OFFICIAL TITLE OF THE STUDY

Effect of Phosphoric Acid Etching Duration on the Performance of Direct Resin-Based Composite Restorations in Permanent Anterior Teeth: A Randomized Controlled Single-Center Trial

NCT NUMBER

NCT ID not yet assigned

SWISSETHICS REFERENCE NUMBERS

HumRes66788 | SNCTP000006373 | BASEC2025-00584

DATE OF THE DOCUMENT

April 22, 2025

Protocol Title

Effect of Phosphoric Acid Etching Duration on the Performance of Direct Resin-Based Composite Restorations in Permanent Anterior Teeth: A Randomized Controlled Single-Center Trial

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Study Type:	Other Clinical Trial according to ClinO, Chapter 4
Risk Categorisation:	Risk category A according to ClinO, Art. 61
Sponsor-Investigator:	PD Dr. med. dent. Florin Eggmann University Center for Dental Medicine Basel UZB Department of Periodontology, Endodontology, and Cariology Mattenstrasse 40 CH-4058 Basel Phone: +41 61 267 26 80 Email: florin.eggmann@unibas.ch
Investigated Intervention:	Application of direct dental restorations using resin-based composite materials on permanent anterior teeth, comparing the impact of two etching regimens during the bonding process.
Protocol ID	ETCH-PRO
Version and Date:	Version 2 (22/04/2025)

PROTOCOL SIGNATURE FORM

Study Title	-	Effect of Phosphoric Acid Etching Duration on the Performance of Direct Resin-Based Composite Restorations in Permanent Anterior Teeth: A Randomized Controlled Single-Center Trial
Study ID	-	ETCH-PRO

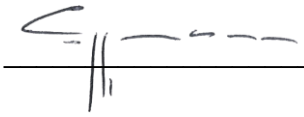
The Sponsor-Investigator has approved the protocol version 1 (18/02/2025) and confirms hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ISO 14155 (as far as applicable) and ICH-GCP guidelines as well as the local legally applicable requirements.

A clinical trial covered by ClinO Chapter 4 may be conducted in accordance with other rules than ICH-GCP guidelines, provided that such rules are recognised in the specialty in question and the protection of participants and data quality and security are guaranteed (ClinO Art. 5, Abs 2). If the clinical trial is not conducted according to ICH-GCP guidelines, the paragraph above must be adapted accordingly.

Sponsor-Investigator:

Name: *Florin Eggmann*

Date: April, 22, 2025 _____ Signature: _____



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GLOSSARY OF ABBREVATIONS

AE	*Adverse Event*
BASEC	*Business Administration System for Ethical Committees*
CRF	*Case Report Form*
CTCAE	*Common Terminology Criteria for Adverse Events*
eCRF	*electronic Case Report Form*
FADP	*Federal Act on Data Protection (in German: DSG, in French: LPD, in Italian: LPD)*
FOPH	*Federal Office of Public Health*
GCP	*Good Clinical Practice*
HRA	*Human Research Act (in German: HFG, in French: LRH, in Italian: LRUm)*
ICH	*International Conference on Harmonisation*
ClinO	*Ordinance on Clinical Trials in Human Research (in German: KlinV, in French: OClin, in Italian: OSRUm)*
PAE	*Phosphoric acid etching*
RBC	*Resin-based composite*
SAE	*Serious Adverse Event*
VAS	*Visual Analog Scale*

1 STUDY SYNOPSIS

Sponsor-Investigator	PD Dr. med. dent. Florin Eggmann University Center for Dental Medicine Basel UZB Department of Periodontology, Endodontology, and Cariology Mattenstrasse 40 CH-4058 Basel Phone: +41 61 267 26 80 Email: florin.eggmann@unibas.ch
Study Title	Effect of Phosphoric Acid Etching Duration on the Performance of Direct Resin-Based Composite Restorations in Permanent Anterior Teeth: A Randomized Controlled Single-Center Trial
Short Title / Study ID	Impact of Etching Time on Resin-Based Composite Restorations Investigation ID: ETCH-PRO
Protocol Version and Date	Version 2 (dated 19/04/2025)
Study Registration	The trial will be registered at ClinicalTrials.gov, a database maintained by the U.S. National Library of Medicine. Additionally, upon submission to BASEC, the trial will be registered in the supplementary federal database, the Swiss National Clinical Trials Portal (SNCTP).
Study Category and Rationale	Other Clinical Trial according to ClinO, Chapter 4 Risk Categorisation: Risk category A according to ClinO, Art. 61 The restorative materials used for fabricating direct restorations in this study are CE-certified. Their use complies with all applicable regulations in Switzerland, where no prohibition exists concerning their use. The study entails only minimal risks and burdens.
Background and Rationale	- Background - Phosphoric acid etching (PAE) enhances enamel bond strength, regardless of the type of dental adhesive that is subsequently applied. For dentin bonding, the use of etch-and-rinse adhesives necessitates the application of PAE. However, PAE of dentin should be avoided when using self-etch adhesives to prevent potential adhesion issues. With the rise of universal adhesives in clinical practice, the decision to etch dentin with phosphoric acid becomes discretionary, allowing dental practitioners to choose between an etch-and-rinse approach and selective enamel etching. However, the challenge lies in selectively etching the enamel without affecting the dentin, as inadvertent or extended etching of dentin can impair adhesion and, consequently, the long-term functionality of the dental restoration. - To mitigate such risks, reducing the PAE duration has been proposed as a viable solution. Laboratory studies suggest that shortening the PAE time does not negatively impact bond strength. Despite this, there is currently a paucity of evidence regarding the clinical effects of reduced PAE times on dental restoration outcomes. - Rationale - This study aims to fill a critical knowledge gap by comparing the restorative outcomes of anterior permanent teeth treated with direct resin-based restorations using either a standard PAE protocol or a reduced PAE duration protocol. Eligible teeth include anterior permanent teeth requiring direct Class III or Class IV resin-based composite restorations owing to one or more of the following conditions: proximal carious lesions with cavitation, defective restorations necessitating replacement, or necessary proximal reshaping. - Importantly, Class IV restorations are limited to cases requiring

	proximal reshaping and explicitly exclude instances involving crown fractures, crown-root fractures, extensive tooth wear, or carious lesions affecting the incisal edge. - The primary goal is to evaluate whether reducing the PAE duration has any effect—positive or negative—on the outcomes of these restorations. The study operates under the null hypothesis, which states that there is no difference in restorative outcomes between the standard and reduced PAE protocols.
Risk / Benefit Assessment	*Study Overview* This study adheres to established, evidence-based practices for restorative patient care, ensuring all procedures meet the highest clinical standards. *Anticipated Clinical Benefits* The study aims to enhance treatment protocols and improve long-term restorative care practices. While participants may not receive direct personal benefits, their involvement will contribute to advancing scientific knowledge for broader patient populations. *Residual Risks and ADEs* The materials used comply with CE marking requirements, presenting minimal residual risks. Expected adverse device effects (ADEs), such as minor postoperative discomfort or sensitivity, are rare and will be closely monitored. Comprehensive assessments have deemed these risks low within clinical use. *Risks Due to Concomitant Treatments* No specific risks from concomitant treatments are anticipated. Participant medical histories will be assessed during screening to monitor potential interactions with ongoing treatments. *Participation Risks and Safety Measures* Participants are fully informed about the study's procedures, potential risks, and lack of direct benefits, with written informed consent obtained before participation. Close monitoring will ensure adverse events are promptly addressed. Post-investigation care includes follow-up visits and immediate intervention if complications arise. *Risk-Mitigation Strategies* • Comprehensive risk analysis and procedural safeguards. • Proper training and calibration of clinical personnel. • Standardized procedures to minimize discomfort and risks. *Risk-Benefit Assessment* The minimal risks involved are outweighed by the potential benefits of improved restorative care and treatment protocols, leading to better long-term patient outcomes.
Objective(s)	*Primary Objective* The main goal of the study is to compare the frequency marginal staining of direct resin-based composite restorations in permanent anterior teeth depending on the choice of PAE protocol (standard PAE protocol or a reduced PAE duration protocol). *Secondary Objectives* The secondary goals of the study are (i) to assess the frequency of postoperative sensitivities post restoration placement, and (ii) to comprehensively evaluate the restoration quality in both groups.
Endpoint(s)	*Primary Endpoint* The primary endpoint of this study is the frequency of marginal staining in direct RBC restorations placed in permanent anterior teeth. Marginal staining will be assessed using the Category A2 guideline from the FDI criteria, incorporating the SQUACE method. *Secondary Endpoints*

	Secondary endpoints include the evaluation of pulpal hypersensitivity and pulpal status 7–10 days post-restoration using the FDI criteria (B3), as well as the assessment of various clinical, esthetic, and functional parameters of the restorations over time. These assessments, performed according to selected FDI criteria, include evaluation of surface luster, color match, caries at the restoration margin, fracture and retention, marginal adaptation, dental hard tissue defect at restoration margins, proximal contact, form and contour, occlusion, and patient satisfaction using visual analogue scales. Primary and secondary outcomes will be assessed at baseline, 1, 2, 3, and 5 years post-restoration placement.
Study Design	This study is designed as a single-center, randomized controlled trial with two parallel study arms.

Inclusion- / Exclusion Criteria	*Eligibility Criteria*
	Subjects fulfilling all of the following inclusion criteria are eligible for the investigation:
	• Signed informed consent by the participant
	• Age: 18 years or older
	• Indication: Class III or Class IV RBC restoration on anterior permanent tooth required owing to one or more of the following conditions:
	  o Proximal carious lesion with cavitation
	  o Defective restoration requiring replacement
	  o Necessary proximal reshaping owing to developmental anomalies, such as peg teeth, proximal gaps resulting from Bolton discrepancies, orthodontic tooth position, or esthetic concerns such as black triangles caused by periodontal tissue recession
	• Vital teeth with regular sensitivity
	• Sufficient language skills to understand and comply with study procedures
	• Preoperative VAS (Visual Analog Scale) scores <3 for tooth sensitivity and biting discomfort
	• Good oral hygiene, including ability to maintain effective oral hygiene
	• Clinical periodontal health on either an intact periodontium or a reduced periodontium (due to non-periodontal causes or following periodontal treatment)
	
	The presence of any one of the following exclusion criteria will lead to the exclusion of the subject:
	• Inability to achieve sufficient isolation and contamination control during restorative procedures
	• Class IV restoration necessary owing to crown fracture, crown-root fracture, extensive tooth wear, or carious lesion affecting the incisal edge
	• Missing antagonist tooth without prosthodontic replacement
	• Intent to undergo professional tooth bleaching within five years following the Class II or IV restoration. (Note: A general desire for professional tooth bleaching is not an exclusion criterion; however, any bleaching procedure must be completed at least a fortnight prior to study enrolment.)
	• Known or suspected allergy to any constituents of the materials used (e.g., methacrylates) or local anesthetics
	• Pregnancy or lactation
	• Acute or chronic health conditions that may impair study participation
	
	Note: Sex and gender dimensions are not relevant to this study for the following reasons:
	• The dental conditions requiring restorative intervention, such as proximal carious lesions or defective restorations, have comparable incidence and prevalence across sexes and genders. Instead, factors such as caries risk and socioeconomic position play a more significant role in determining the need for treatment.
	• The performance of RBC restorations is primarily influenced by material properties and clinical techniques. While biological and social characteristics—such as oral hygiene, dietary habits, and access to care—can affect treatment outcomes, these factors are independent of a patient's sex or gender.

