 dentists performed all the dental procedures following the biosafety measures determined by the biosecurity office of the School of Dentistry. Dentists involved in children's treatment were graduate students and all of them had experience in paediatric dentistry. The clinic has all the equipment necessary for dental treatment, such as dental chairs and x-rays.

### 4.2.4 Comparators – interventions and follow-up

The diagnostic strategies for restorations assessment and management were compared in the present study. In the main trial, children were randomly allocated to the FDI strategy or the CARS strategy. As the FDI criteria comprise many different features of the restorations and can be adapted depending on the purpose of the study, we used the parameter recurrence of caries, and two other parameters that are usually misinterpreted as caries lesions around the restorations: marginal staining and adaptation.

The CARS strategy was used as it is originally proposed. A trained and calibrated examiner (BLPM) performed the assessments and treatment decisions based on the respective diagnostic strategy. This management decision was independent of the outcome assessment, described below. Operators were instructed to perform the treatment plan according to proposed by the examiner and strongly recommended to not change it. Eventual protocol deviations were registered and analyzed further. Consequent solutions for observed deviations were also reported in a specific form (Appendix B).

Paediatric dental emergencies were handled by our team as soon as we were contacted by the children's parents. Restorations were managed according to the same diagnostic strategy group that children were allocated in the baseline. Emergencies were recorded as new interventions and further analyzed.

In the main trial, children would be followed for 24 months. Due to the COVID-19 pandemic situation, the dental clinic was closed from March until December 2020. Therefore, part of the assessments at 18 months and 24 months were not possible to be performed. We proceeded with the evaluations from December 2020, thus some children had their restorations assessed in over 24 months and the actual time of follow-up was registered.

### 4.2.5 Study perspective, time horizon, and discount rate

We adopted the societal perspective, accounting for direct and indirect costs. The time horizon for the CEA was 24 months. For these primary analyses, we did not consider discount rates for costs and effects, as we registered cumulative costs and effects for 24 months. At this stage, one of the ideas was to register the time in which costs and health effects were observed.

### 4.2.6 Measurement of effectiveness

Four different measures of effectiveness were considered to comprise different perspectives important to decision-making and technical appraisal of strategies. The main health effect was the number of new operative interventions (repair, remodelling, replacement, endodontic treatment, and tooth extraction) after the baseline treatment. After examiner evaluation, scores were dichotomized into the need or no need of a new operative intervention. Then, the number of new interventions per restoration was summed up and finally, the number of new interventions registered per child was totalized.

The second health effect was the time until the first event (new operative intervention) in the child. For the main trial, the time to event was registered through survival analyses. The minimum time for the child, after considering all included teeth, was registered for this effect.

Additional secondary effects were the occurrence of new operative interventions per child, which was derived from the first health effect. We dichotomized the effect into the presence (1) or absence (0) of a new intervention at any follow-up time. Finally, another effect was the need for new replacements, in which the need for replacement was considered as a health effect and other new operative interventions were not considered.

#### 4.2.7 Costs

Costs were estimated through a micro-costing approach based on the trial. The direct and indirect costs per child were calculated at the end of the study, following the health economic analysis plan previously described in the first chapter of the present thesis. The direct costs were the costs of the dental office accommodation, dental instruments and equipment, staff expenses, and costs of materials. All the direct costs were valued in January 2020, before the COVID-19 pandemic situation.

The indirect costs included the out-of-pocket expenditures: patients' transportation, opportunity costs of accompanying person's absence from the workplace, and patient's time during the appointments. For indirect costs per tooth, time spent when performing procedures related to each restoration was considered. Then, costs were estimated per child, considering the time spent during appointments and waiting or travelling to and from the clinic.

All costs were estimated per restoration. Then, we calculated all child's included restorations for the final cost per child.

#### 4.2.8 Currency, price date, and conversion

All costs were initially valued in Brazilian Real (BRL). To avoid including the atypical variation in prices due to pandemic, prices collected in January 2020 were used and corrected using the IPCA (Índice Nacional de Preços ao Consumidor Amplo or Extended National Consumer Price Index), a national inflation rate for a group of products and services (18). This price index has as collection units commercial and service-offering establishments, public service and Internet concessionaries, with data collected, in general, from the 1st to the 30th day of the month of reference. The index for correction from January 2020 to September 2021 was obtained on the website (19) and multiplied by the valued cost.

#### 4.2.9 Analytical methods

The analyses presented in this chapter are mainly intention to treat (ITT) analyses. Per Protocol (PP) analyses are only presented for costs and effect partial analyses. Furthermore, other analyses were present considering the ITT approach. We performed imputation to manage missing data in different follow-ups. Imputations were done for each restoration and final events considered the cumulative appraisal of recorded and imputed results (if it was the case). In case more than one follow-up data were missing, a successive conditional imputation was performed until reach the last follow-up period. If the decision had not been reached for planning treatment, but the outcome had been assessed we assumed it to record the need for new interventions.

In case the tooth had not been assessed (for protocol deviation or not compliance with follow-up), we transformed the treatment decision on a scale (0-no treatment, 1-no operative treatment, 2-remodelling, 3-repair, 4-replacement, 5-endodontic treatment and 6-tooth extraction) and imputed the treatment decision using Poisson regression conditioned by baseline treatment decision (and the previous follow-up condition), type of tooth, number of surfaces that restoration involved and group of allocation. Child clustering was also considered including the patient as an independent variable. Costs were also imputed using similar strategies described for effects. Conditional imputation using linear regression was used in this case. Imputation models considered the baseline and previous follow-up treatment statuses and costs, type of tooth, the number of surfaces that restoration involved and group of allocation. Child clustering was also considered including the patient as an independent variable.

Costs and effects were summarized for each group using the mean with a 95% confidence interval (95%CI). As the number of included teeth were slightly different between the two groups, we used a relative measure, considering the cost or effect per patient divided by the number of restorations included in that child. Further comparisons were then focused on those relative measures of cost and effect (if the effect considered the measurement per number of interventions). In those cases, in which only one register per patient was considered, the absolute effect was computed.

Costs between groups were compared using bootstrapped quantile median regression given the distributions profiles (Beta distribution for Cars group and Fisher Tippet distribution for FDI group). The relative number of new operative interventions and their derivation, the relative number of replacements were compared using the negative binomial regression. Time to the first new operative intervention was compared using the t-test, considering this parameter presented a Weibull distribution of one of the groups (alternatively, ordinal logistic regression was also performed but with no difference in the inferences). After comparisons with the complete sample, we also performed subgroup analyses considering the child age (3 to 6 vs 7 to 10 years) and caries experience (≤3 vs>3 restorations) to explore any possible trend in these separate subsamples.

A Bayesian approach was used to explore uncertainties related to the studied parameters for the number of included teeth (since some parameters were relative), costs and effects. The data distribution of costs and effects will be checked using XLSTAT 2021 (Addinsoft, Paris, France). Considering these distributions, 10,000 Monte-Carlo simulations were run and some summary measures were calculated. For simulations, we considered firstly the sample distribution of relative effects (if they were needed) and the final distribution of the absolute effect was generated considering the relative effect was the ratio between the absolute effect and the number of included teeth. Then, for further analyses, we considered the simulated absolute effect that was generated without an unbalance of the included teeth.

Delta cost and delta effects (considering the four possible health effects considered) were calculated with their 95% confidence intervals. For delta calculations, we used the difference between the values (cost or effects, individually) in CARS strategy (alternative intervention) and FDI strategy (standard intervention, as defined a priori). Then, we defined delta $_{\text{cost or effect}}$= CARS $_{\text{cost or effect}}$ – FDI $_{\text{cost or effect}}$. Effects and costs were plotted in a cost-effectiveness plane (CE plane). The proportion of points in each quadrant of the CE plane will be calculated, and the location of points will also be assessed visually. For the positive outcomes (% of children without the need of new operative treatments and time to the first failure -

survival), the positive delta effect values showed the superiority of the CARS strategy. For the negative effects (number of new interventions), negative delta effect values were more favourable for the CARS strategy (it demands fewer operative treatments after baseline). For each one of the adopted health effects, we performed subgroup analyses, considering the subgroups mentioned above.

To contribute to decision-making when choosing the alternative system, we calculated its cost-effectiveness in terms of the incremental Net Monetary Benefit (NMB). For that, we used the following equation: Incremental NMB = Incremental Effect × Ceiling Ratio -Incremental Cost, being value 1 for a positive coefficient and 0 for a negative coefficient value. To facilitate the interpretation, negative outcomes (number of new interventions) had their signal changes for this analysis and positive values for effect symbolized better effects for all outcomes, while the negative values represent the worse effects.

In the first phase, we set a potential value of willingness-to-pay (WTP) or also known, ceiling ratio. We assumed this WTP rate based on data reported in a previous study that evaluated the Brazilians' WTP for a preventive strategy related to dental caries (20). Then, for calculations of NMB, we considered a WTP (and also willingness to accept) of 100 dollars. This reference value has been corrected using IPCA from 2015 (data collection) to 2021 and then, converted from BR$ to US$. For the interpretation, if the difference obtained from the formula above was higher than zero (the value 1), it means that for one additional unit of effectiveness, the incremental cost is below the Ceiling Ratio (the maximum value that decision-makers are willing to pay). If the difference was less than zero (the value 0), then, for one additional unit of effectiveness the incremental cost is above the Ceiling Ratio (21). For this specific ceiling ratio, the mean NMB and their 95% CIs were calculated considering each effect studied. Moreover, the probability of CARS being a cost-effective strategy instead of an FDI strategy was also calculated (with 95% of CI). Subgroup analyses were also performed considering the NMBs.

At a second phase, we calculated the NMB at different ceiling ratios to verify differences that the WTP may cause in the cost-effectiveness of the studied intervention. Then, for each studied effect, cost-effectiveness acceptability curves were plotted considering the probability of being cost-effective according to NMBs interpretation at different ceiling ratios (from 0 to 2000 dollars).

## 4.3 RESULTS

A total of 163 patients were included in the CARDEC-03 trial. The mean (Standard Deviation – SD) age of the participants was 7.0 (1.6) years and 54% of the sample are male. Eighty-two children (50.3%) were assigned to the CARS group and 81 (49.7%) to the FDI group. Participants' characteristics were balanced between groups (Table 4.1). Children were followed up for 24 months. The mean (SD) follow-up was 30 (3.75) months. The main trial had an 87.1% positive response rate and no significant difference in dropouts was observed (Table 4.1). The CONSORT flow diagram is provided in Figure 4.1.

Minor protocol deviations were detected during data monitoring and solutions were proposed to minimise the deviations (Appendix B). Data was also considered in ITT analyses. Besides attrition to follow-up visits (Figure 4.1), the main cause of protocol deviation was treatment was not performed as recommended by the assessor using the randomized criteria (n=9). These deviations were usually explained by the child's absence in treatment sessions or imminence of tooth exfoliation. Other reasons were the lack of assessment of a specific tooth in the follow-up visit (n=6) or those treatments performed outside the trial (n=5). All these cases were solved using data imputation as described above.

We included 650 restorations; therefore, our sample comprises a mean of 4 restorations per child. Despite not statistically significant, the CARS group exhibited a higher mean (95% Confidence Interval – CI) of restorations per child 4.12 (3.59-4.65) than the FDI group, 3.62 (3.15-4.10), p=0.09. Thus, here we present costs and effects as a relative measure, which takes into account the mean number of restorations included per child in the group.

