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Hélène FRON CHABOUIS

Machinable materials for inlays and onlays: composite versus ceramics.

Systematic review, randomized controlled trial and *in vitro* evaluation

PhD director : Dr Jean-Pierre ATTAL

JURY

Monsieur le Professeur J.-F. BERNAUDIN	Rapporteur
Monsieur le Docteur B. JACQUOT	Rapporteur
Madame le Professeur V. MIGONNEY	Président
Madame le Professeur S. SCHERRER	Assesseur
Monsieur le Professeur G. CHATELLIER	Assesseur
Monsieur le Docteur P. DURIEUX	Assesseur
Monsieur le Docteur M. SADOUN	Assesseur
Monsieur le Docteur J.-P. ATTAL	Directeur

Avant-propos

Cette thèse a donné lieu à :

- **Trois publications internationales publiées**

Clinical Oral Investigations. 2013 Mar 1. [Epub ahead of print] *Randomization in clinical trials: stratification or minimization? The HERMES free simulation software.* Fron Chabouis H, Chabouis F, Gillaizeau F, Durieux P, Chatellier G, Ruse ND, Attal JP.

Trials. 2013 Sep 3;14(1):278. *Efficacy of composite versus ceramic inlays and onlays: protocol of the CECOIA randomized controlled trial.* Fron Chabouis H, Prot C, Cazier S, Moussally C, Fonteneau C, Gaucher A, Nasr K, Chabreron O, Ben Jaballah I, Boyer R, Leforestier JF, Caumont Prim A, Chemla F, Maman L, Nabet C, Attal JP.

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Conseuro (Paris). 2013 May. *Properties of four CAD-CAM materials: flexural strength, hardness and adherence to three cements.* Fron Chabouis H, Tang ML, Le Goff S, Attal JP.

- **Trois communications nationales**

Société Francophone des Biomatériaux Dentaires (Toulouse). 2011 Juin. *Choix de la méthode d'allocation des traitements pour un essai clinique en dentisterie restauratrice.* Fron H, Chabouis F, Durieux P, Chatellier G, Gillaizeau F, Attal JP.

Société Francophone des Biomatériaux Dentaires (Clermont-Ferrand). 2012 Juin. *Comparaison in vitro de matériaux usinables pour la fabrication d'inlays par CFAO.* Fron Chabouis H, Le Goff S, Vennat E, Sadoun M, Attal JP.

Journées des sous-sections 58-03 et 57-03 (Nancy). 2012 Sep. *Choix de la méthode de randomisation pour un essai clinique : le logiciel Hermès*. Fron Chabouis H, Chabouis F, Attal JP.

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NCT01724827. Ceramic Versus Composite in the Treatment of Posterior Teeth by Inlays or Onlays (CECOIA).

- **Un site internet (pour l'essai CECOIA)**

CECOIA : CEramic and COmposite Inlays Assessment

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Introduction

Inlays and onlays are fixed prostheses used to restore **posterior teeth affected by medium-to-large substance loss** [1]. An inlay is a prosthetis assembled by cementing or – preferably – bonding, which does not require cusp covering, while an onlay restores one or more cusps of the tooth. Inlays and onlays can be made of metal alloys, resin composite or ceramics.

Despite improved dental care, such substance losses are still common in adults. The World Health Organization (WHO) estimates that about 5 billion people have carious lesions, affecting 60 to 90% of school-aged children and over 50% of adults, whose dental treatment costs may represent 5 to 10% of health expenditures in developed countries [2]. In France, each adult may have 1.1 to 1.2 decayed teeth, on average [3, 4], and the replacement of old restorations represents nearly two-thirds of dental restorations [5, 6].

Previously, these substance losses were usually treated with crowns, sometimes built-up amalgams or rarely, gold inlays [7, 8]. The drawback of **crowns** is the tissue mutilation that results from the preparation [9]. After lengthy discussions of the possible toxicity of **amalgams**, because they contain mercury [10, 11], amalgam use is about to be banned in the European Union for environmental reasons [12]. **Inlays made of precious alloys** are excellent therapy [13], which some consider the gold standard, but they are now sometimes abandoned in favor of other materials because of their cost [14] and aesthetics.