Number of Participants with Rationale	The study includes a total of 66 individuals, with 33 participants in each study arm. An a priori sample size calculation was performed based on published data indicating expected rates of marginal discoloration. Additionally, the sample size calculation accounted for an anticipated dropout rate of 10%, which was factored into the calculation to ensure sufficient power despite potential attrition.
Study Intervention	Class III and Class IV cavities are restored with resin-based composite. The two study arms differ in the PAE regimen: one group undergoes an abbreviated PAE regimen, as part of the bonding protocol of a universal adhesive. The etchant is applied simultaneously to both enamel and dentin and is left to react for a brief 10-second period. The adhesive application after PAE, RBC placement (using a standard layering technique with separately photo-polymerized increments), and polishing procedure follow established restorative dentistry practices.
Control Intervention	The study arm in which participants' cavities receive etch-and-rinse treatment, with the phosphoric acid etchant applied to enamel for 15-30 seconds and to dentin for 10-15 seconds, serves as the control group. To ensure consistency in all aspects of the restorative procedure, except for the PAE regimen, the same universal adhesive, Adhese Universal, and RBC, Tetric plus Flow and Tetric plus Fill, are used across both study arms. Apart from the variation in the PAE regimen, all other steps of the treatment process—including isolation of the operative field and final polishing of the restoration—are standardized across both study arms.
Study procedures	Each participant will receive one or two direct RBCs. The restorations will be evaluated by a blinded assessor using the selected FDI criteria. Assessments will be conducted at baseline (7–10 days after restoration placement) and at 1, 2, 3, and 5 years post-placement. Sensitivity will be recorded using a Visual Analogue Scale (VAS). Intraoral photographs will be taken at baseline and during follow-up visits to document the restorations.
Study Duration and Schedule	The estimated duration of the main investigational plan, including participant screening, recruitment procedures, and a 5-year follow-up period, is approximately 6 years. May 2025 First-subject-in (planned) May 2031 Last-subject-out (planned)
Investigator	PD Dr. med. dent. Florin Eggmann University Center for Dental Medicine Basel UZB Department of Periodontology, Endodontology, and Cariology Mattenstrasse 40 CH-4058 Basel Phone: +41 61 267 26 80 Email: florin.eggmann@unibas.ch
Study Center(s)	The study is designed as a single-center study and will be conducted at the following site: University Center for Dental Medicine Basel UZB Department of Periodontology, Endodontology, and Cariology Mattenstrasse 40 CH-4058 Basel, Switzerland.
Statistical Considerations:	The a priori sample size calculation was performed with a significance level (α) of 0.05 and a power (1-β) of 0.80 to detect differences between groups. This calculation was based on published data reflecting expected rates of marginal discoloration. Furthermore, an anticipated dropout rate of 10% was factored into the sample size to ensure adequate statistical power despite potential attrition. Success and survival rates will be assessed and presented using Kaplan-Meier curves. To compare differences between the two study arms, the log-rank test will be employed.
Data privacy	The study ensures strict confidentiality and adherence to applicable data protection regulations, including ISO 14155, GDPR, and HIPAA standards. Participant data will be pseudonymized, with personal identifiers replaced by unique Participant IDs and securely stored in the web-based electronic data capture platform, Castor. Data entry and management follow rigorous quality control measures, including regular monitoring and validation checks. Data is stored in secure, access-controlled systems with ongoing backups. Participants' data, including medical history and clinical images, will be archived for at least 20 years in compliance with regulatory requirements. Access to the data will be restricted to authorized personnel, including study investigators and staff, with all system actions logged for accountability. Clinical data, including case report forms and informed consent forms, will be securely archived and available for inspection or audit.

	The lay summary of the trial results will be provided to participants and entered into the public register in accordance with Swiss regulations, ensuring transparency and privacy law compliance. All data will be handled with the highest discretion, with no personal identifiers included in scientific reports or presentations.
Ethical consideration	This study evaluates the impact of different PAE protocols on the durability of resin-based composite restorations in adult patients requiring Class III or IV anterior teeth restorations. The primary outcome, marginal staining, will help refine restorative procedures for better long-term outcomes. The study includes adults with common restorative needs and excludes vulnerable populations, ensuring ethical compliance. Both sexes will be included, with randomization designed to ensure an approximately equal representation of male and female participants in both study arms. The intervention involves routine, low-risk treatment. The anticipated benefits of improving restorative techniques outweigh the minimal risks, such as minor postoperative discomfort. Risk mitigation strategies, including staff training and close participant monitoring, are in place. The study will advance restorative practices, benefiting future patient care.
GCP Statement	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP, ISO 14155 (as far as applicable), the HRA as well as other locally relevant legal and regulatory requirements.

2 BACKGROUND AND RATIONALE

- PAE is widely recognized for enhancing enamel bond strength, regardless of the type of dental adhesive subsequently applied [1–3]. For dentin bonding, the use of etch-and-rinse adhesives requires the application of PAE [4]. However, when using self-etch adhesives, PAE on dentin should be avoided to prevent potential adhesion issues [4, 5].
- The introduction of universal adhesives in clinical practice has made the decision to etch dentin with phosphoric acid discretionary, allowing dental practitioners to adopt either an etch-and-rinse technique or a selective enamel etching approach [1]. The primary challenge lies in achieving selective enamel etching without inadvertently affecting the dentin [4]. Over-etching or prolonged etching of dentin can compromise adhesion and adversely impact the long-term functionality of restorations [4, 5].
- To address these concerns, reducing the duration of PAE has been proposed as a practical solution. Laboratory studies indicate that shorter PAE times do not compromise bond strength [6–11]. However, there is a notable lack of clinical evidence on the impact of reduced PAE times on the outcomes of dental restorations, highlighting the need for further investigation [4].
- This study aims to address this knowledge gap by comparing the restorative outcomes of anterior permanent teeth treated with direct resin-based restorations using either a standard PAE protocol or a reduced PAE duration protocol. The goal is to determine whether reducing the PAE duration has any impact, favorable or otherwise, on the outcomes of these restorations.

- Sex and gender dimensions are not directly relevant to this study for the following reasons:
- The dental conditions requiring restorative intervention, such as proximal carious lesions or defective restorations, have comparable incidence and prevalence across sexes and genders. Instead, factors such as caries risk and socioeconomic position play a more significant role in determining the need for treatment.
- The performance of RBC restorations is primarily influenced by material properties and clinical techniques. While biological and social characteristics—such as oral hygiene, dietary habits, and access to care—can affect treatment outcomes, these factors are independent of a patient's sex or gender.

3 STUDY OBJECTIVES AND DESIGN

3.1 Hypothesis and primary objective

- The objectives of this study are to evaluate the effect of different PAE regimens on the outcomes of direct RBC restorations in permanent anterior teeth. The study will compare two different PAE protocols—shortened and unabbreviated PAE duration—focusing on key restoration outcomes.

- The study operates under the null hypothesis, which posits that there is no difference in restorative outcomes between the shortened and unabbreviated PAE protocols.
-
- The secondary objectives of the study are the following:
- To assess the frequency of postoperative hypersensitivity after restoration placement in both study arms.

- To comprehensively evaluate the overall restoration quality in both groups using the selected FDI criteria.

3.2 Primary and secondary endpoints

- The primary outcome of this study is the frequency of marginal staining in direct RBC restorations placed in permanent anterior teeth, with respect to the choice of PAE protocol. The two protocols being compared are the unabbreviated PAE protocol and a reduced PAE duration protocol. Marginal staining will be assessed using the Category A2 assessment guideline from the FDI criteria, incorporating the SQUACE method [12–14].

- Rationale for the Primary Outcome:
- Marginal staining is a key indicator of the long-term durability and clinical performance of resin-based composite restorations, as it directly reflects the quality of the bond at the interface between the restoration and tooth structure [2, 12]. By comparing the frequency of marginal staining between the two PAE protocols, this study aims to determine whether reducing the PAE duration influences the occurrence of marginal staining and, consequently, the long-term effectiveness of the restorations. This outcome is critical for evaluating the impact of PAE protocols on restoration quality and longevity.

Additionally, the restorations will be comprehensively assessed according to selected FDI criteria, which are widely recognized as reliable parameters for evaluating the long-term performance of dental restorations [12]. The following FDI criteria will be used to evaluate the direct RBC restorations in this clinical investigation:

- Surface luster and surface texture (FDI A1)
- Color match (FDI A3)
- Caries at the restoration margin (FDI B1)
- Dental hard tissue defects at the restoration margin (FDI B2)
- Pulpal hypersensitivity and pulpal status (FDI B3)
- Fracture of material and retention (FDI F1)
- Marginal adaptation (FDI F2)
- Proximal contact point (FDI F3)
- Form and contour (FDI F4)
- Occlusion and wear (FDI F5)
- Patient’s view (FDI M1)

Explanation of Outcome Measures:

- Esthetic Outcomes (A1, A3): Color match, surface luster, and texture are secondary outcomes that assess the aesthetic quality of the restoration. Surface luster also indicates the material’s ability to resist plaque accumulation and maintain its appearance over time.
- Clinical Performance Outcomes (F1, F2, F3, B1, B2, B3):
    - Fracture and Retention (F1): This criterion evaluates the fracture rate of the material and the retention of the restoration, providing insights into the clinical performance of the bond between the restoration and the tooth structure.
    - Marginal Quality (F2, B1, B2): Marginal adaptation, caries at the restoration margins, and dental hard tissue defects provide critical information on the quality of the bond between the tooth structure and the RBC.
    - Pulpal hypersensitivity and pulpal status (FDI B3): This criterion allows an assessment of potential postoperative hypersensitivity, reflecting the dental pulp's response to the restorative treatment.

- Functional Outcomes (F3, F4, F5):
    - Proximal Contact Point (F3), Form and Contour (F4), and Occlusion and Wear (F5): These secondary outcomes reflect the physical properties of the material, its ability to maintain its form under clinical conditions, and its resistance to occlusal forces over time.

These outcomes will be assessed through visual examination, including short air drying, as specified in the FDI criteria [12]. All evaluations will be performed with magnifying loupes, and dental examination probes with predefined tip widths (i.e., 250-µm probes) will be used to evaluate surface quality and the transition between the tooth and the filling. For FDI criteria F2, B1 and B2, the percentage of affected margin will be estimated and recorded in the eCRF using the SQUACE (Semi Quantitative Clinical Evaluation) method, as described by Hickel et al. (2007) [13, 14].
To standardize the assessment of proximal contact points (FDI F3), visual evaluations will be supplemented with testing using metal matrices of standard thicknesses (i.e., 25-µm, 50-µm, and 100-µm matrices).
Patient satisfaction with the restoration will be evaluated using a visual analogue scale (VAS), with whole-number scores ranging from 0 to 10. On this scale, a score of 0 indicates "no satisfaction" (completely dissatisfied), while a score of 10 represents "maximum satisfaction" (completely satisfied). The scale allows patients to express their overall satisfaction with the restoration in terms of both function and esthetics.
Secondary outcomes will be assessed at baseline (7–10 days), and at 1, 2, 3, and 5 years post-placement, with all data recorded in the eCRF for the corresponding visits.

