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NATIONAL DEVELOPMENT PLAN 2020

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INVESTING IN YOUR FUTURE

New non-invasive treatments for the control and treatment of early childhood caries

Project/agreement No.1.1.1.2/VIAA/3/19/543, Contract No 9.-14.5/27

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Research protocol

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TABLE OF CONTENT

Title

Public title

New non-invasive treatments for the control and treatment of early childhood caries

Scientific title

Treatment of early childhood caries with three different topical fluoride treatments: a randomised clinical trial

Acronym

NoCaries

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Background

Oral health is essential to general health and significantly influences the development of children. Dental caries has a high economic and social impact due both to the costs associated with its treatment as well as the societal cost of days lost in school by children, in work by their parents and the sequels that remain throughout life (Wadhawan *et al.*, 2003). Also, since caries is associated with excessive sugar intake, it is a predictor of risk for cardiovascular disease and diabetes in children and adults. The aetiology of early childhood caries (ECC) is complex, and the main associated factors are high sugar consumption and inadequate oral hygiene (Leong *et al.*, 2013).

The traditional operative treatment of carious lesions often fails, mainly when tooth restoration is performed early (Raedel *et al.*, 2017). Less invasive caries treatment strategies have been proposed that would have the advantage of lowering the costs of care and decreasing the number of tooth extractions (Stephenson *et al.*, 2010). Fluoride applications effectively decrease the incidence of early childhood caries (Gao *et al.*, 2016), while SDF is effective in arresting the progression of cavitated lesions (Duangthip *et al.*, 2017). However, a usual adverse effect of SDF is that it stains the teeth black. New formulations have appeared that replace silver with copper (Tiefenfluorid) to avoid this. At this moment, the effectiveness of Tiefenfluorid in arresting carious lesions in permanent teeth is proven (Thneibat *et al.*, 2008). Still, there are no studies in deciduous dentition or clinical studies comparing the effectiveness of all those non-invasive treatments. Also, there is a gap in knowledge about which protocols are most effective and how the interval between applications influences clinical effectiveness (Slayton *et al.*, 2018). To date, it is known that a bi-annual application is better than one application per year, but other application protocols have not been studied (Crystal *et al.*, 2017). Due to the mechanisms of enamel and dentin remineralisation, this is a process where maximum fluoride concentration with maximum application frequency can provide the best results.

A new six-arm clinical trial could provide crucial information on the efficacy, cost-effectiveness and potential side effects of these methods for patients.

Aim

The primary objective of the study is to find out which high-concentration fluoride application method and protocol are more effective in preventing complications arising from early childhood caries in preschool children. The secondary objectives are:

- Which fluoride application method and protocol is more effective in arresting non-cavitated and cavitated carious lesions in preschool children?
- What are the parents' and patients' acceptance of SDF and Tiefenfluorid application procedures and staining side-effect?
- What are the costs and cost-effectiveness of each method and application protocol?

Study design and settings

This study is a randomised, patient/parent-blinded, superiority clinical trial with six parallel groups. The hypothesis tested to evaluate two early childhood tooth caries treatment methods with two different application protocols, comparing with placebo, will be performed at the Rīga Stradiņa University's (RSU) Institute of Stomatology Children's Dentistry department.

Changes from the original protocol

In order to optimise the potential gains of our investigation, we implemented certain alterations to our protocol which were authorised by the RSU Ethics Committee (Nr. 2-PĒK-4/627/2022). Specifically, we broadened the scope of our study participants from solely 2-6-year-old healthy children to include children ranging from 0 to 6 years of age who possessed genetic disorders, autistic spectrum disorders, and chronic heart disease. The purpose of these changes was to facilitate less intrusive procedures and to obtain a more all-encompassing comprehension of the potential benefits of the intervention for a more diverse group of children.

Participants

According to the AAPD's (American Academy of Pediatric Dentistry) definition of severe early childhood caries (S-ECC) is a condition when a child up to 3 years old has at least one non-cavitated carious lesion and from 3 to 5 years old with at least one cavitated carious lesion (AAPD). Every week approximately 15 children under six years of age with multiple carious lesions seek consultations about the possibility of receiving planned dental treatment under general anaesthesia (GA) at the RSU Institute of Stomatology. After confirmation of the diagnosis, the children were on a waiting list for treatment, which lasted approx. 12 months. These children are offered to participate in this study while

they wait for dental GA. Every day approximately ten children arrive at an age to be included in the study with acute pain or an infection. As a result, the patients involved in the study have common characteristics: multiple cavitated carious lesions (indicating restorative treatment), a high level of caries risk factors, and possible difficulties with behavioural control. To bring the study's sample patients as close as possible to the overall children's population, participants will be included according to defined criteria.