Today, science and technology have allowed for a changed paradigm [15] and have achieved **adhesive partial restorations** [16], which preserve healthy tissue [17]. For the former need to anchor crowns [18, 19], we substitute the adhesion of partial restorations [20]. For the former Black design preparations oriented toward amalgam retention, "extension for prevention", we substitute a conservative approach, "prevention of extension" [21]. Some clinicians still prefer crowns, because of habit or the longevity or ratio of cost to longevity of the restoration [8, 22-24]. However, any restoration has a lifespan and needs to be repaired or replaced at some point; tissue preservation is thus fundamental to re-intervene as easily and as

late as possible (i.e. conserve teeth on the arch to the end of the patient's life), which is the aim set by the World Health Organization [2]. With the population aging, trying to keep the teeth on the arch until the end of life is a challenge. However, with recent advances, we can achieve this goal. This work explores some of the advances.

Preservation of coronary hard tissues is important from a biological aspect and for guaranteeing strength of the tooth-restoration entity [25]. In particular, **preservation of enamel**, the hard shell that provides both mechanical strength and ensuring absence of microleakage at the adhesive interface over time are essential [26-28]. This preservation is permitted by partial indirect restorations [9].

Preservation of the pulp tissue is also important and is associated with the preservation of hard tissues. For this purpose and before tissue engineering protocols are effective [29, 30], we can conceive treatments to promote the intrinsic potential of tooth repair [31]; the choice of a suitable material and dentin preservation are essential to reduce the likelihood of pulp complications [32]. As well, endodontic treatments implemented in case of pulp complications cause a significant loss of substance and have relatively high failure rates [33].

Still, in this goal for tissue preservation, some authors encourage the use of direct restorations, even in cases of very damaged teeth [34, 35]. However, the indirect technique has many advantages in these cases, whether considering management of the restoration’s morphologic features (occlusal anatomy, proximal and occlusal contacts, emergence profile), control of polymerization shrinkage or materials that can be used [36].

Finally, tissue preservation is associated with **adhesion** [37]. Inlays and onlays need to be adhesively cemented because preparations are generally not retentive; the implementation of the adhesive protocol also allows for strengthening the inlay and onlay materials, enhancing biomechanical strength of the restored tooth and filling undercuts [36, 38-40].

Hence, inlays and onlays are essential treatments in current minimally invasive dentistry.

This thesis discusses inlays and onlays that can be made in a traditional manner by a technician or a dentist or by Computer Aided Design/Computer Aided manufacturing (CAD/CAM). This latter technology is becoming popular, as shown in Figure 1, and many think it will largely replace the traditional technique for producing inlays and onlays [41, 42]. Also, CAD/CAM can be used to standardize the production of inlays and onlays in a clinical trial.

Because CAD/CAM is a technology of the future, this work focused on machined inlays and onlays.

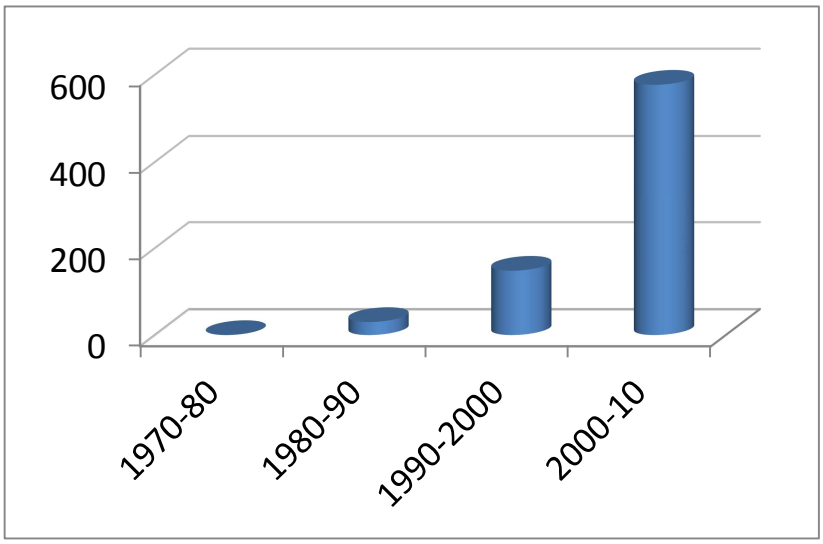


Figure 1. Number of publications on CAD/CAM indexed in PubMed between 1970 and 2010

Finally, two materials can be used to make tooth-colored inlays and onlays: composite and ceramics. The question posed in this work was whether composite or ceramic material is more efficient for CAD/CAM inlays and onlays.