At the baseline, the mean cost of the CARS strategy (95% CI) was $38.68 (32.00-45.36) per child and the FDI strategy mean cost was $30.81 (22.56-39.06) per child. The mean (95% CI) number of new operative interventions per child in the CARS and FDI groups was similar, 1.54 (1.23-1.86) and 1.75 (1.39-2.11), respectively.

Table 4.1 – Baseline characteristics of the participants (n=163) and included teeth

| **Characteristics** | **CARS N (%)** | **FDI N (%)** | **Stayed in * N** | **Dropped out N** |
|---|---|---|---|---|
| **Categorical variables** | | | | |
| **Total** | 82 (50.3) | 81 (49.7) | 142 | 21 |
| CARS strategy | NA | NA | 73 | 9 |
| FDI strategy | NA | NA | 69 | 12 |
| **Sex** | | | | |
| Male | 42 (51.2) | 46 (56.8) | 76 | 12 |
| Female | 40 (48.8) | 35 (43.2) | 66 | 9 |
| **Age** | | | | |
| 3 to 6 years-old | 39 (47.6) | 38 (46.9) | 67 | 10 |
| 7 years-old or more | 43 (52.4) | 43 (53.1) | 75 | 11 |
| **No. of restorations** | | | | |
| 1 to 3 restorations | 30 (36.6) | 33 (40.7) | 52 | 11 |
| 4 restorations or more | 52 (63.4) | 48 (59.3) | 90 | 10 |
| **Characteristics** | **CARS Method Mean (SD)** | **FDI method Mean (SD)** | **Stayed in Mean (SD)** | **Dropped out Mean (SD)** |
| **Quantitative variables** | | | | |
| Age (years) | 7.02 (1.64) | 7.06 (1.49) | 7.00 (1.55) | 7.32 (1.60) |
| Carious teeth | 1.41 (1.99) | 1.70 (2.18) | 1.63 (2.17) | 1.05 (1.32) |
| Restored teeth | 4.76 (2.61) | 4.41 (2.51) | 4.70 (2.53) | 3.76 (2.70) |
| Missed teeth | 0.48 (0.89) | 0.44 (0.79) | 0.51 (0.88) | 0.14 (0.36) |
| dmft + DMFT | 6.65 (3.46) | 6.57 (3.68) | 6.85 (3.55) | 4.95 (3.21) |

* No difference in the drop outs between the methods according to chi-square test (p = 0.619)

CARS = Caries Around Restorations and Sealants; FDI = International Dental Federation

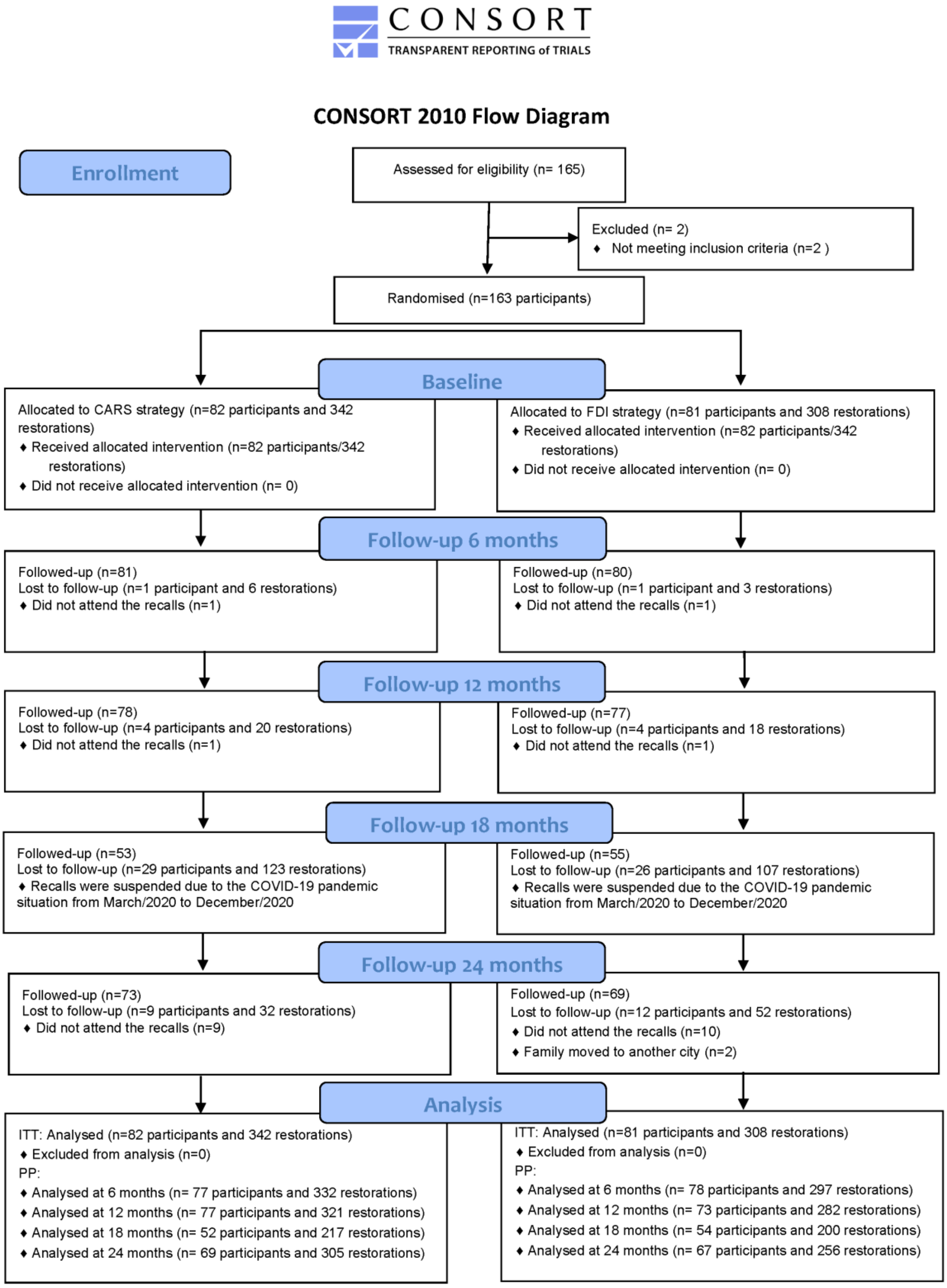
NA = Not applicable; SD = Standard deviation

dmft = number of decayed, restored or missed primary teeth

DMFT = number of decayed, restored or missed permanent teeth

Source: Author

Figure 4.1 – Study flowchart describing participants enrolled, followed-up, and analysed




Source: Author

### 4.3.1 Costs of FDI and CARS diagnostic strategies

Costs of the diagnostic strategies for 24 months are described in Table 4.2. According to both PP and ITT analysis, there was no significant difference in costs between the FDI and CARS. Considering the total cost per child (cumulative cost), different trends may be observed between groups due to the different number of restorations included. We do not believe these values should be interpreted alone, but they are presented in Table 4.2 to express the magnitude of the costs in assessing and managing restorations in primary teeth using different strategies.

There was no statistically significant difference in the relative cost between the two groups on the basis of ITT, both in baseline (p=0.34) and cumulative for 24 months (p=0.87) (Table 4.2). The FDI strategy seems to be less costly than the CARS strategy at the baseline (approximately 1 dollar), however, the confidence intervals are overlapping. An inversion of that tendency is observed in the next follow-ups and at the baseline trend returns at the end of the follow-up (Figure 4.2).

Table 4.2 – Cumulative and relative cost per child of the FDI and CARS strategies in international dollars ($)

| | Cumulative cost PP | No. of restorations | Cumulative cost ITT | Relative cost ITT |
|---|---|---|---|---|
| | Mean (95%CI) | Mean (95%CI) | | |
| **Baseline** | | | | |
| FDI | 30.81 (22.56-39.06) | 3.62 (3.15-4.10) | 30.81 (22.56-39.06) | 9.75 (7.94-11.56) |
| CARS | 38.68 (32.00-45.36) | 4.12 (3.59-4.65) | 38.68 (32.00-45.36) | 10.78 (7.59-13.98) |
| **6 months** | | | | |
| FDI | 51.24 (38.58-63.89) | 3.62 (3.15-4.10) | 52.22 (41.93-62.51) | 9.75 (7.94-11.56) |
| CARS | 61.98 (50.82-73.14) | 4.12 (3.59-4.65) | 62.53 (52.36-72.70) | 14.93 (11.59-18.27) |
| **12 months** | | | | |
| FDI | 64.38 (49.28-79.49) | 3.62 (3.15-4.10) | 67.08 (53.24-80.92) | 23.25 (19.00-27.50) |
| CARS | 77.41 (63.52-91.30) | 4.12 (3.59-4.65) | 79.32 (66.75-91.88) | 18.86 (15.07-22.65) |
| **18 months** | | | | |
| FDI | 73.04 (56.08-90.00) | 3.62 (3.15-4.10) | 78.13 (61.88-94.37) | 24.97 (20.57-29.37) |
| CARS | 84.09 (69.42-98.76) | 4.12 (3.59-4.65) | 86.61 (73.37-99.85) | 21.74 (17.74-25.74) |
| **24 months** | | | | |
| FDI | 74.13 (57.21-91.05) | 3.62 (3.15-4.10) | 86.53 (67.36-105.70) | 24.88 (20.50-29.27) |
| CARS | 86.03 (71.07-101.00) | 4.12 (3.59-4.65) | 96.82 (81.74-111.90) | 25.97 (21.59-30.35) |

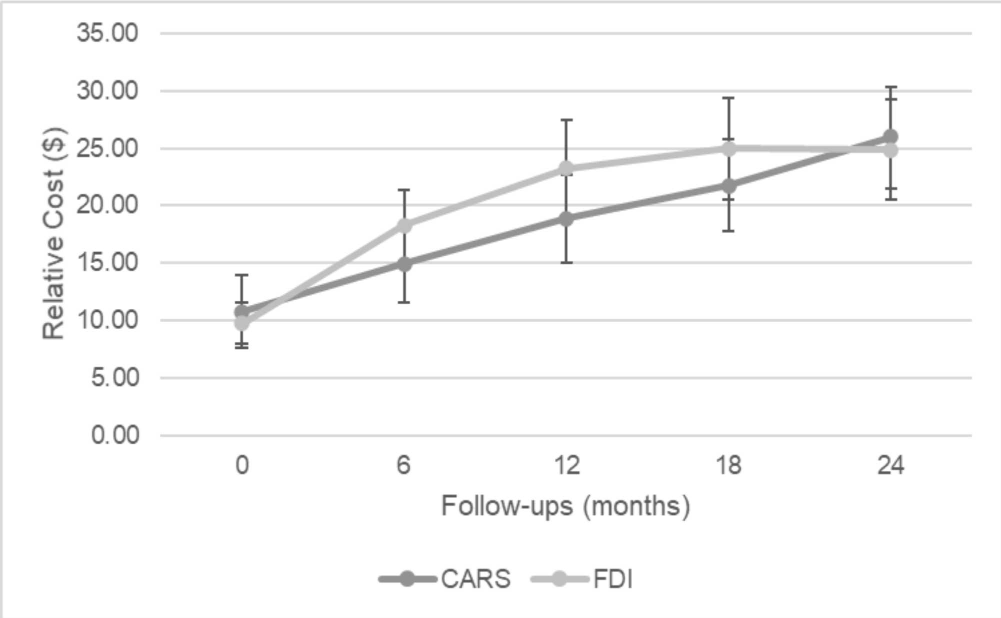
Costs are presented in international dollars (conversion rate = 2.363, October 2021)

* No difference in costs between the groups according to bootstrapping quantile regression

ITT = Intention to Treat analysis; PP = Per-Protocol Analysis; CARS = Caries Around Restorations and Sealants;
FDI = International Dental Federation

Source: Author

Figure 4.2 – Relative cost of the FDI and CARS strategies in international dollars ($)




Source: Author

### 4.3.2 Health effects

The interventions performed at the baseline and follow-ups per group are shown in table 4.3. No treatment was needed for most restorations in both groups at all follow-up assessments. The FDI strategy required over two times more replacements or new restorations than CARS at the baseline and 6 months. At 12 and 18 months, the sum of restorations needing repairs and replacements/new restorations were 61 and 31, respectively, representing a significant portion of the procedures performed at the FDI group at each follow-up (Table 4.3).