Inclusion criteria:

- children under six years of age;
- have at least one active cavitated carious lesion (ICDAS 3-6; comply with the diagnosis of S-EEC);
- parents agree to participate in the study and sign a consent form.

Exclusion criteria:

- the child arrives with an adult who doesn't have the right to sign a consent form, and the person responsible for the child cannot be present;
- does not want to be randomised;
- previously received treatment with products that have a high level of fluoride concentration.

Sample size calculation

The calculation of sample size was based on the question: "Which of the applied caries treatment methods will have the least frequency of complication occurrences, treating severe early childhood caries in children under six years of age?" Since we will compare proportions in six groups, in the sample size calculation, we used formulas, which are shown in Fig 1 (Shao, Chow and Wang, 2003), calculating that the planned number of various proportions for comparison will be 9.

From previous studies, it is known that conventionally treating early childhood tooth caries, the frequency of complications is 10% (Innes *et al.*, 2013), but examining clinical records at RSU's Institute of Stomatology Children's Dentistry department, the frequency of complications for children that are waiting in line for treatment under general anaesthesia and who receive no additional treatment, is approximately 30%, therefore in the study's treatment groups we expect that the frequency of complications will be no greater than 10%, but in the placebo groups - at least 30%. The final sample size calculated was 49 children in each group (a total of 294 children) to ascertain the difference in complication proportions between 30% un 10% with an α error of 0.05 and with a study power of 80%. Wee added 30% of potential losses for follow-up, thus planning to recruit 70 children in each group (420 in total).

$$n = (p_A(1-p_A) + p_B(1-p_B)) \left(\frac{z_{1-\alpha/(2\tau)} + z_{1-\beta}}{p_A - p_B} \right)^2$$

$$1 - \beta = \Phi\left(z - z_{1-\alpha/(2\tau)}\right) + \Phi\left(-z - z_{1-\alpha/(2\tau)}\right) \quad , \quad z = \frac{p_A - p_B}{\sqrt{\frac{p_A(1-p_A)}{n} + \frac{p_B(1-p_B)}{n}}}$$

Fig 1. Formulas to calculate the sample size. n = the sample size (for one comparison, therefore two equivalent groups); Φ = standard normal allocation function; α = I type error; τ = number of comparisons; β = II type error; 1–β = study capacity.

Randomisation, allocation and blinding

Flow chart of the research methodology are shown in Fig 2. If the patient fulfils the inclusion criteria, their parents (caregiver) will be offered the opportunity to participate in the study. The objectives of the study will be explained both orally and in writing, as well as the expected results and side effects of the treatments:

1. arresting of the lesions – restorative treatment may no longer be necessary, but in case the child is waiting for treatment under GA, they will not lose their place, and restorative treatment will be offered if parents will still want it because of esthetic reasons;
2. staining of the teeth – when the lesion is arrested, damaged dental enamel and dentine often change colour, become darker, and the treatment methods can facilitate that (especially SDF), and therefore the teeth can become dark stained;
3. unpleasant taste during the procedure.