No systematic review has answered this question. No clinical trial has provided arguments on the long-term effect or clarification of the clinical factors that affect the choice of the two materials. In addition, *in vitro* studies have shown that no current material fully meets the specifications of these restorations. So we lack information to help choose composite or ceramic inlays and onlays, and further work is needed to answer the question.

The objectives of this work were as follows:

- to review the composite and ceramic materials that can be used to produce inlays and onlays and understand the specifics of machinable materials,

- to review the data and evidence obtained from previous clinical studies comparing ceramic and composite inlays and onlays,

- to develop the methodological tools necessary for clinical trials comparing composite and ceramic inlays and onlays and to design and conduct such a trial,

- to compare the adhesive properties of machinable composites and ceramics used to produce inlays and onlays.

Therefore, this work involved a systematic review, a clinical trial and an *in vitro* study comparing composites and ceramics used to produce inlays and onlays.

In **Chapter 1**, CAD/CAM is defined, as are the specifications of machinable materials used to produce inlays and onlays, and then the manufacturing process – traditional or CAD/CAM – is discussed in terms of modifying the properties of composites and ceramics and whether the current materials meet the specifications listed.

Systematic review and meta-analysis

Systematic reviews and meta-analyses are the optimal approach to evidence-based dentistry [43]. In **Chapter 2**, we therefore conducted a systematic review comparing composite and ceramics for inlays and onlays. Because of lack of clinical studies on the subject, we extended the systematic review to aesthetic inlays and onlays made in the traditional way, although machined inlays and onlays were the focus of the study. We extracted all articles published in several major databases comparing composite and ceramic inlays and onlays in a randomized controlled clinical trial. We synthesized the data from these trials qualitatively and via a meta-analysis. This systematic review provides some information on the types of failures mainly encountered and gives us an idea of the material that works best in the short term. However, the studies do not allow for choosing between composite and ceramic inlays and overlays in the long term and have methodological shortcomings.

Randomized controlled clinical trial

Controlled clinical trials have long been recognized as the gold standard for evidence-based research related to clinical interventions [43]. In **Chapter 3**, we designed and implemented a randomized clinical trial comparing machined composite or ceramic inlays and onlays, trying to apply a methodology as rigorous as possible.

In the first section, we describe the trial design stages and discuss a critical methodological aspect of open and small clinical trials (which is often the case in operative dentistry): the choice of randomization method.

In the second section, we describe the implementation stages of the trial, the protocol applied clinically, and the problems encountered and how they were overcome.

Note that the implemented clinical trial is practice-based because private practitioners participated, the criteria used are almost exactly the same as those usually used for the treatment of patients and the clinicians did not receive additional training before the trial; the

results of the trial should thus have a good external validity and accurately answer the question.

In vitro study

Within the framework of the clinical trial, all clinical aspects of an inlay or onlay realization could not be assessed, so we wrote a protocol in which the only varying parameter, as much as possible, was the material machined: composite or ceramic.

Adhesion is an essential element of tissue preservation and no study has compared the adhesive properties of current machinable composites and ceramics.

To better understand the clinical phenomena related to adhesion of the restoration that occurs in a trial and study various factors that cannot all be simultaneously studied in a clinical trial (in particular the influence of the adhesive cement and the intaglio surface treatment), we performed an *in vitro* study comparing the adhesive properties of these machinable materials to different adhesive cements depending on the surface treatment chosen, presented in **Chapter 4**.