Table 4.3 – Number of interventions per group during the study

| | Baseline | | 6 months | | 12 months | | 18 months | | 24 months | |
|---|---|---|---|---|---|---|---|---|---|---|
| | FDI | CARS | FDI | CARS | FDI | CARS | FDI | CARS | FDI | CARS |
| **Intervention** | No. of restorations (%) | | | | | | | | | |
| No treatment | 160 (52) | 146 (43) | 221 (72) | 238 (70) | 226 (73) | 259 (75) | 232 (75) | 308 (90) | 258 (84) | 280 (82) |
| Non-operative treatment | 0 (0) | 67 (20) | 3 (1) | 25 (7) | 7 (2) | 13 (4) | 31 (10) | 11 (3) | 13 (4) | 14 (4) |
| Remodelling | 10 (3) | 4 (1) | 5 (1.7) | 2 (0.1) | 9 (3) | 6 (1.7) | 10 (3.7) | 1 (0.3) | 0 (0) | 1 (0.3) |
| Repair | 88 (28.7) | 100 (29) | 40 (13) | 54 (16) | 47 (15) | 33 (10) | 19 (6) | 14 (4) | 16 (5) | 21 (6) |
| Replacement/New restoration | 49 (16) | 20 (5.7) | 26 (8) | 10 (3) | 14 (5) | 20 (6) | 12 (4) | 6 (2) | 11 (3.6) | 15 (4) |
| Endodontic treatment | 0 (0) | 1 (0.3) | 1 (0.3) | 3 (0.9) | 0 (0) | 1 (0.3) | 1 (0.3) | 0 (0) | 1 (0.4) | 3 (1) |
| Tooth extraction | 1 (0.3) | 4 (1) | 12 (4) | 10 (3) | 5 (2) | 10 (3) | 3 (1) | 2 (0.7) | 9 (3) | 8 (2.7) |

Source: Author

Similarly to the costs, we represented the health effects according to the mean number of restorations included per group (relative new operative interventions). There was no difference in the relative number of new operative interventions between FDI and CARS after 24 months, p=0.17 (Table 4.4); however, the FDI strategy demonstrated a higher number of new operative interventions for all follow-ups, as demonstrated in Figure 4.3.

Table 4.4 – Number of new operative interventions per child at the follow-ups

| | **No. of operative interventions*** | **Cumulative No. of operative interventions*** | **No. of restorations per child** | **Relative operative interventions*** |
|---|---|---|---|---|
| | **Mean (95%CI)** | | | |
| **6 months** | | | | |
| FDI | 2.20 (1.71-2.69) | 2.20 (1.71-2.69) | 3.62 (3.15-4.10) | 0.66 (0.51-0.81) |
| CARS | 2.43 (1.88-2.99) | 2.43 (1.88-2.99) | 4.12 (3.59-4.65) | 0.59 (0.46-0.71) |
| **12 months** | | | | |
| FDI | 0.95 (0.71-1.19) | 3.15 (2.52-3.78) | 3.62 (3.15-4.10) | 0.94 (0.76-1.12) |
| CARS | 0.89 (0.65-1.13) | 3.33 (2.63-4.01) | 4.12 (3.59-4.65) | 0.81 (0.64-0.97) |
| **18 months** | | | | |
| FDI | 0.58 (0.36-0.79) | 3.73 (3.02-4.44) | 3.62 (3.15-4.10) | 1.10 (0.91-1.29) |
| CARS | 0.30 (0.18-0.43) | 3.63 (2.88-4.38) | 4.12 (3.59-4.65) | 0.88 (0.71-1.06) |
| **24 months** | | | | |
| FDI | 0.44 (0.26-0.61) | 4.16 (3.37-4.96) | 3.62 (3.15-4.10) | 1.22 (1.01-1.43) |
| CARS | 0.58 (0.36-0.79) | 4.20 (3.36-5.05) | 4.12 (3.59-4.65) | 0.99 (0.81-1.18) |

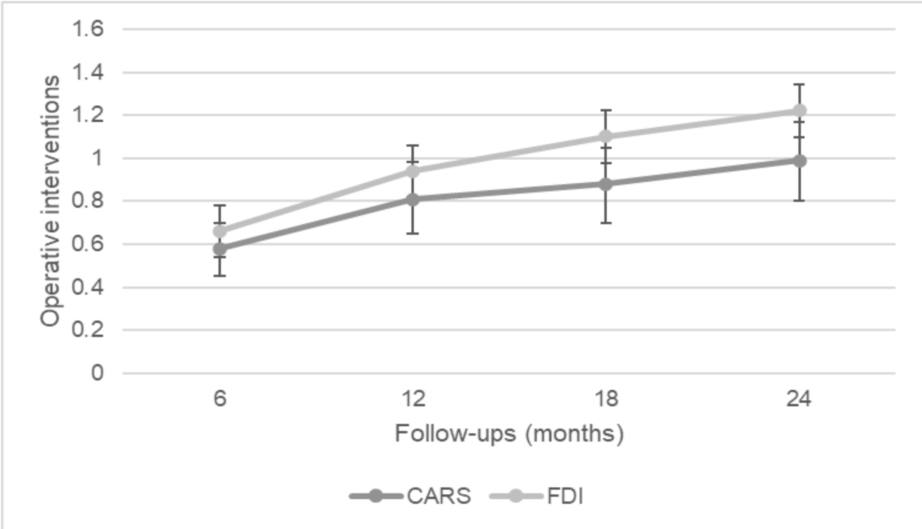
* No difference between groups according to negative binomial regression

CARS = Caries Around Restorations and Sealants

FDI = International Dental Federation

Source: Author

Figure 4.3 – Relative number of new operative interventions per child




Source: Author

Regarding the secondary health effects, we observed no difference between groups up to the time horizon we set (Table 4.5). The CARS strategy tended to lead to a lower proportion of children in need of operative care and a lower number of new replacements during the 24 months of follow-up (Table 4.5). The FDI was associated with, on average, one month longer to fail for the first time than CARS. However, these trends should be interpreted with caution since the confidence intervals of both groups are overlapped for all these health effects (Table 4.5).

Table 4.5 – Secondary health effects

| Health effects | CARS | FDI | P value |
|---|---|---|---|
| | Mean (95%CI) | | |
| Time to the 1st failure | 10.13 (11.01-11.46) | 11.01 (9.42-12.60) | 0.17* |
| Proportion of children with no new operative treatment | 0.21 (0.14-0.32) | 0.15 (0.09-0.25) | 0.29** |
| Number of new relative restoration replacements[ƚ] | 0.13 (0.08-0.18) | 0.18 (0.12-0.24) | 0.79*** |

ƚ ratio between the number of new replacements and included teeth per child

* Value for T-test for equal variances

** Value for likelihood-ratio chi2 test

*** Value for negative binomial regression considering FDI as the reference category.

### 4.3.3 Cost-effectiveness analysis

Analyzing simulated data, the CARS strategy demanded a higher investment of resources (on average, 15 dollars) and demonstrated better results for all health effects evaluated in the present economic study (Table 4.6).

The CARS group was, on average, mostly cost-effective in the simulations performed for the four CEAs (Table 4.6). Mean delta cost and effects were shown to be favourable to CARS strategy (Table 4.6). Besides, considering the WTP of US$ 100, the strategy presented, on average, positive NMBs, except for the percentage of children with no need for new operative interventions (Table 4.6).

Table 4.6 – Summary of simulated data - mean with 95% of confidence interval (CI)

| | CARS | FDI | Δ | Net-Monetary Benefit | Cost-effectiveness probabilities* |
|---|---|---|---|---|---|
| **Cost** | 319.09 (313.37 to 324.81) | 304.09 (298.68 to 309.50) | 15.00 (8.11 to 21.89) | NA | NA |
| **Health Effects** | | | | | |
| Number of new operative interventions | 12.49 (12.17 to 12.39) | 14.94 (12.23 to12.76) | -2.44** (-2.79 to -2.09) | 28.82 (21.28 to 36.36) | 56.60% |
| Time to the 1st failure per child | 9.14 (9.05 to 9.24) | 1.79 (1.78 to 1.80) | 7.52 (7.42 to 7.62) | 737.69 (725.85 to 749.52) | 89.80% |
| Percentage of children with no need of new operative interventions | 9.59 (9.02 to 10.18) | 8.27 (7.74 to 8.82) | 1.32 (0.05 to2.11) | -13.68 (-20.6 to -6.75) | 49.10% |
| Number of new replacements | 1.01 (0.10 to 1.06) | 2.03 (1.97 to 2.08) | -1.03** (-1.03 to -0.96) | 88.97* (78.19 to 97.96) | 57.30% |

Costs are presented in international dollars (conversion rate = 2.363, October 2021)

*Probabilities to be cost-effective considering a $100.00 WTP per unit of health effect considered. Data based on Walshaw et al., 2019 to WTP of a preventive approach for dental caries, adopted as reference.

** Negative values symbolize the CARS presented a fewer number of new interventions. To calculations of Net Monetary Benefit, these values were converted into positive values to facilitate the interpretation.

CARS = Caries Around Restorations and Sealants; FDI = International Dental Federation; NA = Not applicable