3.3 Study design

- This study is a single-center, randomized controlled trial with two parallel study arms designed to assess the performance of restorative resin-based composite materials in Class III and IV cavities of permanent anterior teeth. The study aims to evaluate the impact of two phosphoric acid etching (PAE) protocols—conventional etch-and-rinse and a reduced PAE duration protocol—on the outcomes of resin-based composite restorations. The design addresses a critical knowledge gap regarding the clinical effectiveness of shortened PAE times, operating under the null hypothesis that no significant difference exists between the two protocols in terms of restorative outcomes.

- Type of Study Design
- *Blinding:* The study incorporates a blinded evaluation process where the assessors remain unaware of the intervention allocation. The operators are not blinded, as the interventions involve different PAE times. Study participants are blinded to their assigned intervention.
- *Comparator:* The control group receives the conventional etch-and-rinse treatment, while the test group undergoes the reduced PAE duration protocol. Both groups utilize the same adhesive application and resin-based composite materials.
- *Allocation Ratio:* Participants are allocated in a 1:1 ratio to the two study arms.
- *Framework:* The study adopts a non-inferiority framework to determine whether the shortened PAE protocol yields outcomes comparable to the conventional protocol.
-
- Recruitment and Screening
- Participants will be recruited from the patient base at UZB, with eligibility determined based on predefined inclusion and exclusion criteria. Eligible participants will provide signed informed consent and undergo a detailed medical anamnesis and dental

examination.

Randomization
Participants will be randomized using a computer-generated random sequence, ensuring an equal probability of assignment to either the intervention or control group. The sequence will be generated by the randomized allocation feature of Castor. To minimize potential biases, stratification based on key baseline characteristics—such as age, gender, and required restoration class—will be employed. This stratification ensures an even distribution of these variables across both groups, enhancing their comparability.
Block randomization with variable block sizes will be used to maintain a balanced allocation throughout the enrollment period while preventing predictability of upcoming assignments.

- Baseline Assessment and Treatment
- Participants will receive one or two direct resin-based composite restorations following established restorative dentistry practices. Restorations are applied by a trained operator using a standard layering technique with separately photo-polymerized increments.
-
- Interventions
- *Control Group:* Unabbreviated etch-and-rinse treatment involves applying phosphoric acid etchant to enamel for 15–30 seconds and to dentin for 10–15 seconds.
- *Test Group:* Reduced PAE duration involves a shorter etching time for both enamel and dentin.
-
- Follow-Up and Evaluation
- Restorations are assessed by a blinded evaluator at baseline (7–10 days after placement) and at 1, 2, 3, and 5 years post-placement. Marginal staining is evaluated using the FDI criteria (Category A2, SQUACE method). Postoperative sensitivity is recorded using a Visual Analog Scale (VAS). Intraoral photographs are taken during each follow-up visit.

- Blinding Procedures
- Owing to the nature of the restorative procedures, it is not feasible to blind the operators performing the treatments. However, to minimize bias, several measures are implemented. Study participants will remain unaware of their group allocation throughout the study. Operators will standardize their handling of the etchant syringe in both the control and test groups, ensuring that the visible duration of the procedure remains identical, while the actual PAE duration of dental hard tissues is performed according to the assigned protocol. Additionally, both the operators and dental assistants will take care to avoid providing any visual or verbal cues during treatment that could reveal group allocation. Since participants cannot see their own dental arch during the procedure, they are unable to assess the duration of PAE, effectively maintaining blinding.
- The investigator responsible for outcome assessment will be blinded to the group allocation, ensuring impartial evaluation of the results.
- The statistician conducting the data analysis will also be blinded to the group assignments to prevent any bias in the statistical interpretation.
- This approach helps ensure the integrity of the study by minimizing potential biases related to treatment allocation and outcome evaluation.
-

Unblinding Procedures
Unblinding will be permissible in the following situation:

- Suspension or Premature Termination of the Study: In the event of study suspension or premature termination, unblinding may be performed to facilitate the completion of data

analysis or to ensure proper follow-up care for participants. The process will be carried out by authorized personnel, with clear documentation to ensure transparency.

- Emergency Safety Events: In the case of a serious safety concern or medical emergency, unblinding must be conducted immediately to determine the treatment the affected participant received. The process will be carried out by authorized personnel, with clear documentation to ensure transparency.

All unblinding procedures will be performed with strict adherence to ethical and procedural guidelines to protect the integrity of the data and the safety of the participants.

- Duration of Subject Participation
- From the screening and recruitment phase, estimated to last approximately 12 months, the study spans five years, with participants involved in the following phases:
- Baseline treatment and initial evaluation (7–10 days post-placement)
- Follow-up evaluations at 1, 2, 3, and 5 years post-placement
-
- Population and Sample Size
- The study targets adult participants (18 years or older) requiring Class III or IV resin-based composite restorations in permanent anterior teeth. The total sample size is 66 individuals, divided equally between the two study arms (33 participants per arm). A sample size calculation accounting for a 10% dropout rate ensures sufficient power to detect differences in outcomes.
-
- Known or Potential Problems and Limitations
- *Dropout Rate:* Participant attrition over the five-year follow-up period may affect data completeness. This risk is mitigated by recruiting a sample size larger than the minimum required for statistical power.
- *Blinding Limitations:* Though assessors are blinded, the lack of blinding among participants and operators may introduce bias. This risk is minimized through strict adherence to standardized procedures.
- *Heterogeneity in Restorative Needs:* Variability in cavity size and tooth condition may influence outcomes. However, the inclusion and exclusion criteria ensure a relatively homogenous study population.
- *Limited Generalizability:* The single-center design may limit the applicability of findings to other clinical settings.

3.4. Study intervention

This study is a randomized controlled trial with two arms, designed to investigate the impact of two different PAE protocols on the clinical outcomes of direct RBC restorations in permanent anterior teeth in adults. The study consists of the following two groups:

- Control Group (unabbreviated PAE duration):
    - Phosphoric acid etchant is applied to enamel for 15-30 seconds and to dentin for 10-15 seconds.
- Test group (reduced PAE duration):
    - Phosphoric acid etchant is applied simultaneously to both enamel and dentin for a reduced duration of 10 seconds.

The only difference between the two groups lies in the duration of the PAE step. All other aspects of the restorative procedure, including adhesive selection, composite materials, and restorative techniques, remain consistent across both groups.

4 STUDY POPULATION AND STUDY PROCEDURES

4.1 Inclusion and exclusion criteria, justification of study population

Eligibility Criteria

Subjects fulfilling all of the following inclusion criteria are eligible for the investigation:

- Signed informed consent by the participant
- Age: 18 years or older
- Indication: Class III or Class IV RBC restoration on anterior permanent tooth required owing to one or more of the following conditions:
    - Proximal carious lesion with cavitation
    - Defective restoration requiring replacement
    - Necessary proximal reshaping owing to developmental anomalies, such as peg teeth, proximal gaps resulting from Bolton discrepancies, orthodontic tooth position, or esthetic concerns such as black triangles caused by periodontal tissue recession
- Vital teeth with regular sensitivity
- Sufficient language skills to understand and comply with study procedures
- Preoperative VAS (Visual Analog Scale) scores <3 for tooth sensitivity and biting discomfort
- Good oral hygiene, including ability to maintain effective oral hygiene
- Clinical periodontal health on either an intact periodontium or a reduced periodontium (due to non-periodontal causes or following periodontal treatment)

The presence of any one of the following exclusion criteria will lead to the exclusion of the subject:

- Inability to achieve sufficient isolation and contamination control during restorative procedures
- Class IV restoration necessary owing to crown fracture, crown-root fracture, extensive tooth wear, or carious lesion affecting the incisal edge
- Missing antagonist tooth without prosthodontic replacement
- Intent to undergo professional tooth bleaching within five years following the Class II or IV restoration. (Note: A general desire for professional tooth bleaching is not an exclusion criterion; however, any bleaching procedure must be completed at least a fortnight prior to study enrolment.)
- Known or suspected allergy to any constituents of the materials used (e.g., methacrylates) or local anesthetics
- Pregnancy or lactation
- Acute or chronic health conditions that may impair study participation

Justification for Study Population

Study Population

The investigation population for this study consists of adult patients in need of one or two direct Class III or Class IV RBC restorations in the anterior permanent teeth. Class IV restorations are specifically limited to cases requiring proximal reshaping, excluding those involving crown fractures, crown-root fractures, extensive tooth wear, or carious lesions affecting the incisal edge. The rationale for selecting this population is based on the fact that the outcomes of RBC restorations are most relevant for individuals with common anterior restorative needs, allowing for an accurate assessment of the effect of different PAE protocols on marginal staining and restoration quality [2].

The study population is intended to be representative of the target population of patients requiring anterior restorations. By focusing on individuals who require Class III or Class IV restorations, the results are likely to be applicable to a broad range of patients with common restorative needs [2]. The exclusion criteria ensure that the study population is appropriate for evaluating the

comparative effects of PAE regimens without confounding factors, such as underlying health conditions or severe dental issues that could skew the results.

Vulnerable Subjects

This study does not involve vulnerable populations such as minors, subjects incapable of judgment, or individuals under tutelage. All participants are adults capable of maintaining effective oral hygiene practices. Given the nature of the study—investigating the effect of different PAE protocols on restorative outcomes in adult patients—there is no clinical necessity for the inclusion of vulnerable subjects. The decision to focus on adults ensures the scientific rigor of the study and minimizes ethical concerns related to informed consent and the ability to participate fully in the study procedures.

Sex and Gender Considerations

The recruitment strategy ensures the inclusion of both male and female participants to achieve a balanced representation of sex and gender. The dental conditions requiring restorative intervention, such as proximal carious lesions or defective restorations, occur with similar frequency across sexes and genders. Therefore, sex and gender are not expected to be confounding variables in the study, and the inclusion of both sexes will allow for a comprehensive assessment of the study outcomes.

The randomization process will account for important baseline characteristics, such as age and required restoration class, to ensure that both male and female participants are equally represented in both study arms. While the study does not focus specifically on sex or gender differences, these factors will be considered during statistical analysis to ensure that any potential differences between groups are accounted for and do not impact the validity of the study's results.

Representative Study Population

In summary, the study population has been carefully selected to ensure it is representative of the target group of adult patients requiring restorative treatment for anterior teeth. No vulnerable populations are included, and appropriate steps are taken to ensure sex and gender balance, in line with the guidelines for equitable research practices.