Chapter 1
Definitions and specifications

Computer Aided Design / Computer Aided Manufacturing (CAD/CAM) p.9

Specifications for tooth-colored inlay and onlay materials p.10

Techniques and materials for tooth-colored inlays and onlays p.14

Which of the two machinable materials should we choose? p.27

Résumé du chapitre en français p.29

In this first chapter, we briefly define the terms of the subject. We first define dental CAD/CAM and explain how it appeared and developed. We then describe the specifications of machinable aesthetic materials for inlays and onlays and how they articulate with the properties of dental hard tissues. Then we describe which composites and ceramics can be used to produce inlays and onlays, how their production can be modified to optimize their properties and how CAD/CAM required or allowed for modifying their composition, structure and properties. Finally, whether current machinable composite and ceramic materials meet the specifications defined is discussed.

Computer Aided Design / Computer Aided Manufacturing (CAD/CAM)

CAD/CAM is a recent industrial technology, resulting from the synthesis of CAD and CAM, which appeared with the introduction of numerically controlled machine tools (NCMT) in the 1970s [44]. CAD includes all software and geometric modeling techniques to design and virtually test products, here inlay and onlays. The objective of the CAM is to write the file containing the control program of the NCMT.

Research and development of dental CAD/CAM started in the 1980s [45]. François Duret was the first dentist, in 1971, who became interested in the application of CAD/CAM in dentistry [46]; the second was Dr. Moermann, who invented the CEREC system [47], and the third was Dr. Andersson, who developed the Procera system [48]. Thus, materials that could not be manufactured traditionally by a dental technician became available. Indirect dental CAD/CAM requires the work of a technician, while direct dental CADCAM allows the dentist to perform the restoration chairside, in a single session.

Many believe that CAD/CAM is a technology of the future, destined to grow more for practical and economic reasons [41, 42, 45, 49]. The third chapter discusses the focus on this technology because it allows, in a clinical trial, standardizing much of the clinical procedures and overcoming the technician factor that greatly influences traditional restorations.

For now, the only possible computer-assisted manufacturing method for composites and ceramics is the subtractive mode (i.e., the machining of the inlay or onlay into a block of material). In the future, additive manufacturing techniques will probably appear and will provide less expensive and more environmentally friendly restorations [41, 50].

CAD/CAM being a technology of the future and machinable materials being less well known than the materials used for the traditional technique, **we decided to focus specifically on the tooth-colored machinable materials used to produce inlays and onlays by CAD/CAM**.

Specifications for tooth-colored inlay and onlay materials

Target mechanical and physical properties are difficult to define because there is currently little correlation between the properties of composites and ceramics and their clinical performance [51, 52]. However, modern synthetic materials should be bio-inspired by enamel and dentin, which are the two major hard tooth tissues: enamel is the stiff outer layer, dentin is the softer bulk lying underneath, and the dentin–enamel junction (DEJ) is the interface between these tissues [53]. Thus, these tissue characteristics seem to dictate the specifications for an ideal composite or ceramic inlay and onlay material until optimal properties are defined.

This section describes the mechanical, physical, biological and technical specifications that machinable restorations' materials should have to mimic tooth tissue properties and obtain durable restorations.

Mechanical specifications

According to Ferracane, the main mechanical properties of consideration for use in evaluating direct composites and predicting clinical success are as follows [54]:

- Flexure strength, fracture toughness, fatigue resistance, tensile strength and wear: important
- Hardness, elastic modulus and compressive strength: intuitively important

As Ferracane issued these recommendations for direct composites, we will try to adapt them to indirect composites and ceramics used for inlays and onlays in the following paragraphs.

Flexural strength is especially important, because it includes tensile and compressive components and has some correlation with wear [54]. Thus, since the flexural strength of dental tissues is between 80 and 250 MPa for dentin [55-58] and about 80 MPa for the enamel [58], the flexural strength of the materials used should probably be at least 80 MPa (a superior limit may not exist as some materials with a very high flexural strength, such as zirconia, can perform well as prosthetic materials). ISO6872-1991 recommends that the flexural strength be

at least 100MPa for core dental ceramics and at least 50 and 55MPa for enamel and dentin ceramic masses. ISO10477-2004 mentions the flexural strength should be at least 50MPa for polymer-based crown and bridge materials.