Δcost or effect=CARS cost or effect – FDI cost or effect

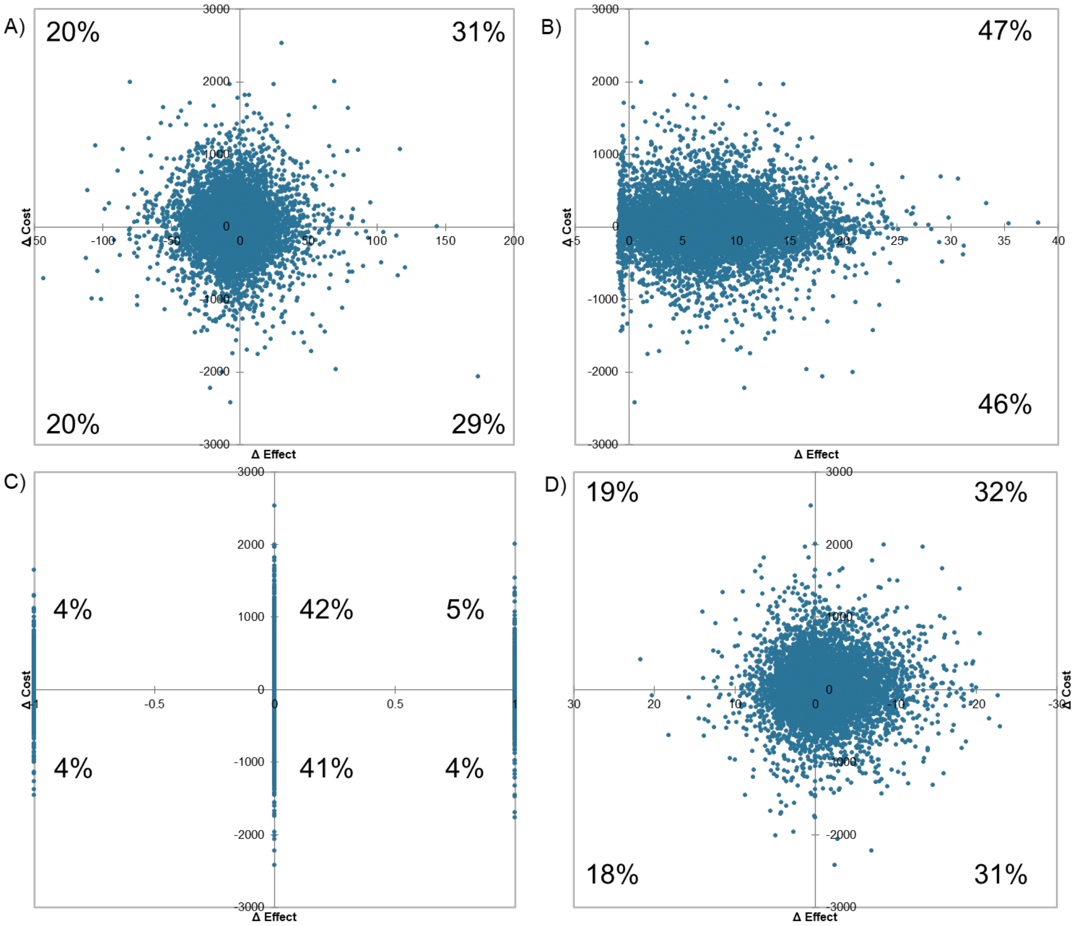
Source: Author

Analyzing the uncertainties, there is a greater concentration of simulated points in the NE and SE quadrants when the time to the first event was considered as health effect. The probability of CARS presenting better effects (positive delta effect) was higher than 90% when this effect was analyzed (Figure 4.4, B). This result; however, especially for quadrant NE, was dependent on a WTP threshold. Assuming a ceiling ratio of US$100 (21), the CARS strategy would be approximately 90% cost-effective to postpone the new operative intervention. At this WTP threshold, such health effect was the one that presented the highest NMB observed. Higher ceiling ratios (up to US$ 2000) slightly increased the probability of being a cost-effective strategy up to approximately 95% (Figure 4.5).

For the number of new operative interventions and new restoration replacements, higher uncertainty compared to the previous outcome. On average, the NMB observed for the new replacements was higher than for new interventions at all (Table 4.6). However, similar patterns of uncertainties were observed between these two negative outcomes (failures). For these health effects, CARS strategy could be classified as a cost-effective strategy in approximately 60% of cases, if the ceiling ratio was set as US$ 100 (Table 4.6). Sixty per cent of simulated points could be found at NE or SE quadrants (better effects for CARS strategy). Besides, 20% of cases could represent cases of lower cost, but also worse effects when CARS strategy was used (Figure 4.4A, 4.4B). Although a slight increase in cost-effectiveness may be observed when increasing the ceiling ratios, the maximum probability of being cost-effective did not exceed 60%.

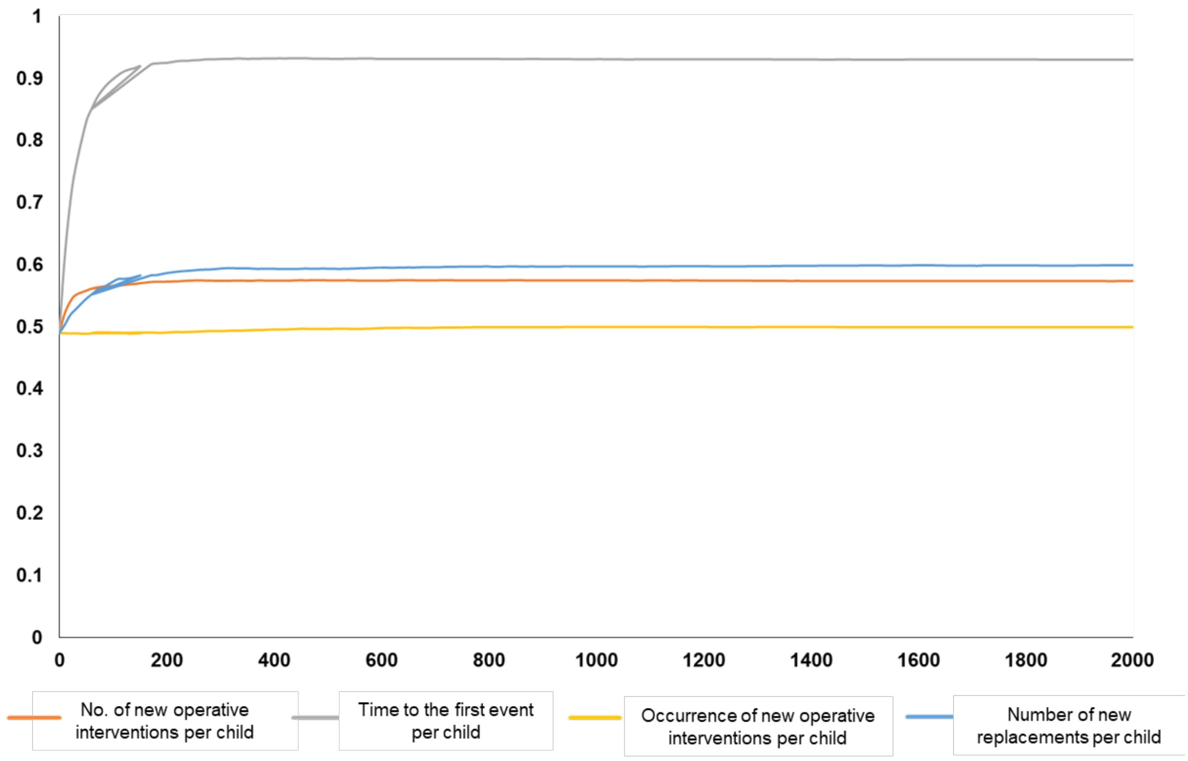
Finally, when the effect was the non-need of operative interventions in the child, we observed the worst scenario, evidencing a negative mean NMB at US$100 threshold and the lowest probability of CARS being a cost-effective strategy (approximately 50%) (Table 4.6). Nevertheless, we can observe in the CE plane the most simulated results presented no difference between strategies in effects (more than 80% of cases) (Figure 4.4, c). Acceptability curves showed no variations in the probability of CARS being a cost-effective strategy despite the ceiling ratios (Figure 4.5).

Figure 4.4 – Cost-effectiveness planes representing simulated data (10,000 simulations). Costs (international dollars) and effectiveness of FDI and CARS were assessed. A) Effectiveness: number of new operative interventions per child. B) Effectiveness: time until the first event (new operative intervention). C) Effectiveness: occurrence of new operative interventions per child. D) Effectiveness: number of new replacements per child




Source: Author

Figure 4.5 – Cost-effectiveness acceptability curve demonstrating the probability of cost-effectiveness of the CARS strategy according to the payer's willingness to pay




Source: Author

### 4.3.4 Subgroup analysis

Subgroup analysis considering caries experience and age did not change the statistical inferences for groups comparison in the statistical analysis in our sample (Appendix C) and demonstrated similar tendencies on distribution of simulated plots in the CE planes compared to the entire group of simulations. In the simulations, younger children (3 to 6 years) tended to present more extreme values at both costs and effects, when compared to older children (7 to 10 years) (Figures 4.8 and 4.9). However, these extreme values occurred for both extremities and did not influence on final trends observed in the mean pooled delta effect or NMB (Table 4.7).

No differences were observed when subgroups regarding caries experience were plotted separately (Figures 4.8 and 4.9), nor when deltas were calculated, except for delta cost (Table 4.8). For children with more than 3 restorations (higher caries experience), costs tended to be higher (positive delta values). However, when children had up to 3 restorations, the mean delta cost was negative (CARS was less costly than FDI). However, the CI of delta costs comprises both negative and positive values.

Table 4.7 – Mean deltas **Δ** /net monetary benefits (95% of confidence intervals) considering subgroups according to age

| | 3-to-6-year-old children | | | 7-to-10-year-old children | | |
|---|---|---|---|---|---|---|
| | **Δ** | **NMB** | **Probability of CE*** | **Δ** | **NMB** | **Probability of CE*** |
| **Cost** | 12.08 (4.60 to 19.57) | -- | -- | 25.93 (9.09 to 42.78) | -- | -- |
| **Health Effects** | | | | | | |
| Number of new operative interventions (units) | -2.54 (-2.93 to -2.16) | 26.65 (18.05 to 35.25) | 0.57 (0.56 to 0.58) | -2.05 (-2.88 to -1.22) | 36.96 (21.40 to 52.52) | 0.57 (0.55 to 0.59) |
| Time to the 1st failure in child (months) | 7.49 (7.38 to 7.59) | 737.22 (724.08 to 750.34) | 0.90 (0.89 to 0.91) | 7.65 (7.44 to 7.86) | 739.46 (712.30 to 766.62) | 0.89 (0.87 to 0.90) |
| Children with no need of new operative interventions (%) | -0.01 (-0.02 to -0.003) | -10.88 (-18.41 to -3.35) | 0.49 (0.48 to 0.51) | -0.02 (-0.04 to 0.003) | -24.17 (-41.09 to -7.26) | 0.48 (0.46 to 0.50) |
| Number of new restoration replacements (units) | -1.02 (-1.09 to -0.94) | 89.39 (78.53 to 100.26) | 0.57 (0.56 to 0.58) | -1.09 (-1.26 to -0.92) | 83.13 (59.80 to 106.46) | 0.57 (0.55 to 0.59) |

Costs are presented in international dollars (conversion rate = 2.363, October 2021)

*Probabilities to be cost-effective considering a $100.00 WTP per unit of health effect considered. Data based on Walshaw et al., 2019 to WTP of a preventive approach for dental caries, adopted as reference.

** Negative values symbolize the CARS presented fewer number of new interventions. To calculations of NMB, these values were converted into positive values to facilitate the interpretation.

CARS = Caries Around Restorations and Sealants; FDI = International Dental Federation; NMB = Net Monetary Benefits; NA = Not applicable; Δcost or effect=(CARS cost or effect) – (FDI cost or effect).