4.2 Recruitment, screening and informed consent procedure

- Recruitment of Study Participants
- Participants for this study will be recruited from the existing patient pool at the UZB, consisting of individuals who already receive regular dental care at UZB. During routine check-ups, treating dentists will evaluate whether patients meet the study's inclusion criteria, particularly the need for Class III or IV resin-based composite restorations in permanent anterior teeth.
- Eligible patients will receive comprehensive information about the study and be invited to participate. Efforts will be made to achieve a balanced gender distribution among participants, with 40–60% of participants being female.
- To ensure an ethical and transparent recruitment process, patients will be given ample time to consider their participation and consult with relatives or other advisors, in alignment with the Swissethics guidelines. Patients will receive comprehensive verbal and written information about the study, including its purpose, procedures, potential risks, and expected benefits.
- As the intervention is low-risk and involves a routine, well-established restorative procedure, the informed consent process may occur on the same day as the treatment. This approach is consistent with the recommendations outlined in the Swissethics position paper. However, if a longer consideration period is requested by the participant or deemed beneficial to their decision-making process, it will be accommodated. The time allotted for consideration will be tailored to each participant, ensuring they can make an informed,

unpressured decision.

-
- *Recruitment Strategy*
- *Study Participants:* Participants will be recruited from the regular patient pool at UZB, where they are already receiving ongoing dental care.
- *Compensation*
    - Participants will cover the cost of resin-based composite restorations performed during the study, following the standard fee-for-service reimbursement model for dental care in Switzerland. Payment may be made out-of-pocket, through insurance, or via welfare or benefits, depending on individual circumstances.
    - For follow-up appointments required for study outcome assessments (not part of regular recall schedules), participants will receive compensation of CHF 90.00 per hour. Shorter appointments will be compensated on a prorated basis.
    - Additionally, travel expenses for study visits will be reimbursed up to CHF 50.00 for second-class public transportation, specifically for the baseline assessment appointment.
- *No Additional Financial Incentives:* No other financial incentives will be provided, ensuring that participants' involvement is motivated by a genuine interest in contributing to the study, rather than financial compensation.

-
- *Recruitment Period*
- The recruitment period is anticipated to span 12 months, providing sufficient time for the identification, screening, and enrollment of participants.

- *Screening Requirements*
- As part of the routine comprehensive dental care at UZB, potential participants will undergo a thorough screening process to confirm their eligibility. This will include the following:
- A detailed dental anamnesis.
- A clinical examination to verify the need for Class III or IV resin-based composite restorations.
- An evaluation of their overall oral health status.
- Screening results will be carefully documented in the participants' medical records, independently of the study.

- *Compensation and Benefits*
- As outlined above, participants will receive reimbursement for travel expenses related to study visits, as well as CHF 90.00 per hour for any follow-up appointments required for study-related outcome assessments. This baseline assessment appointment is not part of the participant's regular recall schedule and is essential for the study's data collection. Additionally, the baseline assessment will be provided free of charge. No other financial incentives will be offered, ensuring that participation is driven by genuine interest in contributing to the research.

-
- *Timeline for Inclusion of the First Study Participant and Trial Continuation Procedures*
- The first study participant must be included in the trial within two years following the issuance of the authorization by the Ethics Committee. An application for an extension is a substantial amendment; in the event of non-compliance, the study is deemed interrupted.

The investigator or the sponsor notifies the Ethics Committee of the first study participant, in accordance with art 62 lit. c ClinO, resp. art 38 ClinO. If the first participating person is not included in the trial within two years following the issuance of the authorization, the trial is considered interrupted (art. 23a ClinO). The clinical trial may not be commenced until an application for an extension of the time limit has been approved. The application for the extension is submitted to the CEC as a substantial amendment.

4.3 Study procedures

Appendix Table 1 presents an overview of the study assessments, while Appendix Table 2 outlines the investigational flowchart in detail.

Screening Visit

- Day: -30 to -0
- Duration: approximately 0.5 hours

During the screening visit, participants will undergo a routine dental check-up to assess potential eligibility for the study. If eligibility criteria are met, the following procedures will be performed:
Participant Information and Consent:

- Participants will be provided with a comprehensive explanation of the study, including its scope, duration, sequence of events, and objectives.
- Detailed information about the investigational medical device will be shared, covering its application, indications, contraindications, benefits, and potential risks associated with the restorative procedure.
- Each participant will receive a patient information sheet and an Informed Consent Form (ICF), which provide a detailed description of the study and its associated risks and benefits.

Decision Period and Support:

- Participants will have up to 30 days to decide about their participation in the study.
- If additional clarification or information is required, an additional visit lasting approximately 0.5 hours can be scheduled.

Note:
Considering the low-risk nature of the intervention, which involves a routine, well-established restorative procedure, the informed consent process may be completed on the same day as the treatment. This approach aligns with recommendations outlined in the relevant Swissethics position paper. However, participants may request an extended consideration period if they feel it is necessary for their well-being.

Visit 1: Restoration Visit

- Day: 0
- Duration: approximately 0.75 - 1.5 hours

Preoperative Hypersensitivity
The sensibility of the tooth to thermal stimuli and biting will be evaluated by the patient using a Visual Analogue Scale (VAS) slider. Whole-number scores ranging from 0 to 10 will be recorded, where 0 signifies "no pain at all," and 10 represents "the worst pain imaginable."

Intraoral Photographs
Standardized intraoral photographs will document the tooth requiring restorative treatment and the anterior teeth within the same dental arch. Flash photographs will be captured from occlusal, buccal, and oral views, both with and without marked occlusion or articulation points, to ensure comprehensive visual records. The following equipment and settings will be used for flash photographs: aperture F29, shutter speed 1/400, and ISO 100 (camera, Canon EOS 77D; lens,

Canon Macro Lens EF 100 mm [both from Canon, Tokyo, Japan], ring flash, Nissin MF18 Macro [Nissin Digital, Tokyo, Japan]).

Dental photography mirrors will be used as needed.

Pulp Sensitivity Test
Pulp sensitivity will be assessed by applying a cold stimulus (carbon dioxide snow) to the cervical area of the facial aspect of the tooth requiring treatment.

Shade Determination
The operator will determine the tooth shade at the start of the dental visit during which the restorative treatment is performed. This will be done using the Vita A-D Shade Guide and a material-specific shade guide (Tetric Plus Fill & Flow). The process will be conducted on a cleaned, moist tooth, with shade guide tabs placed next to it to select the shade that best matches the restoration.

Cavity Preparation
Local anesthesia will be administered as needed, based on the patient's preference and the clinical situation. Either a rubber dam or a dental lip and cheek retractor system (OptraGate, Ivoclar, Schaan, Liechtenstein) will be used to ensure isolation and soft tissue protection.
The cavity preparation will adhere to the principles of adhesive dentistry, shaped to follow the extent of the carious lesion or the failing restoration. Additional undercuts or retentions will not be prepared in caries-free areas. Cavity margins will be beveled (approximately 0.5 mm and 1-2 mm in lingual and facial aspects, respectively) using diamond rotary instruments (25–40 µm). A photograph of the prepared cavity will be taken.
If not already in place, a rubber dam will be applied following cavity preparation. Dental floss ligatures will be employed if necessary.

Matrix Application
The selection and application of the matrix system are based on individual case requirements and are at the discretion of the operator. The following matrix systems may be used, either alone or in combination: segmental metal matrices, Mylar strip matrices, and transparent matrix systems [2]. The operator may modify the matrices as needed to ensure optimal marginal adaptation and contour. Wooden or plastic dental wedges will be used whenever possible to position and secure the matrix. Alternatively, or in addition, other fixation methods, such as the use of RBC on the adjacent tooth—applied without PAE or adhesive—may also be employed.

Pulp Protection
In cases where minimal residual dentin thickness is present, a pulp protection agent, such as a calcium hydroxide-based liner (Ultrablend Plus, Ultradent, South Jordan, UT, USA), may be applied to protect the underlying pulp tissue. The decision to use a pulp protection agent is at the discretion of the operator. Any use of a pulp protection agent will be documented in the eCRF.

PAE Regimen
The etching regimen will vary between the two study arms to evaluate the impact of different protocols.
In one study arm, an abbreviated etching regimen will be employed. The etchant (Total Etch, Ivoclar, Schaan, Liechtenstein) will be applied simultaneously to both enamel and dentin and left to react for a concise duration of 10 seconds. Afterward, the etchant will be thoroughly rinsed off with a vigorous stream of water for at least 5 seconds. The surface will then be dried using oil-free, moisture-free compressed air to ensure proper preparation for adhesive application.
In the other study arm, the standard PAE protocol will be followed. This protocol will involve etching durations of 15–30 seconds for enamel and 10–15 seconds for dentin with Total Etch. Following the prescribed etching period, the etchant will be rinsed off with a vigorous stream of

water for at least 5 seconds. The surface will subsequently be dried using oil-free and moisture-free compressed air, ensuring optimal conditions for the application of the adhesive.

Adhesive Application
A universal adhesive (Adhese Universal, Ivoclar, Schaan, Liechtenstein) will be applied to the cavity surfaces, starting with the enamel and then the dentin. The adhesive will be agitated for 20 seconds, followed by dispersal with an oil- and water-free air stream until no movement of the adhesive layer is observed. It will then be light-cured from the occlusal side for 5 seconds using the Bluephase PowerCure (Ivoclar, Schaan, Liechtenstein) light-curing unit in Turbo mode (2000 mW/cm^2).

Application of the Resin-Based Composite Tetric plus Fill and Tetric plus Flow
Tetric plus Flow, Tetric plus Fill, or both will be applied in layers according to the individual case requirements, with the choice of material and the order of application left to the discretion of the operator performing the treatment. The layering technique will be tailored to ensure maximal increment thickness allowances are respected, while optimizing the C-factor configuration and ensuring proper restoration adaptation and contour [2]. The increments will be sculpted to achieve the desired anatomy using instruments such as OptraSculpt Pad and OptraSculpt (Ivoclar, Schaan, Liechtenstein). Each increment, whether Flow or Fill, will be light-cured for 5 seconds using the Bluephase PowerCure unit in Turbo mode to ensure optimal polymerization and restoration quality.

Finishing and Polishing
The matrix system will be removed, and any excess material will be trimmed using a scalpel blade (No. 12D), fine-grit diamond rotary instruments (25 µm), polishing disks, or a combination of these tools. High-gloss polishing will be performed using OptraGloss VP and OptraGloss HP polishers (Ivoclar, Schaan, Liechtenstein). Static and dynamic occlusion will be checked using articulating paper after the rubber dam is removed [2]. Premature contact points and interferences will be adjusted as necessary [2].

Documentation and Adverse Event Reporting
All materials used during the procedure will be recorded in the eCRFs. Adverse events and device deficiencies will also be assessed and documented in the eCRFs.

Postoperative Instructions
Patients will receive instructions on postoperative care, including guidelines on food and beverage intake and oral hygiene practices. Special emphasis will be placed on precautions owing to lingering local anesthesia effects.

Visit 2: Restoration Baseline Assessment

- Day: + 7-10
- Duration: approximately 0.3 – 1.0 hour

During this visit, the esthetic integration of the restoration will be evaluated by the operator who placed the restoration. The occlusion will be checked and, if necessary, adjusted, followed by repolishing using OptraGloss VP and OptraGloss HP polishers. Any adjustments to the occlusion or re-polishing based on baseline findings are standard practice and will be considered part of the restorative procedure. These adjustments will be performed by the operator who placed the restoration and will be documented in the eCRF.

A blinded evaluator will assess postoperative hypersensitivity by evaluating the intensity of pain in response to thermal stimuli and occlusion, using the Visual Analogue Scale (VAS) (Figure 1).

