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IEGULDĪJUMS TAVĀ NĀKOTNĒ

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

Project/agreement No.1.1.1.2/VIAA/3/19/540, Contract No 9.-14.5/27

BZ01

Clinical Trial Protocol

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

Authors

Principal investigator: Ilze Maldupa (ilze.maldupa@rsu.lv) 0000-0002-5967-956X

Co-authors:

Sergio Uribe - data management (sergio.uribe@rsu.lv) 0000-0003-0684-2025

Anda Brinkmane - consultant (anda.brinkmane@rsu.lv) 0000-0003-1843-0423

Egita Senakola - consultant (egita.senakola@rsu.lv) 0000-0002-6958-4556

Ilona Viduskalne - consultant (ilona.viduskalne@rsu.lv) 0000-0001-6193-2205

Clinical operators:

Jeļena Grišakova

Guna Lagzdiņa

Natālija Protasa

Olga Sļepcova

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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 the 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, especially when tooth restoration is performed at an early age (Raedel *et al.*, 2017). Less invasive caries treatment strategies have been proposed that would have the advantage of lowering the costs of care as well as decreasing the number of tooth extractions (Stephenson *et al.*, 2010). Fluoride applications are effective in decreasing 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 to arrest carious lesions in permanent teeth is proven (Thneibat *et al.*, 2008), but 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 application 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 important information on the efficacy, cost-effectiveness and potential side-effects of these methods for patients.

Study design and settings

This study is a randomised, double-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 a placebo, will be performed at the Rīga Stradiņa University's (RSU) Institute of Stomatology Children's Dentistry department.

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 caries damage without cavitates and from 3 to 5 years old with at least one caries damage with cavitates (AAPD). Every week approximately 15 children ages 2-6 years-old with multiple caries damage seek consultations about the possibility to receive planned tooth treatment under general anaesthesia (GA) at the RSU Institute of Stomatology. After confirmation of the diagnosis, the children are put on a waiting list for treatment, which lasts 12 months. These children are offered to participate in this study, while they wait for rehabilitation with general anaesthesia. Every day approximately 10 children arrive that are at an age to be included in the study, with acute pain or an infection. They are also given the opportunity to participate in the study, if they conform with the criteria. As a result, the patient's involved in the study have common characteristics: multiple caries damage with cavities (indicating restorative treatment); a high level of caries risk factors; 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 aged 2-6;
- have at least one active caries damage with cavitates (comply with the diagnosis of S-EEC);
- wish to participate in the study;
- parents agree to participation 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;
- chronic or serious acute general illness;
- in the last month has used medications, that could affect the secretion of saliva;
- previously received treatment with products that have a high level of fluoride concentration.

Sample size calculation

The calculation of sample size was based on he question: "Which of the applied caries treatment methods will have the least frequency of complication occurrences, treating severe early childhood caries in children from the ages of 2 to 6 years-old?" 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 cards at RSU's Institute of Stomatology Children's Dentistry department, the frequency of complications for children that are waiting in line for treatment with 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 - 30%. From the calculations in the formulas above, we calculated, that for the study we need 49 children in each group, to ascertain the difference in complication proportions between 30% un 10% with α error 0.05 and with a study capacity of 80%. Together 294 children are necessary but, calculating possible losses during the observation time, it is planned to involve 70 children in each group, therefore, 420 in six groups.

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

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

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.

Randomization, allocation and blinding

Flow chart of research methodology is shown in Fig 2. If the patient fulfills the inclusion criteria, their parents (caregiver) will be offered the opportunity to participate in the study. The objective of the study will be explained both verbally 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 are 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 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 unattractive;
3. unpleasant taste during the procedure.