Source: Author

Table 4.8 – Mean deltas **Δ** /net monetary benefits (95% confidence intervals) considering subgroups according to caries experience

| | **Up to 3 restorations** | | | **More than 3 restorations** | | |
|---|---|---|---|---|---|---|
| | **Δ** | **NMB** | **Probability of CE*** | **Δ** | **NMB** | **Probability of CE*** |
| **Cost** | -8.86 (-32.04 to 14.31) | -- | -- | 15.93 (8.84 to 23.04) | -- | -- |
| **Health Effects** | | | | | | |
| Number of new operative interventions (units) | -1.81 (-3.40. to -0.23) | 50.71 (15.41 to 86.02) | 0.57 (0.51 to 0.61) | -2.46 (-2.82 to -2.10) | 27.95 (20.24 to 35.69) | 0.57 (0.56 to 0.58) |
| Time to the 1st failure in child (months) | 8.16 (7.68 to 8.63) | 822.62 (767.97 to 877.28) | 0.94 (0.91 to 0.96) | 7.49 (7.40 to 7.59) | 734.33 (722.23 to 746.44) | 0.90 (0.89 to 0.91) |
| Children with no need of new operative interventions (%) | -0.02 (-0.07 to 0.02) | 10.97 (-12.36 to 34.30) | 0.53 (0.48 to 0.58) | -0.01 (-0.02 to -0.005) | -14.65 (-21.79 to -7.51) | 0.49 (0.48 to 0.50) |
| Number of new restoration replacements (units) | -1.41 (-1.72 to -1.10) | 149.50 (110.41 to 188.58) | 0.64 (0.59 to 0.68) | -1.02 (-1.09 to -0.94) | 85.65 (75.50 to 95.80) | 0.57 (0.56 to 0.58) |

Costs are presented in international dollars (conversion rate = 2.363, October 2021)

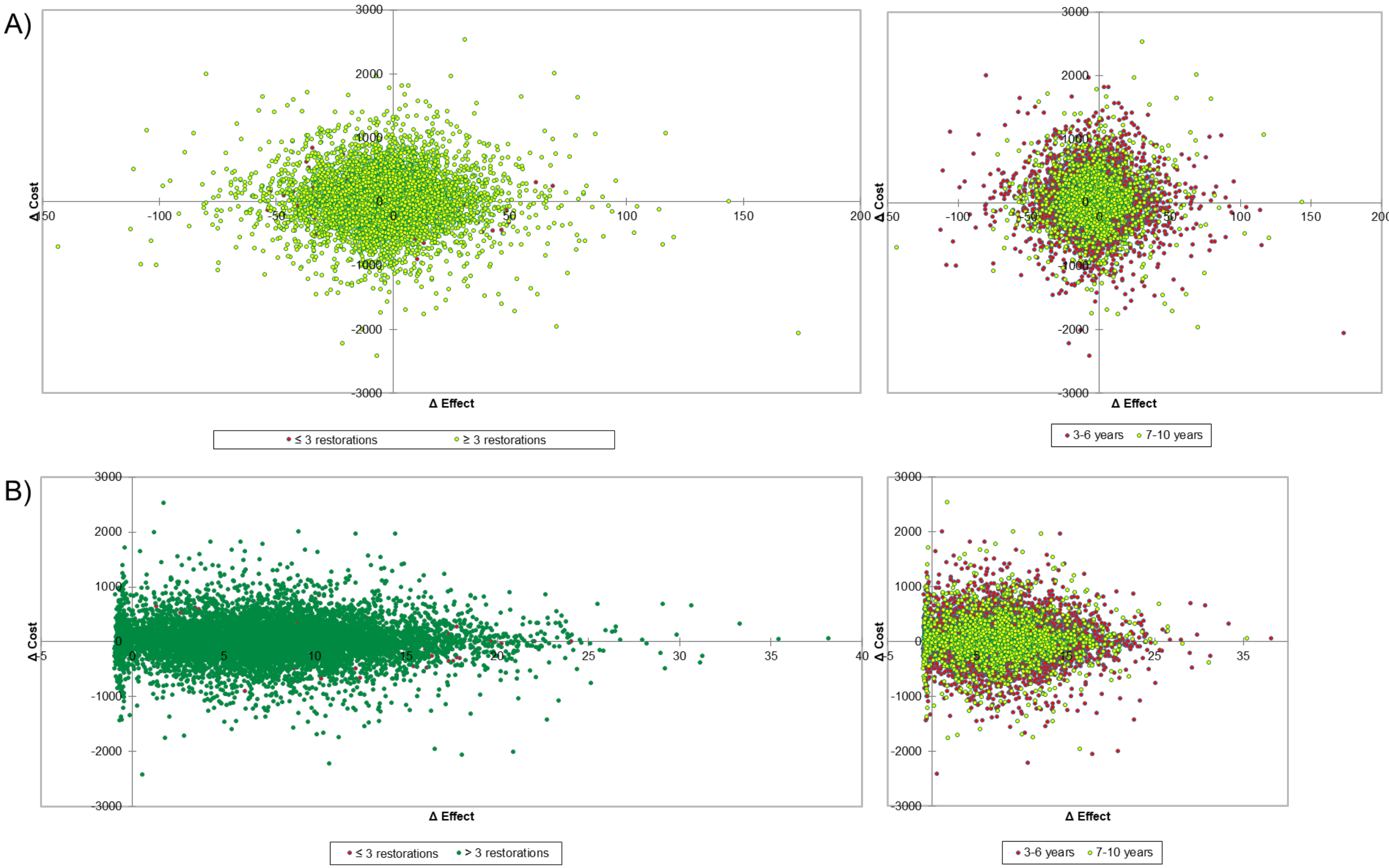
*Probabilities to be cost-effective considering a $100.00 WTP per unit of health effect considered. Data based on Walshaw et al., 2019 to WTP of a preventive approach for dental caries, adopted as reference.

** Negative values symbolize the CARS presented fewer number of new interventions. To calculations of Net Monetary Benefit, these values were converted into positive values to facilitate the interpretation.

CARS = Caries Around Restorations and Sealants; FDI = International Dental Federation; NMB = Net Monetary Benefits; NA = Not applicable; Δcost or effect=(CARS cost or effect) – (FDI cost or effect).

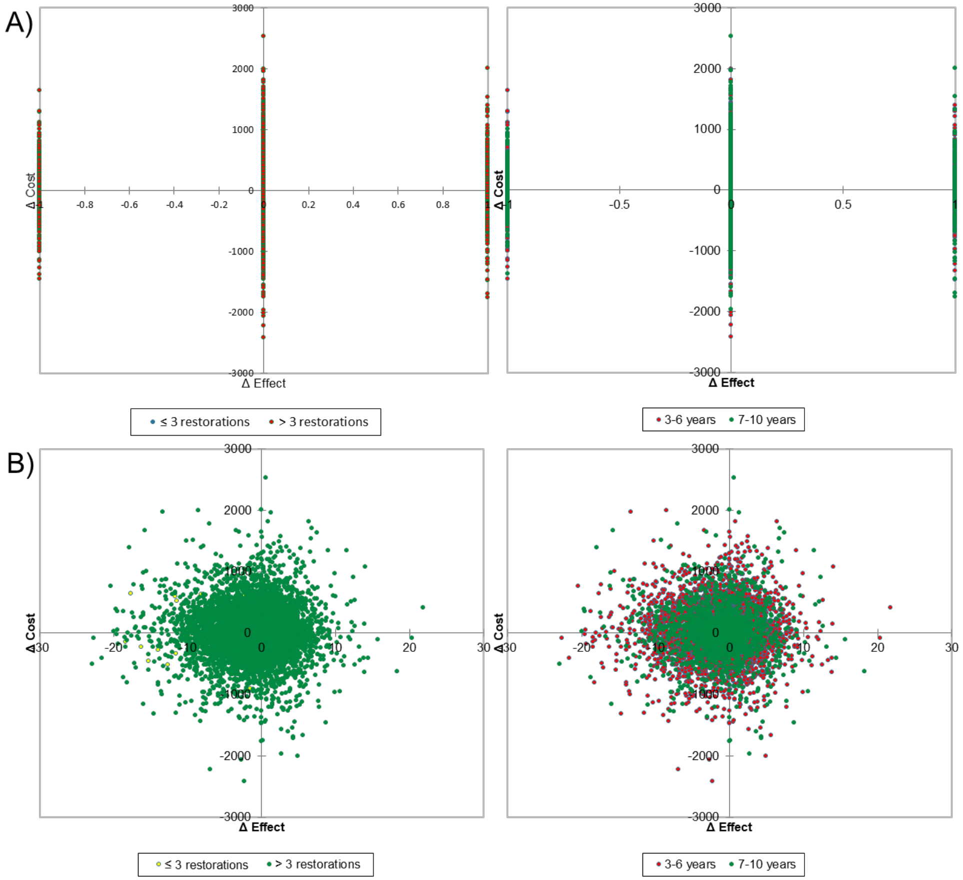
Source: Author

Figure 4.8 – Subgroup analyses, according to caries experience (≤3 restorations or >3 restorations) and age (3 to 6 years old or 7 to 10 years old. A) Costs (international dollars) and effectiveness (number of new operative interventions per child) of CARS compared to the FDI strategy. B) A) Costs (international dollars) and effectiveness (survival in months) of CARS compared to the FDI strategy




Source: Author

Figure 4.9 – Subgroup analyses, according to caries experience (≤3 restorations or >3 restorations) and age (3 to 6 years old or 7 to 10 years old. A) Costs (international dollars) and effectiveness (percentage of children needing new operative interventions) of CARS compared to the FDI strategy. B) A) Costs (international dollars) and effectiveness (number of new replacements) of CARS compared to the FDI strategy.




Source: Author

## 4.4 DISCUSSION

The present study evaluates two diagnostic strategies, FDI and CARS, for the assessment and management of dental restorations in primary teeth through a trial-based full economic evaluation. The CARS strategy is associated with a less invasive approach, as it exclusively focuses on caries lesions around the restorations. The FDI strategy, which was considered the reference for the CEA, is related to a cosmetic approach, including criteria other than caries lesions, such as marginal staining and adaptation. Our findings are the first to report the economic impact of strategies evaluating restorations in children and, highlighting that CARS may be a cost-effective strategy to replace the FDI in clinical practice, especially considering postponing operative interventions in children. Besides, this benefit is still more significant in children with lower caries experience.

Looking at costs alone, the CARS strategy was a cost-increasing alternative to the FDI strategy alongside 24 months, but this difference was not significant for our sample. For this economic evaluation, even when operators did not perform the intervention due to imminence of tooth exfoliation (e.g., high level of tooth mobility), we imputed figures related to cost and effect if the assessor had considered an intervention was needed according to the allocated system. We assumed this conservative approach to avoid leaving out measurement items that might count against one of the interventions and reduce cost measurement omission bias in the present trial-based economic evaluation (22).

On the other hand, this difference was made evident when simulations were generated, making possible the amplification of our sample results. A modest increase in the cost per child (around 15 dollars, on average) should be expected when the CARS strategy is used. As CARS evaluates not only caries lesions' severity but also their activity it demanded a higher number of non-operative treatments for most follow-ups than the FDI strategy. Preventive interventions, such as topical fluoride application, have been a target for several economic evaluations in dentistry and the majority of them provided a positive effect accompanied by an increase in costs (23,24). Different preventive strategies in health have been demonstrated the same (25).

In health economics, it is expected that a new strategy will be costly than the previous one adopted by the health care system, therefore it is relevant to additionally observe the health effects and the payer's WTP to improve efficiency when reorienting resources. Then, the most efficient strategies should be chosen despite the increase in costs by itself. Therefore, health effects must be also considered to guide decision-making in resource allocation.

The main benefit observed when using CARS instead of FDI is the possibility of postponing new operative interventions. Even considering FDI domains more related to caries occurrence, the FDI system tends to focus on characteristics, e.g. restoration margins discolouration/staining, which can lead to early interventions to these restorations. Such characteristics, as staining and some marginal defects, may be poorly associated with the presence of caries lesions (26,27) and demand for intervention even in cases in which such kind of intervention may not be necessary. Additionally, this delay in the operative intervention was neither followed by a higher number of operative interventions later, nor for the need for more severe interventions, corroborating the idea they may have not been necessary at that earlier time. At this glance, the use of CARS strategy would present approximately 90%-probability of being cost-effective in substituting the FDI. Such benefit may be found even when the WTP is around 100 dollars, a value observed for other preventive interventions for dental caries in the Brazilian population (20).

On the other hand, at the same WTP threshold (and even higher ones up to US$2,000), the CARS strategy is a much more modest cost-effective option to be used instead of the FDI strategy to avoid any new operative intervention in children. Very few children did not demand new operative interventions alongside 24 months. On average, the difference between strategies regarding this effect was around 1%. Most cases (more than 80%) were associated with similar effects between strategies, which lead to an unfavourable NMB compared to the other effects. In other words, we can state the CARS is a more cost-effective strategy to substitute FDI when the requirement is to postpone operative interventions, but not exactly to avoid them. This finding must be comprehensible since restoration failures may be very high failure rates, depending on several factors (4).