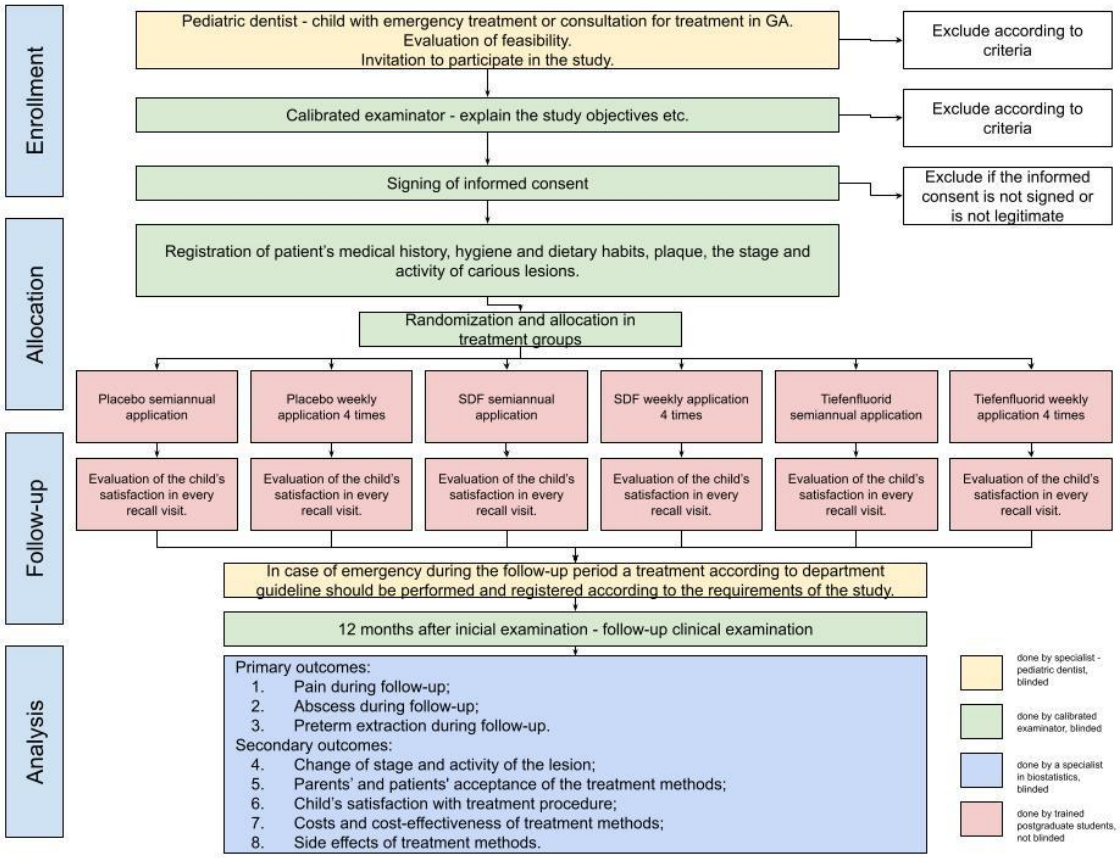

Fig 2. Flow chart of the clinical trial.

If the parents agree to participate in the study, their child will be examined by one previously calibrated examiner, who will again explain the study and in whose presence they will sign the informed consent form. If the parents decide not to participate, they can withdraw without negative consequences. The operator will register the stage and activity of the lesions according to ICDAS and Nyvad criteria (Shoaib *et al.*, 2009; Nyvad and Baelum, 2018).

For randomisation, we will use colour-coded ID cards (six colours) with unique ID numbers. The operator gives the card after signing the consent form in consecutive order, and the patient is assigned to the corresponding colour group. The operator then performs the group-corresponding application, using unlabeled product boxes and bottles to ensure patients' and their parents' blinding.

After the application, we will ask the child to describe their feelings during the procedure by using the visual analogue scale (VAS). The next visit will be set according to the group's corresponding protocol. On all future treatment appointments, the patient will only see the operators of Intervention Staff (IS), who will apply corresponding product, but will not evaluate the final outcomes.

After the 12-month period, patients will be contacted to assign a follow-up examination with the same calibrated examiner, who examined the patient at the first appointment. During the follow-up appointment, the stage and the activity of the lesions will be assessed; registration of any unfavourable outcomes will be done and questionnaires for the parents and children about their satisfaction with the appearance of their teeth will be applied.

Interventions

Patients who agree to participate in the study, will be randomized into one of six groups:

1. The first placebo group – placebo varnish application twice with a six-month interval and a recommendation to brush teeth with a toothpaste containing fluoride (F content of at least 1000 ppm);
2. The second placebo group – placebo varnish application four times with a week's interval and a recommendation to brush teeth with a toothpaste containing fluoride (F content of at least 1000 ppm);
3. The first SDF group – Riva Star SDF (35-40% silver fluoride, 15-20% ammonium) application twice with a six-month interval and a recommendation to brush teeth with a toothpaste containing fluoride (F content of at least 1000 ppm);
4. The second SDF group - Riva Star SDF application four times with a week's interval and a recommendation to brush teeth with a toothpaste containing fluoride (F content of at least 1000 ppm);
5. The first Tiefenfluoride group – Tiefenfluoride (0.4% CuSiF6 x 6 H2O, 10.9% MgSiF6 x 6 H2O, 0.1% NaF, 9.6% Ca(OH)2) application twice with a six month interval and a recommendation to brush teeth with a toothpaste containing fluoride (F content of at least 1000 ppm);
6. The second Tiefenfluorid group - Tiefenfluorid application four times with a week's interval and a recommendation to brush teeth with toothpaste containing fluoride (F content of at least 1000 ppm);

The aim of the treatment is to decrease the progress of the existing lesions and to prevent the development of new lesions; carious tissue removal will not be performed; the products will be applied according to manufacturer recommendations.