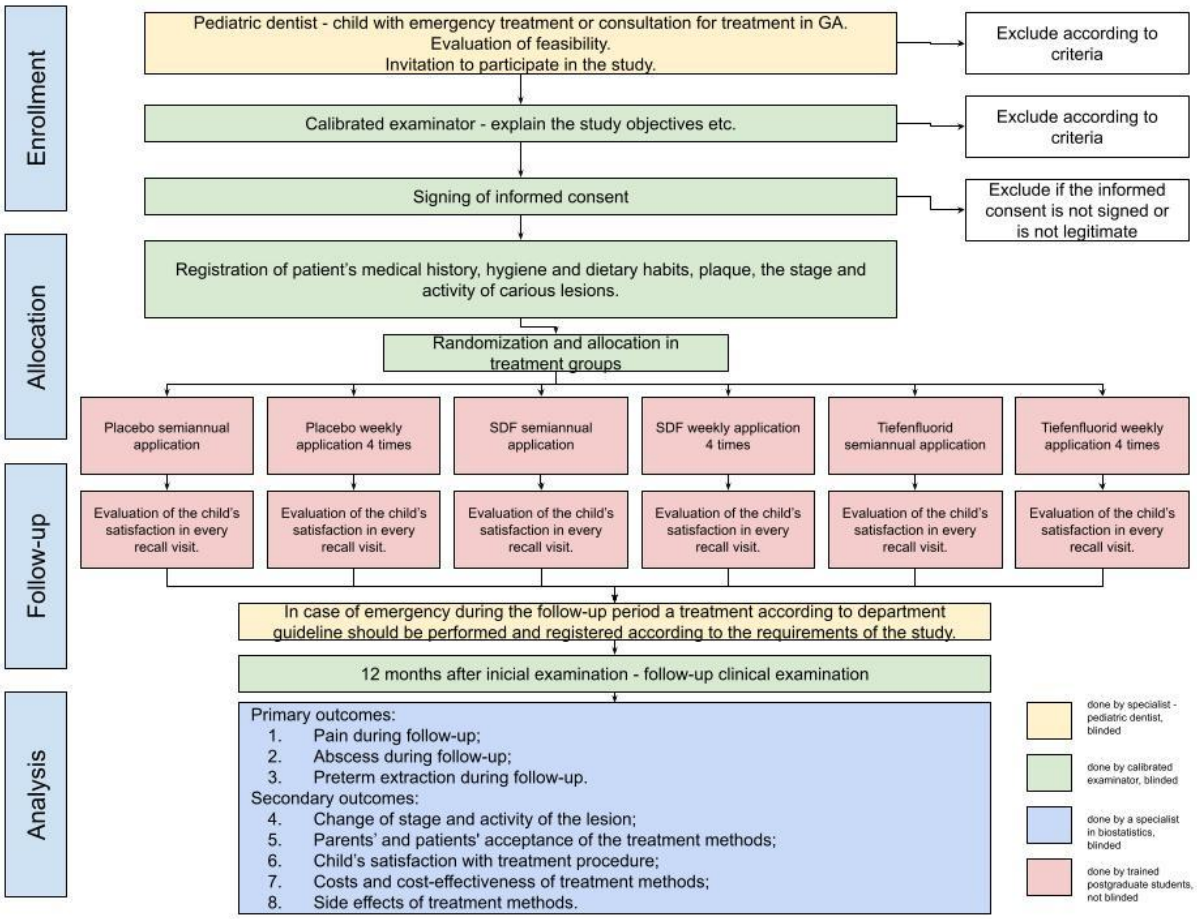

Fig 2. Flow chart of the clinical trial.

If the parents agree to the study, they will be assigned an appointment with one of two calibrated examiners, who will again explain the study and in whose presence, they will sign the informed consent form. If the parents for some reason decide not to participate, they can withdraw without any negative consequences. The calibrated specialist will perform a damage progression and activity register (ICDAS, Nyvad criteria) and draw lots with a closed envelope, of which group the patient will be included in (with a color code).

The patient, with information about their group's color goes to another office, where one of four trained dentists and assistants will be working (Intervention staff - IS). They will be informed about the medication to be used in each of the groups. The corresponding treatment method will be applied, and the child will be asked to describe their feelings during the procedure by using 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 dentists and assistents of IS.