Children with lower caries experience (those who presented fewer restorations) tended to be greatly benefited when the idea was to intervene later (higher survival for restorations). Caries experience has been shown as an important predictive factor to caries incidence and progression (28). However, caries risk is rarely explored in studies related to survival restoration (4). At this trial, since all participants had restorations, we opted to categorize them according to the number of restorations (≤ or > 3 restorations in primary teeth). Restorations' failures in primary teeth have been mainly related to dental caries (4). We believe children with fewer restorations may also have better oral-related habits and consequently, less prone to early restoration failures related to caries, permitting to observe CARS offered the benefit of postponing the first new operative intervention in such cases.

For this economic evaluation, to investigate the influence of restoration survival on the economic impact of the strategies of caries detection around the restoration, we chose the time to the first failure observed among all restorations as the health effect of interest. We can hypothesize this effect could be even more maximized if repeated failures were computed in the child, given the cumulative and recurrent pattern observed for such type of outcome.

The CARS strategy led to fewer new operative interventions when compared to the FDI. We analyzed two different health effects related to that: the total number of new interventions and only the new restoration replacements performed during the time horizon. We had previously observed that when using the FDI strategy, we would tend to indicate more operative interventions since the beginning of the study (7). We confirm that when analyzing baseline operative interventions, more frequent in the FDI group. However, the new interventions here are considered as health effects intended to verify what would happen as a consequence of these additional baseline procedures performed. The more interventionist characteristic of the FDI strategy contributed to a lower number of new operative interventions when the use of CARS strategy was simulated. When analyzing the need for interventions in the trial sample, the differences between groups were mainly caused by more restorations' replacements in the FDI group, especially at - and 18-months follow-ups, also contributing to the increase in costs for this group at this timeframe. Besides the higher costs related to dental materials, those procedures are also more time-consuming, leading to higher direct and indirect costs.

On the other side, reducing the new operative interventions, especially replacements may probably be beneficial since replacements have been appointed as the last resource when dealing with defective restorations in minimally invasive dentistry, due to the higher risk of pulp complications and reduction of tooth survival

(29). At this economic evaluation, we could demonstrate that, also for these health effects, the CARS may be a cost-effective option. The probability of observing such a benefit is slightly lower than that observed for the time to the first failure. This may be explained by a relatively high level of uncertainty in outcomes used for the economic evaluation. One new intervention usually contributes to additional resources used and consequently, extra costs, characterizing the double-counting bias. Then, effects related to the need for new interventions and costs are, correlated, contributing to this panorama of uncertainty. On the other hand, the societal perspective is a good option to minimize the influence of double-counting bias in the results (22). Besides the particularities of the diagnostic strategies by themselves, this aspect may also explain why we could observe a more beneficial effect of using CARS instead of FDI when restoration replacement was set as the health effect.

Certainly, trial-based economic evaluations presented some limitations, especially regarding their power of extrapolation and generalizability (30), as all results are produced/collected in a single sample. The main trial recruited children who were seeking dental treatment had at least restoration in any condition. We believe our results could be extrapolated to this group. However, we should consider that costs and preferences have been strongly related to the perspective and scenario adopted and further studies should explore these additional aspects.

The use of a Bayesian approach was an intentional strategy to minimise some of the limitations expected for trial-based economic evaluations. As the trial-based economic evaluation is usually piggy-backed onto an intervention trial, the sample size calculations were not performed to the economic outcomes studied. This may lead to a problem of statistical power for statistical comparisons performed considering the trial sample. As simulations amplify the trial sample using distributions that reproduce this sample multiple times, we may observe in simulated data what we could expect for a similar, but a greater group of patients. The use of distribution for variables included in the analyses (instead of only values observed inside the sample) permits to predict probable uncertainties that could be expected in a larger group and observe how the results of the analyses change according to variables variation, reducing then the limited sensitivity analysis bias (22). Considering the exposed aspects, we based our inferences on confidence intervals obtained through this simulated sample.

All the studied effects carried on a temporality since they may be accumulated alongside the time horizon (e.g., need of new interventions) or measure the time to event, which justified the non-adoption of discounting rates. Usually, preventive health care may seem to be less cost-effective because such interventions typically involve current costs and future effects (31). This is especially relevant as outcomes may be gathered distant from interventions, e.g. quality of life or quality-adjusted life-years. Besides, the chosen health effects were moderate to strongly associated with costs, as discussed elsewhere in this section.  In this study, we exactly intended to explore the values of effects alongside the time horizon and when they occurred to further propose a differential discounting rate if appropriate and necessary.

The combined evaluation of different health effects permitted to observe a variation in probabilities of CARS being cost-effective varying from 50% to 95%, depending on what is expected from it as a strategy for assessment and management of restorations in primary teeth. All these effects discussed until this point were intentionally chosen to reflect different perspectives of using a system to detect caries around restorations. The idea was the combined evaluation of such findings may help in guiding further budget decisions (and maybe, in the future, resources allocation). We demonstrated previously that the potentially most beneficial (cost-effective) situation is using CARS as an alternative to postpone new operative interventions in primary teeth. Considering a wider time horizon, this trend may become even more relevant considering the lifespan of a primary tooth, since postponing (or currently avoiding an intervention may mean not intervening anymore on that.

As previously described in the first chapter of the present thesis, we will conduct a Markov model to extrapolate our findings considering the primary molar lifetime. Despite the limitations of the present trial-based economic evaluation, which extends beyond the time horizon and will be further discussed, here we provide estimates of costs and health effects for two diagnostic strategies for the assessment and management of restorations in Brazilian children with caries experience. A decision-analytic model is necessary to understand this process considering a time horizon compatible with the longevity of a primary tooth in 3 to 10 years children. Decision modelling will provide a framework in which we will be able to evaluate all relevant aspects using the best available evidence (30).

Implementation gaps for incorporating preventive strategies have been generally identified among health professionals (24), highlighting the importance of showing the cost-effectiveness of such types of strategies as a manner of evidencing the actual benefits of using such interventions. This study may certainly contribute to demonstrating economic benefits and reducing gaps in terms of implementation of CARS in clinical practice to substitute the FDI, a system widely studied and used in clinical practice (6). Patterns observed in this subgroup analysis, besides exploration of uncertainties, may be an important tool to create oral health policies and establish priorities. Our findings are also relevant for building further decision-analytic models to guide decision-making in our health care system.

## 4.5 CONCLUSIONS

The CARS strategy is a cost-effective alternative to the FDI strategy to assess and guide management of restorations in primary teeth considering different health outcomes. Its more relevant benefit compared to FDI is postponing the first new operative interventions in these teeth, which is slightly more evident for children with lower caries experience.

## REFERENCES[11]

1. Gimenez T, Tedesco TK, Janoian F, Braga MM, Raggio DP, Deery C, et al. What is the most accurate method for detecting caries lesions? A systematic review. Community Dent Oral Epidemiol. 2021;49(3):216–24. doi: 10.1111/cdoe.12641.

2. Pontes LRA, Lara JS, Novaes TF, Freitas JG, Gimenez T, Moro BLP, et al. Negligible therapeutic impact, false-positives, overdiagnosis and lead-time are the reasons why radiographs bring more harm than benefits in the caries diagnosis of preschool children. BMC Oral Health. 2021;21(1):168. doi: 10.1186/s12903-021-01528-w.

[11] According to Vancouver style.

3. Pontes LRA, Novaes TF, Lara JS, Gimenez T, Moro BLP, Camargo LB, et al. Impact of visual inspection and radiographs for caries detection in children through a 2-year randomized clinical trial. J Am Dent Assoc. 2020;151(6):407-415.e1. doi: 10.1016/j.adaj.2020.02.008.

4. Chisini LA, Collares K, Cademartori MG, de Oliveira LJC, Conde MCM, Demarco FF, et al. Restorations in primary teeth: a systematic review on survival and reasons for failures. Int J Paediatr Dent [internet]. 2018;28(2):123–39. doi: 10.1111/ipd.12346.

5. Pitts N, Ekstrand K. International Caries Detection and Assessment System (ICDAS) and its International Caries Classification and Management System (ICCMS) - methods for staging of the caries process and enabling dentists to manage caries. Community Dent Oral Epidemiol. 2013;41(1):e41–52. doi: 10.1111/cdoe.12025.

6. Marquillier T, Doméjean S, Le Clerc J, Chemla F, Gritsch K, Maurin J-C, et al. The use of FDI criteria in clinical trials on direct dental restorations: A scoping review. J Dent. 2018;68:1–9. doi: 10.1016/j.jdent.2017.10.007.

7. Moro BLP, Freitas RD, Pontes LRA, Pássaro AL, Lenzi TL, Tedesco TK, et al. Influence of different clinical criteria on the decision to replace restorations in primary teeth. J Dent. 2020;101:103421. doi: 10.1016/j.jdent.2020.103421.

8. Moro BLP, Signori C, Freitas RD, Pontes LRA, Lenzi TL, Tedesco TK, et al. The effect of two clinical criteria in the assessment of caries lesions around restorations in children (CARDEC-03): study protocol for a diagnostic randomized clinical trial. 2021;9:650. doi: 10.12688/f1000research.23801.3.

9. Listl S, Galloway J, Mossey PA, Marcenes W. Global Economic Impact of Dental Diseases. J Dent Res [internet]. 2015;94(10):1355–61. doi: 10.1177/0022034515602879.

10. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. Fourth Edi. Oxford, Uk: Oxford University Press; 2015. 1–445 p.

11. Rogers HJ, Freitas RD, Beeson MJ, Vernazza CR. Economic evaluations in paediatric dentistry clinical trials. Int J Paediatr Dent. 2021;(November 2020):ipd.12772. doi: 10.1111/ipd.12772

12. Ramsey SD, Willke RJ, Glick H, Reed SD, Augustovski F, Jonsson B, et al. Cost-effectiveness analysis alongside clinical trials II - An ISPOR good research practices task force report. Value Heal. 2015;18(2):161–72. doi: 10.1016/j.jval.2015.02.001.

13. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. Eur J Heal Econ [internet]. 2013;14(3):367–72. doi: 10.1136/bmj.f1049.

14. Freitas RD, Moro B, Pontes L, Maia HCM, Pássaro AL, Oliveira R, et al. The economic impact of two diagnostic strategies in the management of restorations in primary teeth: a health economic analysis plan for a trial-based economic evaluation. 2021. doi: 10.21203/rs.3.rs-378301/v1.

15. Hickel R, Peschke A, Tyas M, Mjör I, Bayne S, Peters M, et al. FDI World Dental Federation: Clinical criteria for the evaluation of direct and indirect restorations-update and clinical examples. Clin Oral Investig [internet]. 2010;14(4):349–66. doi: 10.1007/s00784-010-0432-8.

16. Hickel R, Peschke A, Tyas M, Mjör I, Bayne S, Peters M, et al. FDI World Dental Federation - clinical criteria for the evaluation of direct and indirect restorations. Update and clinical examples. J Adhes Dent. 2010;12(4):259–72. doi: 10.3290/j.jad.a19262.

17. Ibge.gov [homepage on the Internet]. Brazil: Brazilian Institute of Geography and Statistics; [citado 03 nov. 2021] Available from: https://cidades.ibge.gov.br/brasil/sp/sao-paulo/panorama.