For ethical reasons, the negative control group will not be used – in each of the study's groups the parents (direct caregivers) will be advised about dental hygiene and diet, using motivational intervention principles and recommending brushing teeth with toothpaste that contains fluoride (at

least 1000 ppm), which is defined as non-restorative caries treatment and which has also proven its effectiveness in arresting cavitated lesions.

Outcome variables

Patients will be examined at the baseline and 12 months.

The patient's baseline examination will determine the following parameters:

1) general information about the child (birth date, gender, medical health history);
2) hygiene and dietary habits (frequency of brushing teeth; whether teeth brushed by the child or by parents; the fluoride concentration in toothpaste);
3) plaque (visible/invisible);
4) the stage and activity of carious lesions (ICDAS, Nyvad criteria).

Outcome measures:

I. Primary outcome measures:
   A. Pain history during the observation period, assessed as Yes/No at 12 months follow-up visit.
   B. Abscess history during the observation period, assessed as Yes/No at 12 months follow-up visit.
   C. The number of newly extracted or teeth treated with invasive methods (restorations, pulp therapy) during the observation period, assessed as a number of extracted or treated teeth during the last year at 12 months follow-up visit.

II. Secondary outcome measures:
   A. The change in the overall activity of caries as active/arrested, assessed at 12 months follow-up.
   B. The progression and change of activity of every lesion, assessed by ICDAS (for progression) and Nyvad (for activity) criteria, at 12 months follow-up.
   C. The parent's satisfaction with the result of the treatment, assessed by questionnaire, asking: "Are you satisfied with the way your child's teeth look like?" and "Would you agree to continue the use of the treatment method?",

both measurements in 5-point Likert scale, assessed at 12 months follow-up visit.

D. The child's satisfaction with their teeth, measured by the visual analogue scale (VAS) with 3 points - happy, not sure, sad, assessed at 12 months follow-up visit.

E. The child's feelings during the treatment, measured by the modified Wong-Baker scale with three options - did not hurt, hurts a little, hurts a lot), assessed during every appointment (depending on the treatment group, can be assessed at baseline, 1, 2, 3 weeks and 12 months; or at baseline, 6 and 12 months).

F. The direct costs of the treatment and the cost-effectiveness, calculated as EUR spent per treatment protocol; EUR per prevented major complications (in patient-level - pain, abscess, extraction) and EUR per prevented minor complications (in tooth-level - progression of caries lesion), the calculation will be made at 12 months follow-up..

Statistical analysis

Data will be digitized, by entering an ad-hoc form in the Google Docs programme. Further, the data will be exported cvs (comma-separated values) to an archive. Missing data will be eliminated from the analyses, marking them NA.

Data will be exported in the statistics programme R (R Core Team, 2013), and program packages Tidyverse (Wickham, 2017) un Lubridate (Grolemund and Wickham, 2011) will be used for data processing.

Ethics

The study will be performed in accordance with the Helsinki Declaration (World Medical Association, 2013), and will observe personal data protection.

The patient will be offered to voluntarily choose, whether to participate in the study, ensuring, that if they decline, they will receive the same quality conventional treatment. The most of patients involved will be waiting for public-funded restorative caries treatment under general anaesthesia, therefore, the possibility to participate in the study can be viewed as an additional beneficial treatment, that the children can receive during the waiting period. All the patients whether they participate or not

in case of needs will be ensured to receive emergency care according to standard protocol at the Institute of Stomatology Children's Dentistry department.

Safety

The medications used are registered for use in professional caries treatment:

1. Riva Star SDF (35-40% silver fluoride, 15-20% ammonium) (SDI Limited, 2015);
2. Tiefenfluorid (0.4% $CuSiF_6$ x 6 H_2O, 10.9% $MgSiF_6$ x 6 H_2O, 0.1% NaF, 9.6% $Ca(OH)_2$) (Knappwost-Gieseke, 2002).