The elastic modulus describes the extent of deformation of a material submitted to a given stress; it is important to maintain form, especially under high forces [54]. Therefore, materials used to make inlays and onlays should probably have a modulus of elasticity close to that of dental hard tissues, so that their deformation is similar during chewing. The elastic modulus is also related to the stress transfer through the restorative material to the underlying tooth structure and adhesive interface and has some correlation with the material's resistance to fatigue loading. The elastic modulus of tooth tissues is about 70-85 GPa [59-61] for enamel and 15-20 GPa [56, 59, 61, 62] for dentin.

Although hardness is not the only factor that influences wear, this surface property is important [54]. Vickers hardness of tooth tissues is about 340-360 HV [63] for enamel and 58-60 HV [63] for dentin. Because hardness is a surface property, an ideal restoration material would have a hardness close to that of enamel (except if the dentin of the antagonist tooth is exposed).

Fracture toughness, which describes a material's ability to resist the propagation of an existing crack under a particular state of stress [64], relates clinically to chipping and bulk fractures. The next chapter discusses that fracture is the most frequent failure type for ceramic inlays and onlays and is also a frequent cause of failure for composite partial restorations; it is thus an essential characteristic.

Fracture toughness of tooth tissues is about 1-2 $MPa.m^{0.5}$ for dentin [65, 66] and 0.7-1 $MPa.m^{0.5}$ for enamel [63, 67], depending on the measurement method chosen and the orientation of the dentinal tubules or enamel prisms. A restoration material should thus probably have a fracture toughness of at least 0,7 $MPa.m^{0.5}$ (a superior limit cannot be defined as maximizing fracture toughness could be desirable).

Compressive stress was reported by Ferracane as intuitively important, but most restorations likely fail in tension or shear. Fatigue resistance, tensile strength and wear are harder to test so they are not always reported and tests can vary. Enamel wear in the molar region is about 25-30 microns per year and about 15 microns per year in the premolar region; therefore acceptable clinical wear would be between 15 and 30 µm per year [68, 69].

Finally, Anusavice pointed out that computational methods and finite element stress analysis for predicting the time-dependent survivability of prostheses – ceramic prostheses in particular – because many factors can be taken into account (prosthesis design, elastic properties of the materials etc.), can be considered a future alternative to routine testing or, at least, as a complementary approach to fatigue testing [52].

Physical specifications

Still according to Ferracane, the main physical properties of consideration for use in evaluating composites and predicting clinical success are as follows [61]:

- Adhesion, contraction/expansion stress, extent/depth of cure, solubility/sorption: important
- Thermal expansion: questionable importance

Ferracane also mentioned color stability, although he stated that it is mostly important for anterior teeth, and other properties that concern direct composites but not indirect ones (shrinkage during curing and viscosity). As far as possible, the material should still mimic the optical properties of dental tissues (transparency, translucency, reflection of light, color, fluorescence, opalescence etc.).

The thermal expansion coefficient (TEC), which might affect marginal integrity [61], is about 17 10^{-6}/°C for enamel and 10.5 10^{-6}/°C for dentin [70]; therefore, a TEC of about 12 10^{-6}/°C is often aimed for. However, due to the low conductivity, diffusivity and effusivity of dental composite and ceramic materials, this property is not essential [61].

In terms of biocompatibility, the extent/depth of cure and solubility/sorption should be maximal and minimal, respectively, for inlay and onlay materials. Adhesion should be good and long lasting to optimize retention and longevity of the bond; it is mainly dictated by shrinkage and quality of the adhesive/cement [61] and by the surface treatment applied to the intaglio inlay-onlay surface [71]. ISO10477-2004 mentions the shear bond strength should be at least 5MPa for polymer-based crown and bridge materials.

Contraction/expansion stress is difficult to test and thus rarely reported.

Biological specifications

Some properties of the material are essential biologically: biocompatibility and non-toxicity in particular. They can be correlated with some physical properties (solubility/sorption and adhesion in particular).