Fig. 1 VAS slider for the assessment of subjective postoperative hypersensitivity

The evaluator will take standardized intraoral photographs to document the restored tooth and the anterior teeth within the same dental arch. The evaluator will visually and with tactile inspection using a dental probe examine the restoration, under optimal lighting and with the aid of magnifying loupes. The primary and secondary outcome parameters will be assessed according to the FDI criteria [12]. All measurements will be recorded in the baseline eCRF.

Any adverse events or device deficiencies will be assessed and documented in the eCRFs.

Visit 3, 4, 5, and 6: Follow-Up at 1, 2, 3, and 5 Years Post-Placement

- Year(s): + 1, 2, 3, and 5 years
- Duration: approximately 0.5 hour

During the annual follow-up appointments, a blinded evaluator will assess hypersensitivity by evaluating the intensity of pain in response to thermal stimuli and occlusion, using the VAS. The pulp status of the tooth will be evaluated.

Standardized intraoral photographs will be taken to document both the restored tooth and the anterior teeth within the same dental arch. The restoration will be examined visually and with tactile inspection using a dental probe, under optimal lighting conditions and with the aid of magnifying loupes. The primary and secondary outcome parameters will be assessed in accordance with selected FDI criteria [12]. All measurements will be recorded in the respective eCRF.

Any adverse events or device deficiencies will be assessed and documented in the eCRFs.

4.4 Withdrawal and discontinuation

Subjects may be withdrawn from the investigation under the following circumstances:

- Voluntary Withdrawal: If a participant no longer wishes to continue with the trial, they may withdraw at any time without providing a reason.
- Safety Concerns: Withdrawal will occur if safety concerns arise, such as allergic reactions to components of the filling material.
- Logistical Barriers: Participants are unable to attend scheduled recall visits will be withdrawn from the study.

Procedures for Withdrawal and Replacement

- If a participant withdraws before all baseline examinations are completed, they will be replaced with a new participant to ensure the study maintains its required sample size.
- If withdrawal occurs after the completion of all baseline examinations, the participant will not be replaced.

Investigation and Intervention Discontinuation

The investigation may be discontinued in the following situations:

- Voluntary Withdrawal: A participant requests to cease participation.
- Non-Compliance: Participants failing to adhere to the protocol requirements or missing critical study visits may result in discontinuation.
- Safety Concerns: The study or intervention will be discontinued if safety concerns arise that pose risks to participants' health.

Assessments for Subjects Who Prematurely Discontinue the Clinical Investigation

For subjects who withdraw or drop out from the investigation prematurely, a final follow-up dental examination will be conducted to assess their clinical status, including the evaluation of adverse events, restoration performance, and overall oral health. Any adverse events reported by the participant will be recorded, including details such as onset, duration, resolution, and their relationship to the investigational device or procedures. Additional assessments, such as pulp vitality testing or radiographic evaluation, may be conducted as deemed clinically necessary.

The follow-up period for withdrawn subjects extends up to the final data collection at the time of withdrawal. Data collected from these subjects until the point of withdrawal will be included in the analysis, provided consent for the use of their data has not been explicitly revoked. If a participant revokes their consent, all data collected up to that point will be anonymized prior to analysis.

After the analysis is completed, anonymized data will be securely stored and handled in accordance with data protection regulations. This ensures compliance with ethical standards and guarantees the confidentiality of participant information. These procedures align with the details provided in the patient information and consent form.

If additional care is required due to a participant's involvement in the investigation, such as addressing adverse effects related to the investigational procedure or materials, these needs will be met as part of the post-investigation follow-up. This care will be provided at no additional cost to the participants and goes beyond the standard dental care typically expected for their condition.

All participants in this study are regular patients at UZB. Regardless of whether their participation ends prematurely or upon regular study completion, they will continue to be offered the necessary dental treatments and routine check-up examinations at UZB without prejudice or interruption.

5 STATISTICS AND METHODOLOGY

5.1. Statistical analysis plan and sample size calculation

Statistician

The following statistician is responsible for providing statistical guidance throughout all phases of the study, including its conception, design, and data analysis:

Dr. Urs Simmen

Simmen - Statistical Consulting

Malzgasse 9

CH-4052 Basel

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Hypothesis

Null Hypothesis (H_0): There is no statistically significant difference in the restorative outcomes of anterior permanent teeth treated with direct resin-based restorations when comparing the standard PAE protocol to a reduced PAE duration protocol.

Alternative Hypothesis (H_1): There is a statistically significant difference in the restorative outcomes of anterior permanent teeth treated with direct resin-based restorations between the standard PAE protocol and the reduced PAE duration protocol.

The primary endpoint for evaluating these hypotheses will be the clinical measure of marginal discoloration rates. This endpoint is highly relevant for the subject population, as it directly reflects treatment effectiveness and patient benefit.

Justification: The stated hypothesis is grounded in the investigation objective of determining whether reducing the PAE duration impacts restorative quality. The justification for testing this hypothesis lies in its potential to optimize clinical protocols. Given the direct applicability of the findings to everyday dental practice, this investigation is particularly relevant for dental practitioners and patients alike.

Determination of Sample Size

An a priori power calculation was performed to determine the appropriate sample size for this study. The calculation was based on detecting a clinically significant difference in the primary outcome, marginal staining (Category A2 from the modified FDI criteria), between the two study arms.

The following assumptions were used for the power calculation:

- The expected incidence of marginal staining in the standard phosphoric acid etching (PAE) protocol arm is 2.4%, while the reduced PAE duration arm is estimated to have an incidence of 19.5%. These estimates are derived from a previous clinical study investigating the adhesive Adhese Universal in different etching modes.
- A clinically relevant difference of 5% or greater in marginal staining incidence between the study arms was considered significant.
- The anticipated dropout rate is 10%, which was incorporated into the sample size calculation to account for potential attrition and ensure adequate statistical power.
- The calculation assumes a significance level (α) of 0.05 and a power (1-β) of 0.80 to detect differences between groups.
- The sample size was calculated using the following formula:
    - $n = ((Z\alpha/2+Z\beta)2\cdot(p1\cdot(1-p1)+p2\cdot(1-p2)))/(p1-p2)2$
- Substituting the assumed parameters into the formula:
- $n = ((1.96+0.84)2\cdot(0.195\cdot0.805+0.024\cdot0.976))/(0.195-0.024)2 \approx 48.45$
- Based on data from the Department of Periodontology, Endodontology, and Cariology at the University Center for Dental Medicine Basel (UZB), most patients typically receive two or more Class III restorations in a single appointment. Given that approximately 49 restorations are needed in each study arm, we estimate that 11 individuals will require a single restoration, while 19 will require two restorations. This results in a sample size of 30 individuals per study arm.
- Adjusted Sample Size:
    - Considering a 10% dropout rate, the adjusted sample is as follows
        - $n = 30/(1-0.10) \approx 33$
        - Thus, the required sample size per group is approximately 33 individuals, for a total of 66 individuals across both study arms.

Clinical and Statistical Assumptions

The clinical assumption is that a clinically relevant difference in marginal staining incidence can be detected between the two study arms, with the expected incidence rates based on prior studies.

The statistical assumptions include the use of a significance level (α) of 0.05 and a power (1-β) of 0.80 to detect the difference, with a 10% expected dropout rate factored into the calculation to

maintain sufficient power.

The total sample size required for this study is 66 individuals, with 33 participants in each study arm. The sample size calculation, based on clinical and statistical assumptions, ensures that the study has adequate power to detect meaningful differences in the primary outcome, marginal staining, while accounting for potential participant attrition.

Sex and Gender Considerations

Sex and gender dimensions are not directly relevant to this study for the following reasons:

- The dental conditions requiring restorative intervention, such as proximal carious lesions or defective restorations, have comparable incidence and prevalence across sexes and genders. Instead, factors such as caries risk and socioeconomic position play a more significant role in determining the need for treatment.
- The performance of RBC restorations is primarily influenced by material properties and clinical techniques. While biological and social characteristics—such as oral hygiene, dietary habits, and access to care—can affect treatment outcomes, these factors are independent of a patient's sex or gender.

Planned Analyses

The statistical analysis for this study will be conducted by a qualified statistician, using R software (R Core Team, R Foundation for Statistical Computing, Vienna, Austria). The primary analyses will focus on the success and survival rates of the resin-based composite restorations, which will be calculated and presented using Kaplan-Meier survival curves. The log-rank test will be applied to compare differences between the two study arm groups (standard PAE protocol vs. reduced PAE duration protocol).

The statistical analysis will be performed using the final dataset once all follow-up data are collected. Any interim analyses, if applicable, will be specified in the final statistical analysis plan (SAP), which will be developed after finalizing the CIP. The SAP will outline detailed methods, variables to be analyzed, and the timing of the analyses.

Primary Analysis

The analysis of the primary outcome will be conducted in several stages:

- Preliminary Analysis: Performed immediately after baseline assessments to establish the initial status of restoration quality.
- Interim Analyses: Conducted at the 1-year, 2-year, and 3-year follow-up visits.
- Final Analysis: Performed at the completion of the 5-year follow-up.

The primary outcome will be evaluated using the Category A2 assessment guideline from the FDI criteria, incorporating the SQUACE method [12–14]. The results will be standardized into FDI scores for consistent evaluation [12–14].

The primary analysis will be carried out by statistician Dr. Urs Simmen within three months of data collection completion.

Secondary Analyses

The analysis of the secondary outcomes will be conducted in several stages:

- Preliminary Analysis: Performed immediately after baseline assessments to establish the initial status of restoration quality and clinical signs.
- Interim Analyses: Conducted at the 1-year, 2-year, and 3-year follow-up visits.
- Final Analysis: Performed at the completion of the 5-year follow-up.

The secondary outcome, postoperative hypersensitivity, will be specifically evaluated based on FDI Criterion B3, which considers hypersensitivity of clinical relevance. A one-sided binomial

exact test will be applied to determine whether the postoperative hypersensitivity rate remains below 10%.

- Pass Criterion: If the postoperative hypersensitivity rate is below 10%, the reduced PAE duration protocol will be deemed clinically acceptable based on this outcome.
- Fail Criterion: If the postoperative hypersensitivity rate is 10% or higher, the reduced PAE duration protocol will not meet the predefined threshold for clinical acceptance.

Only FDI Grades 3-5 will be classified as cases of postoperative hypersensitivity, as Grade 2 is considered self-limiting, clinically insignificant, and does not require intervention.

The secondary analysis will also be conducted by a statistician, Dr. Urs Simmen, within three months after data collection is completed.

Interim Analyses

The interim analysis will be conducted to monitor early trends in the data, ensuring patient safety, assessing the effectiveness of the protocols, and identifying any potential need for protocol modifications. This analysis is critical for verifying that the study is proceeding as planned and that no unexpected safety concerns arise.

Interim analyses will occur after data collection at each scheduled baseline assessment visit.

The scope of the interim analysis includes:

- Monitoring safety outcomes, particularly the occurrence and severity of postoperative hypersensitivity, as indicated by FDI Criterion B3.
- Ensuring data completeness and protocol adherence.