Work packages

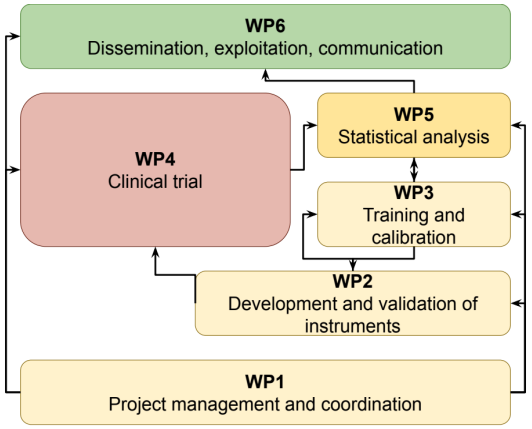

Fig 3. Work packages of the clinical trial.

Work breakdown structure can be seen in Fig 3.

1. **WP1** Project management and coordination. **The objective of WP1** is the coordination of all administrative issues before and during the study. It includes the administration of the study, obtaining all permissions needed for the study, financial management, communication with a partner institution, communication with the project commission, controlling the project and assessment of project quality and progress. Tasks to be performed in WP1 are described in details in point 3.2 of this proposal.

Deliverables of WP1

D1.1 Mid-time report, financial and technical reports.
D1.2 Final project report.

2. **WP2** Development and validation of instruments. **The objective of WP2** is to create and validate questions to patients and parents, visual analogue scales (VAS) and systems to assess the stage and activity of carious lesions. The following tasks will be performed:
    1. Creation of informative letter to patients and informed consent form.

2. Formulation of questions to detect patient factors, which could potentially affect the outcome of treatment.
3. Creation of a questionnaire to assess children's level of satisfaction with the treatment procedure.
4. Creation of a questionnaire to assess children's satisfaction with the appearance of their deciduous teeth.
5. Creation of a questionnaire to assess parent satisfaction with the appearance of their child's teeth.
6. Modification of existing systems to detect the stage of a carious lesion (ICDAS) and activity (Nyvad).

Deliverables of WP2

D2.1 Informative letter with informed consent form.
D2.2 VAS to assess patient satisfaction after treatment.
D2.3 Form to register any emergency treatment performed in the time of the study.
D2.4 Examination form to be used at the beginning of the study – includes questions about risk factors and clinical examination form.
D2.5 Examination form to be used at the follow-up visit – includes Likert scale questions about parental acceptance of the performed treatment, questions about risk factors, VAS to evaluate patient satisfaction with the treatment performed and clinical examination forms.
D2.6 Report of adaptation of ICDAS and Nyvad systems to be used in deciduous dentition with the objective of analysing the effectiveness of treatments performed according to the type of lesion.

Milestones of WP2

MS2.1 Communication with scientific consultants and experienced partners from the University of Michigan and the University of Dundee.
MS2.2 Workshop with Carlos Gonzalez-Cabezas and Margherita Fontana in the University of Michigan.
MS2.3 Preparation of informed consent.
MS2.4 Preparation of Patient satisfaction assessment form.
MS2.5 Preparation of Emergency treatment form.
MS2.6 Preparation of initial examination form.
MS2.7 Preparation of follow-up examination form.
MS2.8 Preparation of the report on the adaptation of ICDAS and Nyvad systems used within the context of the specific aims of the study(related to WP3, task 3.3).

3. **WP3** Training and calibration. **The objective of WP3** is to train dentists, assistants (dental hygienist students) and postgraduate students of RSU Institute of Stomatology to perform different tasks during the study and to calibrate two examiners to ensure the quality of the data:
    1. Training of staff at the Department of Paediatric Dentistry of Institute of Stomatology – for their role in patient recruitment, dissemination of information and activities in case of emergency treatment required for children in the study (general staff (GS) training).
    2. Training of four dentists (postgraduate students in paediatric dentistry) – and two assistants (dental hygienist students) for treatment methods to be applied to all groups of the study ("Intervention staff" (IF)).

3. Training and calibration of two examiners on detecting the stage and activity of carious lesions – postdoctoral researcher and another dentist from the Department of Paediatric Dentistry.