18. Ibge.gov [homepage on the Internet]. Brazil: Brazilian Institute of Geography and Statistics; [citado 03 nov. 2021] Available from: https://www.ibge.gov.br/en/statistics/economic/prices-and-costs/17129-extended-national-consumer-price-index.html?=&t=o-que-e.

19. BCB.gov [homepage on the Internet]. Brazil: Central Brank of Brazil; [citado 03 nov. 2021] Available from: https://www3.bcb.gov.br/CALCIDADAO/publico/exibirFormCorrecaoValores.do?method=exibirFormCorrecaoValores.

20. Walshaw EG, Adam NI, Palmeiro ML, Neves M, Vernazza CR. Patients' and Parents' Valuation of Fluoride. Oral Health Prev Dent. 2019;17(3):211–8. doi: 10.3290/j.ohpd.a42666.

21. Hounton S, Newlands D. Applying the net-benefit framework for assessing cost-effectiveness of interventions towards universal health coverage. Cost Eff Resour Alloc. 2012;10(1):8. doi: 10.1186/1478-7547-10-8.

22. Evers SM, Hiligsmann M, Adarkwah CC. Risk of bias in trial-based economic evaluations: identification of sources and bias-reducing strategies. Psychol Health. 2015 Jan;30(1):52-71. doi: 10.1080/08870446.2014.953532.

23. Eow J, Duane B, Solaiman A, Hussain U, Lemasney N, Ang R, et al. What evidence do economic evaluations in dental care provide? A scoping review. Community Dent Health. 2019; doi: 10.1922/CDH_4426Eow08.

24. Levine S, Malone E, Lekiachvili A, Briss P. Health Care Industry Insights: Why the Use of Preventive Services Is Still Low. Prev Chronic Dis. 2019 Mar 14;16:E30. doi: 10.5888/pcd16.180625.

25. Cohen JT, Neumann PJ, Weinstein MC. Does preventive care save money? Health economics and the presidential candidates. N Engl J Med. 2008 Feb 14;358(7):661-3. doi: 10.1056/NEJMp0708558.

26. Kidd EA, Beighton D. Prediction of secondary caries around tooth-colored restorations: a clinical and microbiological study. J Dent Res. 1996 Dec;75(12):1942-6. doi: 10.1177/00220345960750120501.

27. Magalhães CS, Freitas BDA, Moreira AN, Ferreira EF. Validity of staining and marginal ditching as criteria for diagnosis of secondary caries around occlusal amalgam restorations: an in vitro study. Brazilian Dental Journal [internet]. 2009;20(4):307-313. doi: 10.1590/S0103-64402009000400008.

28. Guedes RS, Piovesan C, Floriano I, Emmanuelli B, Braga MM, Ekstrand KR, Ardenghi TM, Mendes FM. Risk of initial and moderate caries lesions in primary teeth to progress to dentine cavitation: a 2-year cohort study. Int J Paediatr Dent. 2016 Mar;26(2):116-24. doi: 10.1111/ipd.12166.

29. Kanzow P, Wiegand A. Retrospective analysis on the repair vs. replacement of composite restorations. Dent Mater. 2020;36(1):108–18. doi: 10.1016/j.dental.2019.11.001.

30. Sculpher MJ, Claxton K, Drummond M, McCabe C. Whither trial-based economic evaluation for health care decision making? Health Econ [internet]. 2006;15(7):677–87. doi: 10.1002/hec.1093.

31. Brouwer WB, Niessen LW, Postma MJ, Rutten FF. Need for differential discounting of costs and health effects in cost effectiveness analyses. BMJ. 2005 Aug 20;331(7514):446-8. doi: 10.1136/bmj.331.7514.446.

## APPENDIX A - Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist

**Table 1 CHEERS checklist—Items to include when reporting economic evaluations of health interventions**

| Section/item | Item No | Recommendation | Reported on page No/ line No |
|---|---|---|---|
| **Title and abstract** | | | |
| Title | 1 | Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared. | 57 |
| Abstract | 2 | Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions. | NA |
| **Introduction** | | | |
| Background and objectives | 3 | Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions. | 57 |
| **Methods** | | | |
| Target population and subgroups | 4 | Describe characteristics of the base case population and subgroups analysed, including why they were chosen. | 59 |
| Setting and location | 5 | State relevant aspects of the system(s) in which the decision(s) need(s) to be made. | 59 |
| Study perspective | 6 | Describe the perspective of the study and relate this to the costs being evaluated. | 61 |
| Comparators | 7 | Describe the interventions or strategies being compared and state why they were chosen. | 60 |
| Time horizon | 8 | State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate. | 61 |
| Discount rate | 9 | Report the choice of discount rate(s) used for costs and outcomes and say why appropriate. | 61 |
| Choice of health outcomes | 10 | Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed. | 61 |
| Measurement of effectiveness | 11a | *Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data. | 61 |
| | 11b | *Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data. | NA |
| Measurement and valuation of preference based outcomes | 12 | If applicable, describe the population and methods used to elicit preferences for outcomes. | NA |
| Estimating resources and costs | 13a | *Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs. | 62 |
| | 13b | *Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs. | NA |
| Currency, price date, and conversion | 14 | Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate. | 62 |
| Choice of model | 15 | Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended. | NA |
| Assumptions | 16 | Describe all structural or other assumptions underpinning the decision-analytical model. | NA |
| Analytical methods | 17 | Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty. | 63 |

**Table 1 CHEERS checklist—Items to include when reporting economic evaluations of health interventions** *(Continued)*

| | | | |
|---|---|---|---|
| **Results** | | | |
| Study parameters | 18 | Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended. | 69-89 |
| Incremental costs and outcomes | 19 | For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios. | 69-79 |
| Characterising uncertainty | 20a | *Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective). | 79-88 |
| | 20b | *Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions. | NA |
| Characterising heterogeneity | 21 | If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information. | 88-93 |
| **Discussion** | | | |
| Study findings, limitations, generalisability, and current knowledge | 22 | Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge. | 94 |
| **Other** | | | |
| Source of funding | 23 | Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support. | Preface |
| Conflicts of interest | 24 | Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations. | NA |

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist.

APPENDIX B – Protocol deviations

| Participant | Protocol deviations | Time Frame | Solution |
|---|---|---|---|
| 107 | Repair (85) was done instead of replacement | Baseline | Actual treament (repair) costs considered for analysis |
| 139 | Endodontic treatment (55) was necessary during restoration replacement | Baseline | Actual treament (endodontic treatment) costs considered for analysis |
| 59 | Tooth was not assessed (75) | 6m | Data imputation about condition* and treatment based on 6m data in this group |
| 101 | Tooth was not assessed (75) | 6m | Data imputation about condition* and treatment based on 6m data in this group |
| 112 | Treatment was not performed as recommended by the assessor (85) | 6m | Data imputation about treatment† based on others of same type at 6m |
| 116 | Treatment was not performed as recommended by the assessor (85) | 6m | Data imputation about treatment† based on others of same type at 6m |
| 157 | Treatment was not performed as recommended by the assessor (55, 54, 52, 62, 63, 65, 74) | 6m | Data imputation about treatment† based on others of same type at 6m |
| 162 | Tooth was not assessed (84) | 6m | Data imputation about condition* and treatment based on 6m data in this group |
| 67 | Child did not comply with this follow-up | 6m | Data imputation about condition* and treatment based on the related follow-up in this group |
| 140 | Child did not comply with this follow-up | 6m | Data imputation about condition* and treatment based on the related follow-up in this group |
| 65 | Treatment was performed outside the trial (54) | 12m | Data imputation about treatment† based on others of same type at 12m |
| 76 | Tooth was not assessed using one of the tested strategies (55, 64, 75, 74, 84, 85) | 12m | Data imputation about treatment† based on outcomes observed at 12-month follow-up |
| 85 | Treatment was performed outside the trial (84) | 12m | Data imputation about treatment† based on others of same type at 12m |
| 96 | Treatment was not performed as recommended by the assessor (85) | 12m | Data imputation about treatment† based on others of same type at 12m |
| 100 | Treatment was not performed as recommended by the assessor (55, 54, 64, 74) | 12m | Data imputation about treatment† based on others of same type at 12m |
| 67 | Child did not comply with this follow-up | 12m | Data imputation about condition* and treatment based on the related follow-up in this group |
| 94 | Child did not comply with this follow-up | 12m | Data imputation about condition* and treatment based on the related follow-up in this group |
| 134 | Child did not comply | 12m | Data imputation about condition* and treatment |

| | | | |
|---|---|---|---|
| | with this follow-up | | based on the related follow-up in this group |
| 139 | Child did not comply with this follow-up | 12m | Data imputation about condition* and treatment based on the related follow-up in this group |
| 140 | Child did not comply with this follow-up | 12m | Data imputation about condition* and treatment based on the related follow-up in this group |
| 142 | Child did not comply with this follow-up | 12m | Data imputation about condition* and treatment based on the related follow-up in this group |
| 162 | Child did not comply with this follow-up | 12m | Data imputation about condition* and treatment based on the related follow-up in this group |
| 137 | Treatment was performed outside the trial (85)49 | 12m | Data imputation about treatmentᵼ based on others of same type at 12m |
| 163 | Treatment was not performed in the supposed follow-up | 12m | Data replacement considering costs measured in the following follow-up |
| 168 | Treatment was not performed as recommended by the assessor (74, 84) | 18m | Data imputation about treatmentᵼ based on others of same type at 18m |
| 76 | Tooth was not assessed (55) | 18m | Data imputation about condition* and treatment based on 6m data in this group |
| | Child did not comply with this follow-up | 18m | Data imputation about condition* and treatment based on the related follow-up in this group |

* conditioned to the baseline and/or previous follow-up health status.
ᵼ conditioned to the present health status.

APPENDIX C – Subgroup analysis

| | 3-to-6-year-old children | | | 7-to-10-year-old children | | |
|---|---|---|---|---|---|---|
| | **CARS** | **FDI** | **P value** | **CARS** | **FDI** | **P value** |
| **Relative Cost for 24 months** | 27.53 (22.70 to 32.36) | 31.57 (24.43 to 38.70) | 0.14 | 24.51 (17.32 to 31.70) | 18.36 (13.94 to 22.78) | 0.74 |
| **Health Effects** | | | | | | |
| Relative number* of new operative interventions (units) | 1.30 (1.04 to 1.56) | 1.58 (1.28 to 1.88) | 0.29 | 0.71 (0.47 to 0.94) | 0.86 (0.61 to 1.11) | 0.44 |
| Time to the 1st failure per child (months) | 9.22 (7.63 to 10.22) | 11.36 (8.81 to 13.90) | 0.08 | 10.98 (8.84 to 13.11) | 10.67 (8.64 to 12.71) | 0.42 |
| Children with no need of new operative interventions (%) | 10.00 (3.72 to 24.17) | 4.76 (1.16 to 17.54) | 0.36 | 32.56 (20.13 to 48.05) | 25.58 (14.60 to 40.86) | 0.48 |
| Relative number * of new replacements (units) | 0.21 (0.13 to 0.30) | 0.24 (0.15 to 0.33) | 0.93 | 0.05 (0.007 to 0.10) | 0.12 (0.05 to 0.19) | 0.09 |
| | **≤ 3 restorations** | | | **> 3 restorations** | | |
| | **CARS** | **FDI** | **P value** | **CARS** | **FDI** | **P value** |
| **Relative Cost for 24 months** | 32.80 (23.42 to 42.19) | 26.84 (18.04 to 35.64) | 0.94 | 21.89 (18.02 to 25.75) | 23.70 (19.05 to 28.36) | 0.63 |
| **Health Effects** | | | | | | |
| Relative number* of new operative interventions (units) | 1.10 (0.71 to 1.49) | 1.41 (1.00 to 1.83) | 0.28 | 0.93 (0.75 to 1.11) | 1.10 (0.88 to 1.32) | 0.39 |
| Time to the 1st failure per child (months) | 10.48 (8.41 to 12.56) | 11.69 (8.81 to 14.57) | 0.25 | 9.92 (8.14 to 11.70) | 10.66 (8.60 to 12.54) | 0.30 |
| Children with no need of new operative interventions (%) | 35.48 (20.57 to 53.88) | 25.00 (12.80 to 43.05) | 0.36 | 13.46 (6.47 to 25.91) | 9.43 (3.92 to 21.00) | 0.52 |
| Relative number* of new replacements (units) | 0.26 (0.10 to 0.42) | 0.25 (0.07 to 0.43) | 0.95 | 0.83 (0.43 to 1.22) | 1.04 (0.63 to 1.44) | 0.46 |

Costs are presented in international dollars (conversion rate = 2.363, October 2021)

*Number of interventions alongside 24 months divided by the number of included teeth.