The interim analysis will primarily focus on descriptive statistics to summarize key outcomes, in particular hypersensitivity rates. A one-sided binomial exact test may be applied if early signals regarding hypersensitivity rates warrant a formal evaluation. Adjustments for multiple testing will not be implemented for interim analyses because they are exploratory in nature and not intended to affect final conclusions.

Data Monitoring Committee (DMC) and Stopping Guidelines

Given the small-scale nature of this study, a formal Data Monitoring Committee (DMC) will not be established. Instead, the PI will oversee the interim analyses and ensure adherence to ethical and scientific standards. Stopping guidelines will include:

- Ethical Stopping Rules: If interim results indicate a hypersensitivity rate exceeding 20% across all patients, the study will be paused for a safety review.
- Operational Stopping Rules: If substantial protocol violations or data integrity concerns are identified, the study may be temporarily halted for corrective measures.

The interim analyses will be performed by the PI, leveraging anonymized data sets to ensure impartiality. Results will be documented and reviewed within two weeks of each recall visit.

No statistical adjustments will be made to account for interim analyses in the final evaluation. The interim analyses will solely guide ongoing monitoring and safety oversight.

Deviation(s) form the Original Statistical Plan

Any deviations from the original statistical plan will be documented, reported, and justified as follows:

- Notification to the Sponsor-Investigator:
    - All deviations from the pre-specified statistical plan will be promptly reported to the sponsor. This notification will include a detailed description of the deviation, the rationale behind the change, and its potential impact on the study's validity and conclusions.
- Documentation in the Clinical Investigation Plan (CIP):

    - If deviations occur before or during the study, they will be formally incorporated into an amendment to the CIP. This amendment will outline:
    - The nature of the deviation (e.g., changes in statistical methods, sample size adjustments, or endpoint definitions).
    - Justifications for the deviation, referencing new information or unforeseen circumstances necessitating the change.
    - The anticipated implications for the study outcomes.
- Inclusion in the Final Report:
    - All deviations will be transparently detailed in the final study report, regardless of their timing. The final report will include:
    - A clear comparison between the original statistical plan and the revised approach.
    - A justification for each deviation, supported by relevant data or context.
    - An assessment of the impact of these changes on the interpretation of the study results.

5.2. Handling of missing data and drop-outs

Approach to Missing Data

- Primary Outcomes: Missing data for primary outcomes will be addressed using complete case analysis, where only cases with available data for the primary endpoint will be included in the primary analysis. Sensitivity analyses will be conducted to assess the robustness of the findings, as detailed below.
- Secondary Outcomes: Depending on the nature and extent of missing data, methods such as multiple imputation may be employed to minimize bias and ensure a representative analysis. Alternative methods, such as last observation carried forward (LOCF) or other conservative imputation strategies, may be considered if appropriate to the outcome and context.

Efforts to Minimize Missing Data

Efforts will be made to minimize missing data through the following measures:

- Active Follow-Up: Proactive measures, such as reminder calls and written notifications, will be implemented to reduce no-shows at recall appointments.
- Tracking Lost to Follow-Up: For participants who miss follow-up visits, the study team will make at least three attempts to contact them using the preferred communication method recorded at enrollment (e.g., phone, mail, or email). These attempts will be documented.
- Data Completeness Checks: Real-time data monitoring during study visits will help ensure data completeness and identify any issues early.

Replacement of Dropouts

- Participants who drop out after baseline will not be replaced.

Sensitivity Analyses

Sensitivity analyses will be performed to evaluate the impact of missing data on the study results. These may include:

- Comparing the results of the complete case analysis with those obtained using multiple imputation.
- Conducting a worst-case scenario analysis to test the robustness of conclusions under extreme assumptions about missing data.

Documentation of Dropouts and Withdrawals

All participants will be accounted for and documented, including those who withdraw from the investigation or are lost to follow-up. The reasons for withdrawal, if provided, will be recorded and

included in the final study report to ensure transparency.

6 REGULATORY ASPECTS AND SAFETY

6.1 Local regulations / Declaration of Helsinki

This study is conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP, ISO 14155 (as far as applicable) the HRA as well as other locally relevant legal and regulatory requirements.

6.2 (Serious) Adverse Events and notification of safety and protective measures

An Adverse Event (AE) is any untoward medical occurrence in a patient or a clinical investigation participant which does not necessarily have a causal relationship with the trial procedure. An AE can therefore be any unfavourable or unintended finding, symptom, or disease temporally associated with a trial procedure, whether or not related to it.

A Serious Adverse Event (SAE) (ClinO, Art. 63) is any untoward medical occurrence that

- Results in death or is life-threatening,
- Requires in-patient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability or incapacity, or
- Causes a congenital anomaly or birth defect

The Sponsor-Investigator makes a causality assessment of the event to the trial intervention, (see table below based on the terms given in ICH E2A guidelines). Any event assessed as possibly, probably or definitely related is classified as related to the trial intervention.

Relationship	**Description**
Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probably	Temporal relationship Improvement after dechallenge No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

The Sponsor-Investigator makes a severity assessment of the event as mild, moderate or severe. Mild means the complication is tolerable, moderate means it interferes with daily activities and severe means it renders daily activities impossible.

Reporting of SAEs (see ClinO, Art. 63)

All SAEs are documented and reported immediately (within a maximum of 24 hours) to the Sponsor-Investigator of the study.

If it cannot be excluded that the SAE occurring in Switzerland is attributable to the intervention under investigation, the Sponsor-Investigator reports it to the Ethics Committee via BASEC within 15 days.

Follow up of (Serious) Adverse Events

- In cases where participants terminate the study with reported ongoing (Serious) Adverse Events (S)AEs, a detailed follow-up procedure will be implemented. The Sponsor-Investigator will continue monitoring the participant's condition until the (S)AE is resolved or stabilized. Follow-up assessments will be conducted at regular intervals based on the severity and nature of the (S)AE, with additional medical support provided if necessary. The Sponsor-Investigator will ensure that the participant receives appropriate care and will document any significant changes or updates in the eCRF. If the (S)AE persists, the Sponsor-Investigator will provide further reports as required, following the relevant timelines for Sponsor-Investigator reporting to the Ethics Committee.
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Notification of safety and protective measures (see ClinO, Art 62, b)

In cases where immediate safety or protective measures need to be implemented during the study, the Sponsor-Investigator will take all necessary actions to ensure the well-being of the participant. Any such measures, including the reasons for their necessity, will be promptly communicated to the Ethics Committee within 7 days, in accordance with ClinO, Art. 62, b. These actions may include temporary suspension of the study intervention or other appropriate clinical interventions to address the safety concern. All documentation related to the safety and protective measures will be recorded and monitored closely throughout the study.

6.3 Periodic reporting of safety and general progress of the clinical trial.

Once a year, the investigator submits to the Ethics Committee a list of the safety events including the severity of the events, their causality to the intervention and the safety of the study participants. The investigator also informs the Ethics Committee about the general progress of the clinical trial (ClinO, Art. 43).
The safety report and the general study progress report can be merged in one single report.

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6.4 Radiation

- Routine use of dental X-rays is not required for this study. X-rays will only be taken when strictly necessary for diagnostic purposes, such as assessing vitality loss or severe toothache. Standard radiation protection measures will be followed, in accordance with established dental practice. The study will adhere to the ALARA (As Low As Reasonably Achievable) principle, as well as the dose guidelines set by the SADMFR (Swiss Association of Dentomaxillofacial Radiology), to minimize radiation exposure [15].

6.5 Pregnancy

Pregnant or lactating individuals are ineligible for inclusion in this study. To ensure eligibility, women of childbearing age will be provided with free, on-demand pregnancy tests prior to enrollment, with negative results documented in the eCRF.

Pregnancy or lactation occurring during the follow-up period will not disqualify participants from continued enrollment in the study. However, the timing of follow-up visits, which include brief clinical assessments, may be adjusted based on the participant's preferences and/or gynecological recommendations.

6.6 Amendments

- Substantial changes to the study setup and study organization, the protocol and relevant study documents are submitted to the Ethics Committee for approval before implementation. Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of participants may proceed without prior approval of the Ethics Committee. Such deviations shall be documented and reported to the Ethics Committee as soon as possible.
- Substantial amendments are changes that affect the safety, health, rights and obligations of participants, changes in the protocol that affect study objective(s) or central research topic, changes of study site(s) or of investigator and sponsor (ClinO, Art. 29).
- A list of substantial changes is also available on www.swissethics.ch.
- A list of all non-substantial amendments will be submitted once a year to the competent EC together with the safety report / general study progress report.

6.7 Notification and reporting upon completion, discontinuation or interruption of the study

Upon regular study completion, the Ethics Committee is notified via BASEC within 30 days (ClinO, Art. 38). The last follow-up visit of the last study participant is defined as the end of the trial.

- The Sponsor-Investigator and any other competent authority may terminate the study prematurely under certain circumstances, including but not limited to:

- Ethical concerns
- Inadequate participant recruitment
- Doubts regarding the safety of participants or when the benefit-risk assessment no longer supports continuation
- Significant changes in accepted clinical practice that render the study unfeasible or unwise
- Early evidence of harm or unexpected benefit from the experimental intervention

Upon premature study termination or study interruption, the Ethics Committee is notified via BASEC within 15 days (Article 38 ClinO).

- All documents related to the investigation will be archived at UZB's secure facilities for a minimum of 20 years following the regular or premature termination of the investigation.
- If any use is made of ionising radiation, the investigator documents all information relevant to radiation protection in the final study report and includes a retrospective participant dose estimation.

A final report is submitted to the Ethics Committee via BASEC within a year after completion or discontinuation of the study, unless a longer period is specified in the protocol (ClinO, Art. 38).

6.8 Insurance

- Since this is a risk category A study, it is exempt from liability coverage requirements).

In the event of study-related damage or injuries, the liability of the UZB provides compensation, except for claims that arise from misconduct or gross negligence.

7 FURTHER ASPECTS

7.1 Overall ethical considerations

This study is designed to offer valuable insights into the long-term performance of RBC restorations in anterior teeth, with a focus on marginal staining and other clinical and functional outcomes. The results are expected to have significant scientific and social value, particularly in enhancing restorative dental practices and improving the durability of dental treatments. By evaluating the effects of different PAE protocols on restoration quality, the study aims to provide data that can lead to better treatment outcomes for patients in clinical practice, benefiting both individual patients and broader populations [1, 2, 16].

The study design, including its methodology and population selection, is grounded in clinical practice and aims to provide robust and generalizable data. The inclusion of adult patients with common restorative needs ensures the relevance of the results to a wide patient demographic, while the exclusion of vulnerable populations (e.g., minors, those incapable of giving informed consent) ensures the ethical integrity of the study. Participants are fully informed about the study procedures at the outset. Their voluntary participation is a cornerstone of the study design. Informed consent is obtained at the beginning of the study, with participants being made fully aware of the risks and benefits of their involvement, as well as their right to withdraw at any time without consequence. Participants will also be kept informed about the current status of the study throughout its duration.

With respect to study procedures, all steps have been carefully considered to minimize participant risk and discomfort. The anticipated risks, such as minor postoperative discomfort, are minimal, and risk-mitigation strategies are in place, including staff training, close monitoring, and clear protocols for addressing any adverse events.