Deliverables of WP3

D3.1 Report on GS training.
D3.2 Guidelines and registration form to enrol patients in the study.
D3.3 Guidelines about performing and documenting emergency treatment for children of the clinical trial.
D3.4 Report on IS training.
D3.5 Report of examiners calibration.

Milestones of WP3

MS3.1 GS training session.
MS3.2 IS training session.
MS3.3 Examiner calibration session.

4. **WP4** Clinical trial. **The objective of WP4** is to perform the clinical trial according to an established protocol and the highest ethical standards with the primary aim of finding out which high-concentration fluoride application method and which application protocol more effectively protects pre-school children from complications arising from early childhood dental caries. Secondary objectives are to evaluate at which stage of development (carious lesions) the methods are the most effective; which fluoride application method and protocol is more effective in arresting non-cavitated and cavitated carious lesions in preschool children; how satisfied are parents and patients with SDF and Tiefenfluorid application procedures and side-effects (staining) and what are the costs and cost-effectiveness of each method and application protocol.
    1. Enrolment of patients in the study. General staff will offer suitable patients the chance to register for the procedures. A calibrated examiner (postdoctoral researcher) will inform parents about all details of the study. If the offered is accepted, parents sign the informed consent form.
    2. Initial examination and interviewing of enrolled patients and their parents by a calibrated examiner (postdoctoral researcher).
    3. Random allocation in six intervention groups. This will be done by a calibrated examiner (postdoctoral researcher) using six closed envelopes containing colour codes.
    4. Performing interventions according to the protocol of each study group. Those interventions will be done by Intervention Staff (IS) - four trained postgraduate students and assistants (dental hygiene students).
    5. Performing and documenting emergency treatment during the follow-up period. Done by trained general staff on a daily basis according to patient needs. Registration will be done using a pre-prepared form.
    6. Follow-up examination. Done by calibrated examiner (postdoctoral researcher).

Deliverables of WP4

D4.1 Enrolment registration form.
D4.2 Signed informed consent forms.
D4.3 Initial patient examination forms (including parent questionnaire).
D4.4 Intervention registration forms (including Visual Analogue Scale [VAS] of patient satisfaction).

D4.5 Emergency treatment forms (including VAS of patient satisfaction).
D4.6 Follow-up examination forms (including VAS of patient acceptance and Likert scale questions of parents acceptance).

Milestones of WP4

MS4.1 Meetings about enrollment, randomization and allocation.
MS4.2 Communication between project management and all staff involved in the study.
MS4.2 Meeting about follow-up examination.

5. **WP5** Data management and statistical analysis. **The objective of WP5** is to manage the research forms, process them using a data management plan and convert them into digital data that will be analysed statistically. This includes converting physical fact sheets into digital ones, cleaning and tabulation of data and descriptive and inferential statistical analysis. Due to the focus on open and reproducible science research, the data will be anonymised, the data and the codebook and script of the statistical analysis will be published as part of the results.
    1. Preparing data management plan.
    2. Digitisation of data.
    3. Checking and cleaning of data.
    4. Data analysis.
    5. Data visualisation.
    6. Data storage and preservation of access.
    7. Publishing of data.

Deliverables of WP5

D5.1 Data management plan.
D5.2 Anonymised database
D5.3 Codebook
D5.4 Script for data analysis in R
D5.5 Detailed results report with frequency tables and graphs

Milestones of WP5

MS5.1 Data management plan available on the Open Science Foundation website (OSF.IO)
MS5.2 Anonymised database available on the Open Science Foundation website (OSF.IO)
MS5.3 Codebook available on the Open Science Foundation website (OSF.IO)
M5.4 Script for data analysis in R available on the Open Science Foundation website (OSF.IO)
M5.5 Detailed results report with frequency tables and graphs available on the Open Science Foundation website (OSF.IO)

6. **WP6** Dissemination, exploitation, communication. **The objective of WP6** is to disseminate and exploit the results obtained in the study. It will involve several tasks:
    1. Raising public awareness of the ECC and non-invasive treatment methods used in the study. It will be done throughout the study by adding and updating information regarding the research on websites of RSU, RSU Institute of Stomatology, in social media (Facebook, Instagram, Twitter) and by doing presentations on the progress of the study during different events

(Researchers' Night, meetings organised by State Education Development Agency Republic of Latvia).

2. Facilitating networking with the scientific community by attending international conferences, mobility activities and publications.
3. Ensuring efficient exploitation of the project results.