After the last application foreseen in the protocol, the patient will be assigned a control appointment, which will be 12 months after the first examination. During the control appointment one of the calibrated examiners will perform a documentation of stage and activity of carious lesions, not knowing which treatment had been applied. The 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 randomly placed 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% $CuSiF_6 \times 6 H_2O$, 10,9% $MgSiF_6 \times 6 H_2O$, 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 a toothpaste containing fluoride (F content of at least 1000 ppm);

The goal of the treatment is to stop the progress of the existing damage progress and avert the formation of new damage; caries tissue removal will not be performed; the products will be applied to dried teeth.

For ethical reasons, the negative control group will not be used – in each of the study's groups the parents (direct caregivers) will be given advice about tooth cleaning 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 stopping caries damage.

Outcome variables

Patients will be examined at the baseline and at 12 months.

The patient's primary 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; are teeth cleaned by the child or by parents; the fluoride concentration in toothpaste);
3) plaque (visible/invisible);
4) the level and development of the caries damage and activity (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 otherwise surgically treated teeth during the observation period, assessed as a number of extracted 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/Non-active, assessed at 12 months follow-up visit.
   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 visit.
   C. The parent's satisfaction with the way their children's teeth look, assessed by questionnaire, asking: "Are you satisfied with the way your child's teeth look?"

and "Would you agree to repeat the treatment procedure used?", 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 3 options - no hurt, hurts a little, hurts a lot), assessed during every appointment (depending on 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.

G. The treatment method's undesirable side effects, assessed by parents' questionnaire at the 12 months follow-up visit.

Statistical analysis

Data will be digitized, by entering in 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 patients involved will be the ones that are waiting in line for state-funded restorative caries treatment under general anaesthesia, therefore, the possibility to participate in the study can be viewed as an additional treatment, which the children can receive during the waiting period. All the patients – both those that

participate in the study, as well as those who decline, if during the waiting period an emergency situation arises which requires immediate intervention, it will be ensured according to standard protocol at the Institute of Stomatology Children's Dentistry department.

In the attachment you can find the parent's informed consent form (1st attachment), a questionnaire for the children (2nd attachment), a description of acute aid form (3rd attachment) and a clinical examination form (4th and 5th attachment). Using ad hoc, the forms data will be digitized, entering the data anonymously and ensuring, that patients cannot be identified from the stored data.

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% CuSiF6 x 6 H2O, 10,9% MgSiF6 x 6 H2O, 0,1% NaF, 9,6% Ca(OH)2) (Knappwost-Gieseke, 2002).

Work packages

Work breakdown structure can be seen in Fig 3.

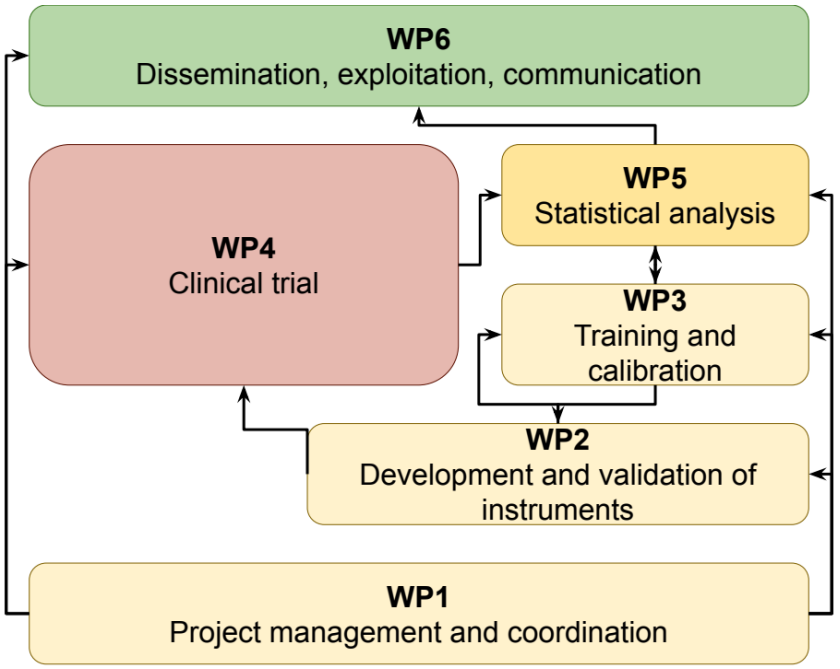

Fig 3. Work packages of the clinical trial.