The study does not involve genetic data or any other high-risk interventions; however, all ethical guidelines regarding patient confidentiality, privacy, and the handling of sensitive data will be strictly followed.

Overall, the study upholds a fair balance between advancing scientific knowledge and ensuring participant safety and rights. All study procedures are designed to respect the dignity, autonomy, and safety of the participants, while contributing to the broader goal of improving dental care practices.

7.2 Risk-benefit assessment

The study follows established, evidence-based practices for restorative patient care, ensuring that all procedures are performed to the highest clinical standards.

- Anticipated Clinical Benefits:
    - The data gathered from this study may contribute to enhancing treatment protocols and improving long-term restorative care practices. While participants may not receive direct personal benefits from the study, their involvement is pivotal in advancing scientific knowledge, which could improve future restorative care for broader patient populations.
- Residual Risks and Adverse Device Effects (ADEs):
    - The materials used in the study carry minimal residual risks, as they adhere to CE marking requirements and are utilized within the approved indications. The expected adverse device effects (ADEs) are rare and will be actively monitored. Potential risks include minor postoperative discomfort, hypersensitivity, and complications related to the restorative procedure, such as temporary sensitivity to biting or thermal stimuli. These risks will be minimized through careful procedural planning and close monitoring.
    - Any potential residual risks associated with the intervention, such as material reactions, mechanical failure, or longevity of restoration, have been assessed and are deemed low in the context of clinical use.
    - Residual risks also include those inherent to any dental intervention in the oral cavity, such as:

        - Postoperative hypersensitivity or postoperative pain of the tooth
            - Consequences: Depending on severity, follow-up appointments may be required to monitor the situation. Pain relief can be managed with a suitable analgesic. In cases of severe pain, the restoration may need to be replaced, or a root canal treatment might be necessary.
        - Chipping or fractures of the restoration and/or adjacent tooth structure
            - Consequences: The restoration may need to be refurbished, repaired, or replaced.
        - Failure of the adhesive bond, leading to partial or total restoration loss
            - Consequences: The restoration may need to be repaired or replaced.
        - Air entrapment within or beneath the restorative material during placement
            - Depending on the location and size of the air entrapment, the restoration may need to be refurbished, repaired, or replaced.
        - Minor, superficial injury to oral soft tissues
            - Consequences: Such injuries typically heal within 1-2 weeks without intervention. If necessary, wound ointments or mouth rinses can be used to support healing.
        - Accidental ingestion of material
            - Consequences: In most cases, ingestion of small amounts does not cause any issues owing to the minimal quantities involved.
        - Allergic reactions to components of the restorative materials, local anesthetics, or tools used during the procedure
            - Consequences: Patients with known or suspected allergies to these substances are excluded from treatment using such materials. These precautions notwithstanding, in rare cases, severe allergic reactions, such as anaphylactic reactions, may still occur, necessitating immediate emergency management.
- Risks Due to Concomitant Treatments:
    - While no specific risks related to concomitant treatments are anticipated, it is essential to ensure that participants inform the study team of any ongoing medical conditions or medications. Potential interactions with other treatments will be assessed during screening, and the investigator will monitor participants accordingly throughout the study.
- Risks Associated with Participation:
    - Informed Consent and Awareness of Risks: Participants are fully informed about the nature of the study, including all procedures, potential risks, and the absence of direct personal benefits. Written informed consent is obtained prior to participation, ensuring that all individuals understand the conditions of their involvement and voluntarily consent to participate.
    - Monitoring and Safety Procedures: Participants will be closely monitored during the study to ensure any adverse events or complications are identified and addressed promptly. Immediate action will be taken to manage any potential adverse events.
    - Post-Investigation Care: Post-investigation care will include regular follow-up visits and prompt intervention in case of adverse effects or complications. The study protocol ensures participants are not exposed to undue harm from the study procedures.
- Risk-Mitigation Measures:

- To address the potential risks associated with the study procedures, the following mitigation measures are implemented:
    - Proper training and calibration for all clinical personnel involved in the study.
    - Close monitoring and timely intervention in case of adverse events.
    - Use of standard, meticulous clinical procedural techniques to minimize patient discomfort and risk during restorative treatments.

- Risk-Benefit Assessment:
    - The anticipated benefits of improved restorative treatments outweigh the minimal risks involved in the study. The knowledge gained will improve future restorative procedures, leading to better patient outcomes in the long term. The study aims to enhance treatment protocols, offering long-term benefits for patients beyond the individual participants in the study.

8 QUALITY CONTROL AND DATA PROTECTION

8.1 Quality measures

For quality assurance the sponsor, the Ethics Committee or an independent trial monitor may visit the research sites. Additionally, Ivoclar Vivadent AG reserves the right for audits. Direct access to the source data and all study related files is granted on such occasions. All involved parties keep the participant data strictly confidential.

8.2 Data recording and source data

Data Handling and Record Keeping / Archiving

All data collected during the investigation will be handled in accordance with ISO 14155 standards and applicable data protection regulations, ensuring integrity, accuracy, and confidentiality. Investigation-related documents will be archived securely for the required retention period as specified by regulatory requirements. Essential documents, as outlined in ISO 14155 Annex E, including the clinical CIP, signed informed consent forms, investigator's brochure, CRFs, monitoring visit reports, and regulatory correspondence, will be maintained in both the investigation site and sponsor files. Electronic data will be stored on secure, password-protected servers, with regular backups performed. Physical documents will be stored in a locked, access-controlled facility. An inventory of archived documents will be maintained to facilitate retrieval for audits or inspections, ensuring traceability and compliance with GCP.

Case Report Forms

Each enrolled subject has a dedicated eCRF created and managed within Castor, a secure electronic data capture platform. At the clinic, computers near each dental chair are connected to Castor via an internet browser, facilitating seamless data entry during treatment and recall visits.

- Data Entry Process:
    - Primary Data Collection: The evaluator communicates findings verbally to a trained dental assistant, who documents them directly into the eCRF within Castor in real-time.
    - Review and Validation: Data entries are reviewed and verified by the dentist before being accepted and stored in the system, ensuring accuracy and completeness. The review is proven by electronic signature of each CRF.
    - Integration with Clinical Imaging: Clinical images captured during treatment are downloaded from the camera on a weekly basis and saved in Microsoft OneDrive, a secure and encrypted file-hosting service. They are kept in password-protected

folders accessible exclusively to authorized study personnel. The folders are labeled with the Castor Participant ID and detail of the study visit.

Pseudonymization and Coding:

Each participant is assigned a unique Participant ID in Castor, ensuring pseudonymization. No personal identifiers, such as names, initials, or birth dates, are recorded in the eCRF. The coding structure complies with guidance from Swissethics, utilizing a participant number in combination with study-specific identifiers. The list linking Participant IDs to personal identifiers is securely stored in a locked and restricted-access area at the clinic.

Data Integrity and Security:

- Access Control: Only authorized personnel, including investigators and dental assistants listed on the delegation log, have individual login credentials for Castor.
- Audit Trail: All actions within Castor are automatically recorded in an audit trail, tracking data entry, modifications, and review activities.
- Compliance: Castor adheres to global standards for medical research, including GCP, 21 CFR Part 11, General Data Protection Regulation (GDPR, EU), and Health Insurance Portability and Accountability Act (HIPAA, US).
- Certifications: Castor and its hosting service, Microsoft Azure, are certified under ISO 27001 for information security. Additionally, Microsoft Azure holds ISO 9001 certification for quality management.

Data Export and Analysis:

Castor allows for seamless data export into statistical software for analysis. This ensures efficient processing of the study's data while maintaining its integrity and security.

Data Recording and Retention:

All eCRFs are kept up-to-date to reflect each subject’s status throughout the investigation, from treatment to follow-up. Clinical data and associated images are retained in compliance with regulatory requirements and stored securely to ensure long-term accessibility for audits or inspections.

Specification of Source Data and Source Documents

The source data for the investigation will be maintained at the clinical site to document the existence of investigation subjects and ensure the integrity of collected information. These data include original documents related to the investigation as well as the subject's medical treatment and history. The following outlines the source data, the associated documents, and their handling and storage:

Source Documents at the Site

- List with Record Numbers:
    - A secure list linking participant IDs in Castor to their personal identifiers is maintained at the clinic.
    - This list is stored in a locked, access-controlled area to ensure confidentiality.
- Signed Informed Consent Forms (ICFs):
    - Original signed ICFs are stored as hard copies in a secure, locked drawer at the clinical site.
    - These documents confirm each participant's voluntary participation and understanding of the investigation.
- Photographs:

- Clinical photographs taken during the investigation document the intraoral situation.
- These photographs are securely stored in folders labeled with the Castor IDs and details of the study visit during which they were captured.
- The photographs are saved in Microsoft OneDrive, a secure and encrypted file-hosting service. They are stored in restricted-access folders, accessible exclusively to authorized study personnel. The folders are labeled with the Castor Participant ID and details of the study visit. OneDrive uses a distributed cloud storage system, ensuring that image data is not stored in a single location but is replicated across multiple servers for redundancy. The Microsoft data centers hosting these files are located in various regions worldwide, including North America, South America, Europe, Asia, and Australia.

Medical History (Managed in Vitodent/Stomanet/Denvis):

- The participant's medical history, including demographic data, visit dates, and relevant medical conditions, is managed using Vitodent/Stomanet/Denvis, the comprehensive UZB software solution for electronic dental health records.
- Access to Vitodent/Stomanet/Denvis is restricted to authorized personnel and protected by one-factor authentication.

SAE/SADE/USADE Reports:

- Source documents for all SAEs, SADEs, and USADEs are stored at the site.
- These reports include investigator narratives, supporting data, and follow-up information.

Handling, Transfer, and Storage of Source Data

- Electronic Source Data:
  - Data in Castor are pseudonymized, with access limited to authorized personnel through individual login credentials.

Directly Recorded CRF Data:

- Data directly recorded in Castor (e.g., demographic data, visit dates, randomization codes, and examination results) are also considered source data.
- The system tracks all entries and modifications via an audit trail to ensure data integrity.

Source Data Location

- Paper Documents:
  - Signed ICFs, participant ID linking lists, and other physical records are stored in a secure, locked cabinet accessible only to authorized clinic staff.

Electronic Records:

- In accordance with UZB's data safety protocols, backup data are stored in multiple, redundant locations, guaranteeing continuous availability in the event of hardware failure.

Accessibility and Oversight

The Sponsor-Investigator and authorized staff listed in the delegation log have access to all source documents as needed. These documents and data will be made available for monitoring, auditing, and inspections by authorized parties to ensure compliance with GCP and ISO 14155 guidelines.

8.3 Confidentiality and coding

The Sponsor-Investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall

be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.
The Sponsor-Investigator has appropriate knowledge and skills in the areas of data security and data protection or is able to ensure compliance by calling in appropriate expertise (Art. 6, ClinO).
Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited.
Trial and participant data will be handled with the utmost discretion and is only accessible to authorised personnel who require the data to fulfil their duties within the scope of the study. On the CRFs and other study specific documents, participants are only identified by a unique participant number.