Deliverables of WP6

D6.1 Report of dissemination activities.
D6.2 Conference abstracts.
D6.3 Publication about the effectiveness of SDF and Tiefenfluorid treatment in preschool children with S-ECC (to be published in Caries Research (impact factor: 2.188) or in BMC Oral Health (impact factor: 1.602).
D6.4 Publication about the effectiveness of fluoride treatment according to the type of carious lesion in deciduous dentition (to be published in the International Journal of Paediatric Dentistry (impact factor: 2.18) or in European archives of paediatric dentistry: official journal of the European Academy of Paediatric Dentistry (impact factor: 1.48).
D6.5 Evidence-based recommendations and economic evaluation report for national policymakers.

Milestones of WP6

MS6.1 Meeting with Communication Department and IT department of RSU.
MS6.2 Scientific conferences.
MS6.3 Meeting with policymakers.

Gantt chart

The workflow in each work packages and relevant deliveries are illustrated in the Gannt chart (Fig 4.).

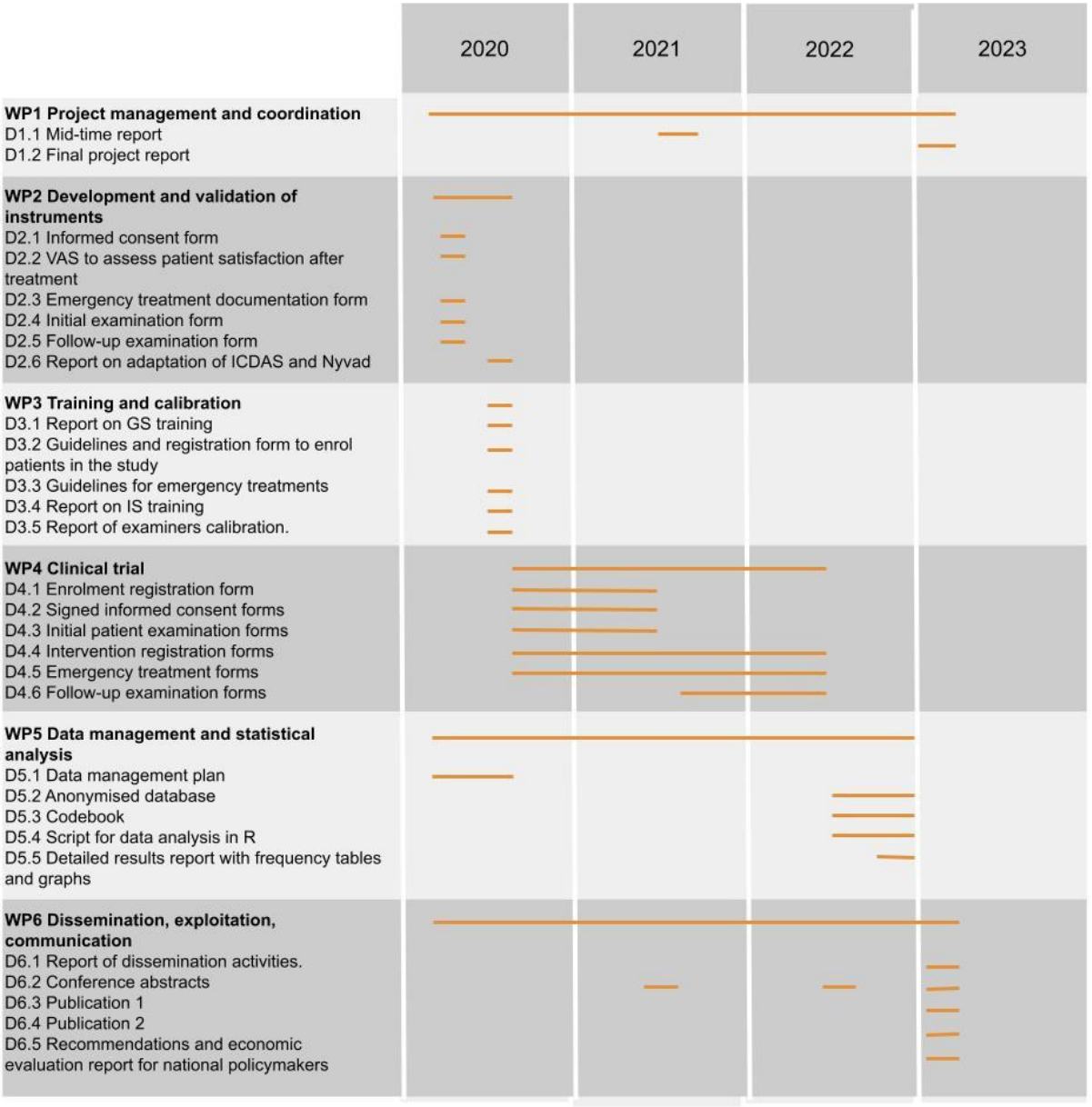

Fig 4. The Gannt chart of the clinical trial.