CARS = Caries Around Restorations and Sealants; FDI = International Dental Federation

# 5 FINAL CONSIDERATIONS

Economic evaluations are a relevant source for decision-making in clinical practice. Despite the limitations, trial-based economic evaluations may answer technical questions regarding efficient use of resources. Elaborating a health economic analysis plan is important to pre-stablish parameters, corroborating with research transparency. Despite the increasing number of economic evaluations in child oral health care, there is still paucity of high-quality reports, especially in the cariology field. Detection of dental caries around the restoration is still a challenge in the clinical practice, therefore the use of strategies to guide clinicians aid in treatment decision. The CARS strategy is focused in detecting caries lesions, which are the main reported reason for reintervention in restored primary teeth. Through our cost-effectiveness analysis the CARS strategy is cost-effective in replacing the FDI as a diagnostic strategy for primary teeth. Further economic evaluations using analytic model frameworks are needed for investigating a wider time horizon. Moreover, preferences assessment for health states related to dental caries has been already performed and will be reported in a subsequent publication.

# REFERENCES[1]


1. Listl S, Galloway J, Mossey PA, Marcenes W. Global Economic Impact of Dental Diseases. J Dent Res [internet]. 2015;94(10):1355–61. doi: 10.1177/0022034515602879.

2. Kassebaum NJ, Bernabé E, Dahiya M, Bhandari B, Murray CJL, Marcenes W. Global burden of untreated caries: A systematic review and metaregression. J Dent Res [internet]. 2015;94(5):650–8. doi: 10.1177/0022034515573272.

3. Rogers HJ, Rodd HD, Vermaire JH, Stevens K, Knapp R, El Yousfi S, et al. A systematic review of the quality and scope of economic evaluations in child oral health research. BMC Oral Health [internet]. 2019;19(1):1–15.

4. Rogers HJ, Freitas RD, Beeson MJ, Vernazza CR. Economic evaluations in paediatric dentistry clinical trials. Int J Paediatr Dent. 2021;(November 2020):ipd.12772. doi:10.1111/ipd.12772

5. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. Fourth Edi. Oxford, Uk: Oxford University Press; 2015. 445 p.

6. Pontes LRA, Lara JS, Novaes TF, Freitas JG, Gimenez T, Moro BLP, et al. Negligible therapeutic impact, false-positives, overdiagnosis and lead-time are the reasons why radiographs bring more harm than benefits in the caries diagnosis of preschool children. BMC Oral Health. 2021;21(1):168. doi: 10.1186/s12903-021-01528-w

7. Pontes L, Novaes T, Lara J, Gimenez T, Moro B, Camargo L, et al. Impact of visual inspection and radiographs for caries detection in children: a 2-year randomized clinical trial. J Am Dent Assoc [internet]. 2020;151(6):407–15.

8. Moro BLP, Signori C, Freitas RD, Pontes LRA, Lenzi TL, Tedesco TK, et al. The effect of two clinical criteria in the assessment of caries lesions around restorations in children (CARDEC-03): study protocol for a diagnostic randomized clinical trial. F1000Res. 2021;9:650. doi: 10.12688/f1000research.23801.3

9. Moro BLP, Freitas RD, Pontes LRA, Pássaro AL, Lenzi TL, Tedesco TK, et al. Influence of different clinical criteria on the decision to replace restorations in primary teeth. J Dent. 2020;101:103421. doi:10.1016/j.jdent.2020.103421


[1] According to Vancouver style.

ANNEX A - Ethics Committee Approval

FACULDADE DE ODONTOLOGIA USP - SÃO PAULO

## PARECER CONSUBSTANCIADO DO CEP

**DADOS DO PROJETO DE PESQUISA**

**Título da Pesquisa:** Impacto do uso de diferentes critérios clínicos na avaliação de lesões de cárie ao redor de restaurações em dentes decíduos: estudo clínico randomizado

**Pesquisador:** Fausto Medeiros Mendes

**Área Temática:**

**Versão:** 2

**CAAE:** 73013417.0.0000.0075

**Instituição Proponente:** Faculdade de Odontologia da Universidade de São Paulo

**Patrocinador Principal:** Financiamento Próprio

**DADOS DO PARECER**

**Número do Parecer:** 2.291.642

**Apresentação do Projeto:**

Trata-se de uma proposta de estudo clínico randomizado controlado com dois braços paralelos para comparar dois índices visuais de avaliação de lesões de cárie ao redor de
restaurações. Em um braço, o critério de diagnóstico utilizado será o sistema proposto pela Federação Dentária Internacional (FDI) e no outro, o sistema proposto pelo International Caries Classification and Management System (ICCMS). O desfecho primário será a necessidade de intervenção operatória durante o acompanhamento das restaurações avaliadas pelos diferentes índices durante os dois anos de acompanhamento.

**Objetivo da Pesquisa:**

O objetivo primário do estudo é avaliar e comparar a influência da utilização de dois diferentes critérios visuais para avaliação de restaurações em dentes decíduos, sobre desfechos importantes para os pacientes a médio e a longo prazo, por meio de um estudo clínico randomizado. Estes critérios são o sistema proposto pela Federação Dentária Internacional (FDI) (Hickel et al., 2010) e pelo International Caries Classification and
Management System – ICCMS (Ismail et al., 2015).

**Avaliação dos Riscos e Benefícios:**

Avaliação de riscos e benefícios descritos adequadamente no corpo do projeto e no TCLE.

**Endereço:** Av Prof Lineu Prestes 2227
**Bairro:** Cidade Universitária **CEP:** 05.508-900
**UF:** SP **Município:** SAO PAULO
**Telefone:** (11)3091-7960 **Fax:** (11)3091-7814 **E-mail:** cepfo@usp.br

**Comentários e Considerações sobre a Pesquisa:**

Projeto com proposta clara e com grande potencial para gerar evidências que colaborem na tomada de decisão clínica sobre diagnóstico de cárie ao redor de restaurações.

**Considerações sobre os Termos de apresentação obrigatória:**

Todos os termos apresentados: Projeto Detalhado, TCLE, Termo de Assentimento, Autorização da Clínica Odontológica, Folha de Rosto.

**Recomendações:**

Projeto responde a todos as recomendações da CONEP.

Tendo em vista a legislação vigente, devem ser encaminhados ao CEP-FOUSP relatórios parciais anuais referentes ao andamento da pesquisa e relatório final, utilizando-se da opção "Enviar Notificação" (descrita no Manual "Submeter Notificação", disponível na Central de Suporte - canto superior direito do site www.saude.gov.br/plataformabrasil).

Qualquer alteração no projeto original deve ser apresentada "emenda" a este CEP, de forma objetiva e com justificativas para nova apreciação.

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

Não há pendências.

**Considerações Finais a critério do CEP:**

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

| Tipo Documento | Arquivo | Postagem | Autor | Situação |
|---|---|---|---|---|
| Informações Básicas do Projeto | PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_942976.pdf | 15/09/2017 11:15:29 | | Aceito |
| Projeto Detalhado / Brochura Investigador | Projeto.pdf | 15/09/2017 11:11:37 | Fausto Medeiros Mendes | Aceito |
| TCLE / Termos de Assentimento / Justificativa de Ausência | TCLE.pdf | 15/09/2017 11:11:23 | Fausto Medeiros Mendes | Aceito |
| Declaração de Pesquisadores | Carta_ao_CEP.pdf | 12/09/2017 11:06:12 | Fausto Medeiros Mendes | Aceito |
| Declaração de Instituição e Infraestrutura | Autorizacao_uso_da_clinica.pdf | 03/08/2017 13:42:31 | Fausto Medeiros Mendes | Aceito |
| TCLE / Termos de Assentimento / | Assentimento.pdf | 03/08/2017 13:37:26 | Fausto Medeiros Mendes | Aceito |

| | | | | |
|---|---|---|---|---|
| Justificativa de Ausência | Assentimento.pdf | 03/08/2017 13:37:26 | Fausto Medeiros Mendes | Aceito |
| Folha de Rosto | Folha_de_rosto.pdf | 03/08/2017 13:35:42 | Fausto Medeiros Mendes | Aceito |

**Situação do Parecer:**
Aprovado

**Necessita Apreciação da CONEP:**
Não

SAO PAULO, 22 de Setembro de 2017

**Assinado por:**
**Maria Gabriela Haye Biazevic**
**(Coordenador)**

**Endereço:** Av Prof Lineu Prestes 2227
**Bairro:** Cidade Universitária **CEP:** 05.508-900
**UF:** SP **Município:** SAO PAULO
**Telefone:** (11)3091-7960 **Fax:** (11)3091-7814 **E-mail:** cepfo@usp.br

ANNEX B – Trials final decision and acceptance e-mail

From: **Trials (TRLS)** <em@editorialmanager.com>
Date: Wed, Oct 13, 2021 at 7:57 AM
Subject: Decision has been reached on your submission to Trials - TRLS-D-21-00392R1 - [EMID:97f8881d0365df6a]
To: Mariana Minatel Braga <mmbraga@usp.br>

TRLS-D-21-00392R1
The economic impact of two diagnostic strategies in the management of restorations in primary teeth: a health economic analysis plan for a trial-based economic evaluation
Raiza Dias Freitas; Bruna Lorena Pereira Moro; Laura Regina Antunes Pontes; Haline Cunha Maia; Ana Laura Passaro; Rodolfo Carvalho Oliveira; Jonathan Rafael Garbim; Maria Eduarda Vigano; Cristopher Deery; Daniela Prócida Raggio; Maximiliano Sergio Cenci; Fausto Medeiros Mendes; Tamara Kerber Tedesco; Mariana Minatel Braga; collaborative group CARDEC
Trials

Dear Prof. Braga,

I am pleased to inform you that your manuscript "The economic impact of two diagnostic strategies in the management of restorations in primary teeth: a health economic analysis plan for a trial-based economic evaluation" (TRLS-D-21-00392R1) has been accepted for publication in Trials.

Before publication, our production team will check the format of your manuscript to ensure that it conforms to the standards of the journal. They will be in touch shortly to request any necessary changes, or to confirm that none are needed.

Articles in this journal may be held for a short period of time prior to publication. If you have any concerns please contact the journal.

Any final comments from our reviewers or editors can be found, below. Please quote your manuscript number, TRLS-D-21-00392R1, when inquiring about this submission.

We look forward to publishing your manuscript and I do hope you will consider Trials again in the future.

Best wishes,

Daniela Hesse
Trials
https://trialsjournal.biomedcentral.com/