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.).

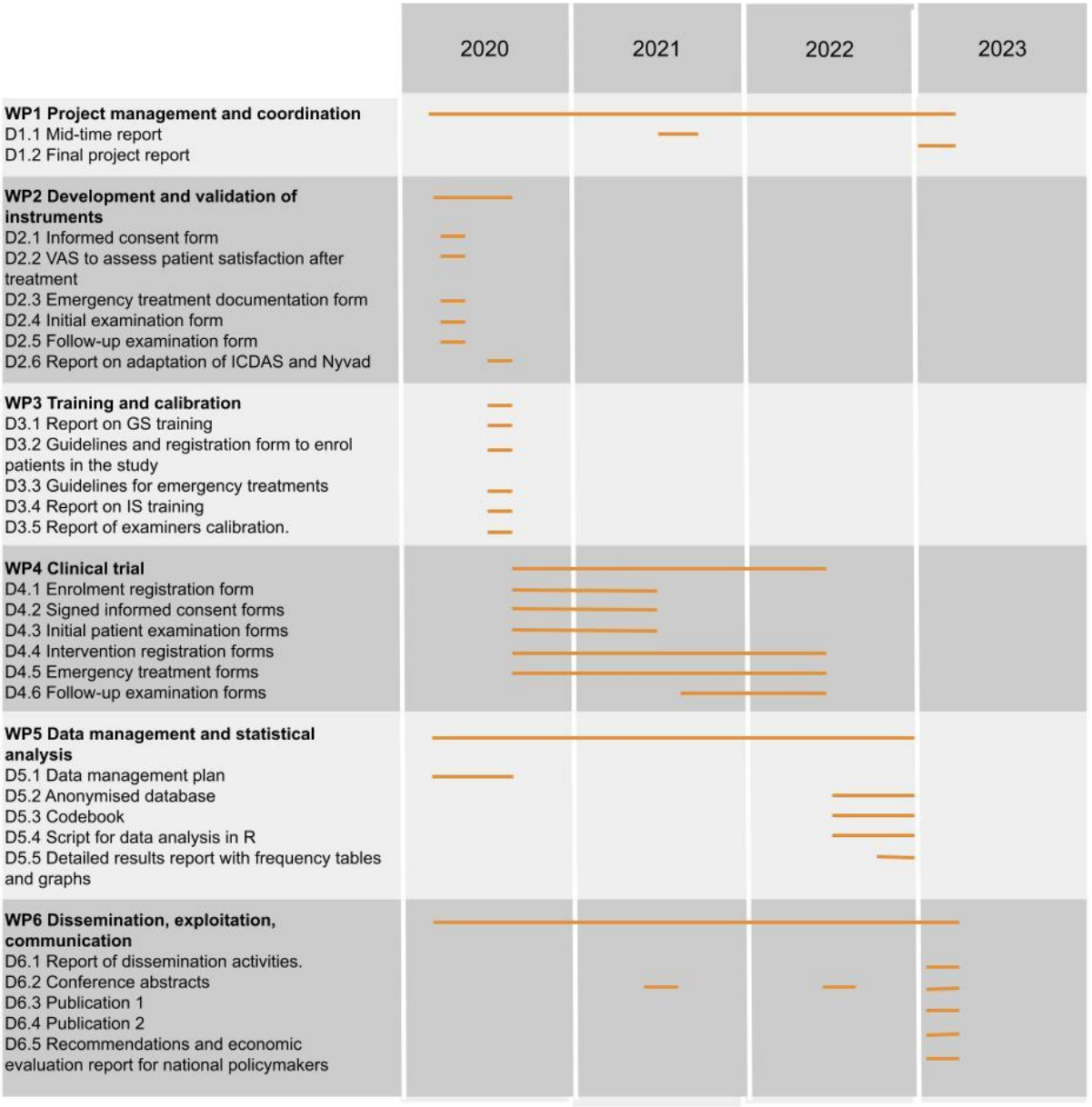

Fig 4. The Gannt chart of the clinical trial.