Data Management

Data entry for this investigation will be conducted using Castor, an electronic data capture (EDC) system. To minimize errors and ensure the accuracy of recorded information, the following procedures will be followed:

- Data Entry Process:
    - Real-time Data Recording: The dentist will dictate all observations and measurements immediately after performing the treatment or examination. A trained dental assistant will enter the data into the eCRF in Castor during the visit.
    - Data Review and Validation: After the data is entered, the dentist will review the information for completeness and accuracy before approving the eCRF. This process helps ensure data integrity and minimize the risk of errors.
- Data Verification and Validation:
    - Clinical Pictures: At each visit, clinical photographs of the treated tooth will be taken. These images will serve as additional source data and may be used for visual validation during the analysis. For example, parameters such as marginal quality can be assessed from the photographs, allowing verification of any outliers identified during data analysis.
    - Verification of Outliers: If data analysis reveals outliers or discrepancies, the corresponding clinical photographs will be reviewed to verify the validity of the data.
- Data Quality Measures:
    - Range Checks: Automatic range checks will be applied within Castor to ensure that entered data fall within predefined, acceptable ranges for each parameter, helping to identify potential data entry errors at an early stage.
- Data Coding and Anonymization:
    - Data will be pseudonymized in Castor, with each participant being assigned a unique Participant ID. This ensures the protection of personal data, as no personal identifiers (such as names or birthdates) will be used within the database.
    - After the statistical analysis, if data is not anonymized, it will remain in a coded format, with identifiers linked only to the pseudonymized Participant ID, ensuring that the identity of participants cannot be directly revealed.
- Data Storage and Security:
    - Castor Platform: All data will be stored on Castor's secure servers, which are compliant with regulatory standards, including ISO 27001 for information security and GDPR for data protection.
    - Backup Procedures: Regular backups of the database will be conducted to ensure data integrity and availability in the event of system failure.
    - Access Control: Access to the data will be restricted to authorized personnel only. All users will have unique login credentials, and actions within the system will be tracked in an audit trail to ensure accountability.

Data Management System

The Castor system is a web-based Electronic Data Capture (EDC) platform used for managing clinical investigation data. Castor is widely used in clinical investigations worldwide, ensuring its robustness and reliability.

The Castor system is hosted in secure, ISO 27001-certified data centers, which provide a high level of data security and compliance with global data protection regulations, such as GDPR. This ensures the protection of sensitive investigation data throughout the study.
The administration and programming of the Castor system for this investigation will be carried out by the Sponsor-Investigator in collaboration with employees from Ivoclar Vivadent AG.

Data Security, Access and Back-Up

Access to uncoded data is restricted to the Sponsor-Investigator, operators, evaluators, dental assistants, monitors, and Ivoclar Vivadent staff with audit permission. Each individual is provided with a unique personal login key. Microsoft Azure performs data backups at least four times per year.

Analysis and Archiving

As previously mentioned, data captured in the eCRFs on Castor are stored on a dedicated Castor server. This server is hosted by Microsoft Azure and located in the Netherlands, with backups and disaster recovery solutions stored within the same company in Ireland.

Once all visits for a given time points are completed, the Sponsor-Investigator will export the data from Castor for analysis by the statistician using R software. The analyzed data will be stored on a secure server, with regular backups maintained by UZB. Access to this specific folder on the server is restricted to the Sponsor-Investigator only.

Electronic and Central Data Validation

Each question in the eCRF on Castor can only be answered with valid values (e.g., VAS scores between 0 and 10). After completing a recall, the Sponsor-Investigator will review the data for outliers. Most parameters can be verified through photo documentation, eliminating the need for additional recalls.

8.4 Retention and destruction of study data

All documents related to the investigation will be archived at UZB’s secure facilities for a minimum of 20 years following the regular or premature termination of the investigation.

The Sponsor-Investigator is responsible for ensuring the proper archiving of all investigation-related documents. This includes ensuring that all essential documents are stored securely and are accessible for inspection or audit by relevant authorities for the specified retention period. The Sponsor will oversee the archiving process and ensure that all data, including the case report forms (CRFs), informed consent forms (ICFs), adverse event reports, and other clinical investigation documents, are preserved and stored properly.

The Sponsor-Investigator is responsible for maintaining and securing all source data and clinical documentation at the study site. The Sponsor-Investigator ensures that records are archived according to regulatory requirements and are accessible to authorized personnel. The Sponsor-Investigator also oversees the safeguarding of all study documentation and ensures that they are available for audits or inspections throughout the retention period.

9 MONITORING AND REGISTRATION

The monitoring duties for this study will be led by Prof. Dr. M. M. Bornstein, Head of Dental Research at UZB, with his designated deputy overseeing the activities in his absence. The monitors are responsible for ensuring the study's compliance with GCP guidelines and Swiss

regulations. Regular monitoring visits will be conducted at the investigator's site both before the study begins and throughout its course. These visits are designed to ensure the proper conduct of the study and confirm that all relevant processes and procedures are being followed according to the study protocol.

The monitoring activities will focus on reviewing and verifying various data and documents, including participant recruitment, informed consent forms, CRFs, source documents, and any other records required for the study. Additionally, monitoring will include the assessment of the data integrity, protocol compliance, adverse event reporting, and other essential aspects of the study's conduct.

Monitors will have access to all necessary source data and documents during the monitoring visits, and the study team is committed to responding promptly to any questions or requests for clarification. This ensures full transparency and compliance with regulatory requirements, as well as timely identification and resolution of any issues.

In line with Swiss regulations, the study will be registered in the Swiss National Clinical Trial Portal (SNCTP) via BASEC in the appropriate national language prior to the initiation of recruitment. Additionally, the trial will be registered in ClinicalTrials.gov, a database maintained by the U.S. National Library of Medicine.

10. PUBLICATION / DECLARATION OF INTEREST

Publication and Dissemination Policy

We plan to submit the study report for consideration for publication in a highly ranked dental journal. In accordance with the University of Basel’s open access policy, open access publication will be preferred to maximize visibility and engagement within the dental community.

We also plan to share the findings with healthcare professionals and the public through presentations at national and international conferences. Additionally, the results will be reported in relevant results databases, in line with ethical guidelines and regulatory requirements.

In line with ClinO Art. 65a, the sponsor will ensure that a summary of the trial results is entered into a public register within one year of the study's completion or discontinuation. In case of an interruption lasting more than two years, the study will be considered discontinued. Furthermore, the sponsor will ensure that a lay summary of the trial results is published in BASEC in at least the national languages of Switzerland where the study participants were recruited.

The publication process will follow standard authorship eligibility guidelines, with the Sponsor-Investigator serving as either the first or last author. Co-authors will include the operators who were involved in the study. No professional writers will be used in the preparation of the study report intended for submission to a dental journal.

If any gender and/or sex effects are observed during the study, they will be reported in the final study report. If no gender and/or sex effects are observed, this will also be included in the final publication to ensure transparency.

Data Sharing

Raw data generated during the study will be available to authorized personnel upon request, in accordance with ethical guidelines and the University of Basel’s data sharing policy. The data will be made accessible to collaborators, regulators, and researchers for further analysis and transparency, as appropriate.

Lay Summary and Participant Notification

In accordance with regulatory requirements, the Sponsor-Investigator will provide each study participant with a lay summary of the trial results at the end of the study. Participants will be informed of where the lay summary will be published online in the patient information document.

This summary will be available in German. The Sponsor-Investigator will ensure that the lay summary is entered into BASEC within one year of study completion or discontinuation.

Declaration of Interest

The personnel involved in the conception, execution, and statistical analysis of this study declare that they have no conflicts of interest related to the research. There are no financial, professional, or personal relationships that could influence the integrity or outcomes of the study. Ivoclar Vivadent provides financial funding as well as non-financial support by supplying restorative materials and selected instruments at no cost for the duration of the study.

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Appendix 1:

Appendix Table 1 Schedule of Assessments

Time (day/year)	-30 to -0 (Screening)	Day 0	+7 to +10 Days	+1 year (Visit 3)	+2 years (Visit 4)	+3 years (Visit 5)	+5 years (Visit 6)
Visit	Screening Visit	1st Visit (Restoration Visit)	2nd Visit (Restoration Baseline Assessment)	3rd Visit (Follow-up)	4th Visit (Follow-up)	5th Visit (Follow-up)	6th Visit (Follow-up)
Oral and written patient information	+						
Written consent	+						
Inclusion/exclusion criteria	+						
Medical history	+			+	+	+	+
Dental examination	+			(+)*	(+)*	(+)*	(+)*
Participant characteristics	+						
Preoperative hypersensitivity assessment		+					
Postoperative hypersensivity assessment			+				
Standardized intraoral photographs		+	+	+	+	+	+
Pulp sensitivity test		+	+	+	+	+	+
Shade determination		+					
Cavity preparation		+					
Adhesive application		+					
Resin-based composite application		+					
Finishing and polishing		+	(+)				
Occlusion check and adjustment		+	+				
Postoperative instructions		+					
Primary/secondary outcome assessment			+	+	+	+	+
Adverse events documentation		+	+	+	+	+	+

*Dental examination conducted according to each participant's routine check-up schedule.

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Appendix Table 2 Clinical Investigation Flowchart

Study Flow	Visit	Approximate Duration
	Screening Visit • Eligibility assessment and routine dental examination • Participant recruitment and informed consent ○ n = 66 participants	0.5 h (depending on individual case requirements)

	Visit 1: Intervention (Day 0)
	• **Cavity preparation**
	  ○ Caries removal and cavity shaping
	  ○ Isolation with rubber dam or retractor system
	• **Conditioning**
	  ○ Phosphoric acid etching (variable per study arm)
	• **Adhesive application**
	  ○ Universal adhesive application and light curing (5 seconds)
	• **Restorative procedure**
	  ○ Application of Tetric plus Flow and Tetric plus Fill
	  ○ Light curing (5 seconds per layer)
	  ○ Sculpting and shaping of the restoration
	• **Finishing and polishing**
	  ○ Removal of excess material and occlusion adjustments
	  ○ Static and dynamic occlusion check
	
	Documentation of materials and procedure details (including photographs)
		0.75 - 1.5 h

	Visit 2: Baseline Recall (Day +7 to +10)
	
	Important Note: This visit is study-specific, and participants will receive financial compensation for their time spent on this visit, as well as reimbursement for travel expenses associated with this visit.
	
	• **Assessments:**
	  ○ Hypersensitivity (VAS scale)
	  ○ Pulp vitality
	  ○ Esthetic, biological, and functional outcomes (selected FDI criteria)
	• **Adjustments:**
	  ○ Occlusion correction and repolishing (if needed)
	• **Documentation:**
	  ○ Standardized intraoral photographs
	Adverse event reporting
		0.3 - 1 h

	Visits 3, 4, 5, and 6: Follow-Up Recalls (1, 2, 3, and 5 Years)
	• **Annual Assessments:**
	  ○ Hypersensitivity (VAS scale)
	  ○ Pulp vitality
	  ○ Restoration evaluation using selected FDI criteria
	• **Documentation:**
	  ○ Standardized intraoral photographs
	
	Recording of adverse events
		0.5 h per visit

	End of Study • Completion of final assessments at 5-year recall.	