Risks

1. Research achievability risks
    a. Number of patients recruited less than expected - sample size calculation was estimated using conservative assumptions. The expected difference in the prevalence of severe caries complications in different treatment groups and the placebo group is expected to be 20% (10% complication rate for treatment groups and 30% for placebo). From previous studies, the expected prevalence in treatment groups could be even less, meaning the observed difference would be greater. In such a case, statistical power can be achieved even with a lower number of patients.
    b. Loss of follow-up – we plan to include 70 patients in every group in order to ensure that there are still at least 49 in every group at the end of the project (we assume the potential loss of follow-up examinations to be 30%, which we consider to be sufficient).
2. Research methodology risks
    a. Patients received treatment outside the RSU Institute of Stomatology – every case will be analysed separately; if, for any reason, the patient attended a dentist who was not trained for the study (in the Institute of Stomatology or in another dental clinic), the recordings of treatment performed will be analysed – if there is no doubt regarding the information gained and if the treatment was done according to the guidelines used in the study, the patient will be kept in the study. In case of doubt, he/she will be excluded from analysis. This increases the risk of loss of follow-up, but it is important that we are sure about the impact of the treatment performed. Evenmore, as described above, we will include more patients than required to assure the study power even after some losts of follow-up.
    b. Blinded research team members are informed about colour codes of the treatment groups – we will consider changing the person in case the this knowledge leads to performance or detection bias. We also will include as less personal as possible and the most motivated colleagues to avoid such errors.
    c. Patients find out which treatment group they have been assigned to– it is possible that the groups which receive SDF “feel” the treatment to be more effective because of the staining side effect. However, we are not yet sure how important this effect will be, as all of those children have tooth damage which includes some colour change of the lesions. It is also known that arrested lesions tend to become darker even without the application of any agent. We will be able to address this risk by evaluating the patient and parent satisfaction in different treatment groups.

Infrastructure

The Riga Stradiņš University is the lead partner of the National Importance Research Centre of Public Health and Clinical Medicine (the Centre). The Centre has been designed as the cooperation framework for the concentration of resources for research activity at European level. The partners of the Centre are: the Riga Stradiņš University, the University of Latvia and the Pauls Stradiņš Clinical University Hospital. Following approval of research objectives and assignments, the partners of the Centre have created a mutually supplementing research infrastructure. There were 7.6 million EUR invested in the restoration of research infrastructure in the timeframe from 2012 – 2015, providing for proper quality infrastructure for the leading research directions. An agreement on the infrastructure access and terms of use has been entered into between the institutions of the Centre.

The main tasks for RSU as a scientific institution will be to provide administrative support, financial management, scientific consultation and interdisciplinary cooperation (support in biostatistics and public health). The main tasks for the partner – RSU Institute of Stomatology – will be to provide informative support during patient recruitment, human resources and infrastructure to facilitate the clinical trial. The following infrastructure, materials, human resources, logistics, and facilities will be required to facilitate the planned clinical trial:

- Personnel - postdoctoral researcher, students (four postgraduate students of paediatric dentistry), dental assistants (dental hygiene students from RSU);
- Equipment - dental clinics (Department of Paediatric Dentistry at RSU Institute of Stomatology);
- Facilities to perform training and calibration - Department of Paediatric Dentistry at RSU Institute of Stomatology;
- Consumables - dental instruments, hygiene materials, disinfection and sterilisation facilities - Department of Paediatric Dentistry at RSU Institute of Stomatology;
- Treatment materials - SDF, Tiefenfluoride, placebo (from project resources);
- Mobility activities - from project resources;
- Attendance of conferences - from project resources;
- Publication expenses - from project resources;
- Printing informative materials and clinical examination forms - RSU;
- Administrative and financial management support - RSU;
- Scientific consultations - RSU;
- IT facilities - RSU.

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