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.

References

Definition of Early Childhood Caries (ECC) - AAPD. Available from: http://www.aapd.org/assets/1/7/D_ECC.pdf

Crystal, Y. O. *et al.* (2017) 'Use of Silver Diamine Fluoride for Dental Caries Management in Children and Adolescents, Including Those with Special Health Care Needs', *Pediatric dentistry*, 39(6), pp. 146–155.

Duangthip, D. *et al.* (2017) 'Managing Early Childhood Caries with Atraumatic Restorative Treatment and Topical Silver and Fluoride Agents', *International journal of environmental research and public health*, 14(10). doi: 10.3390/ijerph14101204.

Gao, S. S. *et al.* (2016) 'Caries remineralisation and arresting effect in children by professionally applied fluoride treatment - a systematic review', *BMC oral health*, 16, p. 12.

Grolemund, G. and Wickham, H. (2011) 'Dates and Times Made Easy with lubridate', *Journal of Statistical Software, Articles*, 40(3), pp. 1–25.

Innes, N. P. T. *et al.* (2013) 'The FiCTION dental trial protocol - filling children's teeth: indicated or not?', *BMC oral health*, 13, p. 25.

Knappwost-Gieseke, C. (2002) *Safety Data Sheet Tiefenfluorid*. Humanchemie GmbH. Available at: https://www.bcodental.nl/producten/sdb/Tiefenfluorid_20070701_GB.pdf.

Leong, P. M. *et al.* (2013) 'A systematic review of risk factors during first year of life for early childhood caries', *International journal of paediatric dentistry / the British Paedodontic Society [and] the International Association of Dentistry for Children*, 23(4), pp. 235–250.

Raedel, M. *et al.* (2017) 'Re-interventions after restoring teeth-Mining an insurance database', *Journal of dentistry*, 57, pp. 14–19.

R Core Team (2013) *R: A language and environment for statistical computing. R Foundation for Statistical Computing*. Vienna, Austria.

SDI Limited (2015) *Safety Data Sheet Riva Star*. SDI Limited. Available at: http://www.sdi.com.au/images/stories/MSDS/MSDS_EN/Riva_Star_DS_EN.pdf.

Shao, J., Chow, S.-C. and Wang, H. (2003) 'Sample Size Calculations in Clinical Research, Second Edition', *Chapman & Hall/CRC Biostatistics Series*. doi: 10.1201/9780203911341.

Slayton, R. L. *et al.* (2018) 'Evidence-based clinical practice guideline on nonrestorative treatments for carious lesions: A report from the American Dental Association', *Journal of the American Dental Association* , 149(10), pp. 837–849.e19.

Stephenson, J. *et al.* (2010) 'A competing risk survival analysis model to assess the efficacy of filling carious primary teeth', *Caries research*, 44(3), pp. 285–293.

Thneibat, A. *et al.* (2008) 'Anticariogenic and antibacterial properties of a copper varnish using an in vitro microbial caries model', *Operative dentistry*, 33(2), pp. 142–148.

Wadhawan, S. *et al.* (2003) 'Early childhood caries-related visits to hospitals for ambulatory surgery in New York State', *Journal of public health dentistry*, 63(1), pp. 47–51.

Wickham, H. (2017) 'tidyverse: easily install and load the "Tidyverse". R package version 1.2. 1', *R Core Team: Vienna, Austria*. Available at: https://CRAN.R-project.org/package=tidyverse.

World Medical Association (2013) 'World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects', *JAMA: the journal of the American Medical Association*, 310(20), pp. 2191–2194.