Technical specifications

Good reproduction of details, dimensional accuracy, short processing and finishing times and machinability for CAD/CAM blocks are important technical parameters for a material's sustainability as an inlay-onlay material.

After referring to the structure and composition of materials and making the connection with the manufacturing process, whether current machinable composites and ceramics used to produce inlays and onlays meet these specifications is evaluated.

Techniques and materials for tooth-colored inlays and onlays

Many techniques and materials have been and are available to make tooth-colored inlays and onlays. The materials are not discussed exhaustively but rather how the structural and technical advances have modified the properties of these materials.

Composite inlays and onlays

The introduction of resin composites in the 1960s was a decisive step in the evolution of dentistry: this was the beginning of a cosmetic alternative to amalgams. The two major factors responsible for their properties are their structure/composition and their mode of polymerization [54]. These two aspects have evolved considerably for traditional and now machinable resin composites.

Structure/composition of the material: resin composites

Resin composites are all composed of a polymeric matrix – typically a dimethacrylate –, reinforcing fillers – typically made from radiopaque glass – (Figure 2), a silane coupling agent for binding the filler to the matrix, and chemicals that promote or modulate the polymerization reaction [51]. Increasing filler load improves various properties, including the mechanical properties, the wear and water absorption resistance of the material and the coefficient of thermal expansion [72-74].

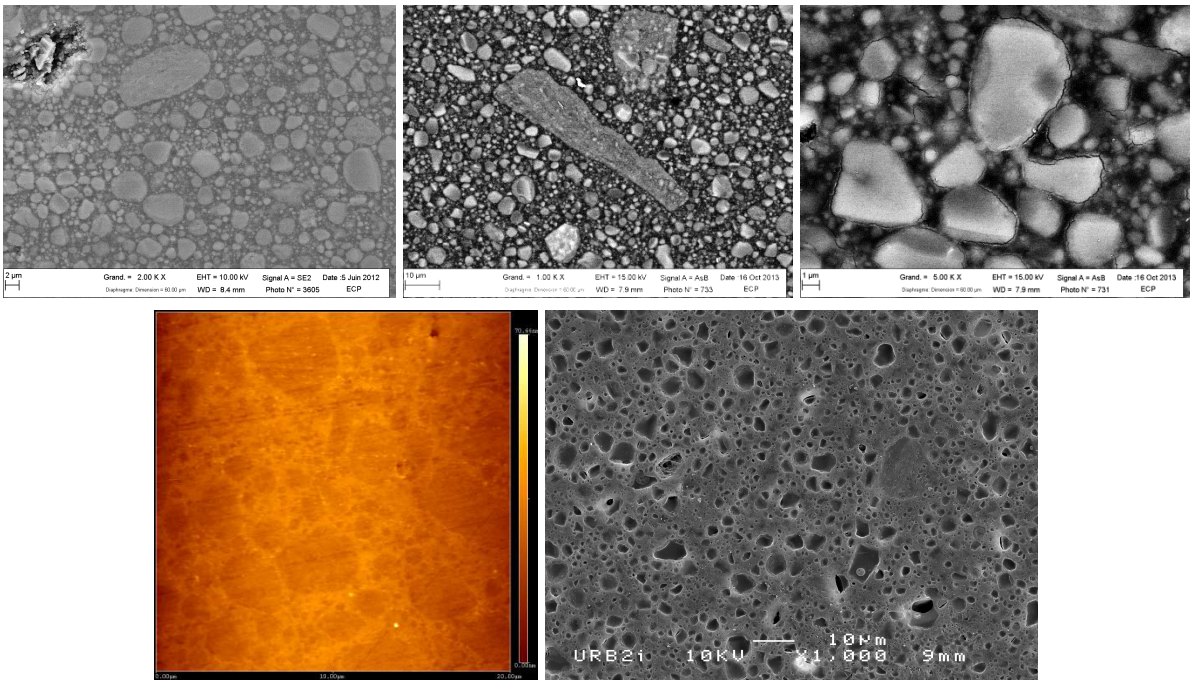


Figure 2. Structure of a machinable composite (Lava Ultimate, 3M Espe)
Above: after polishing by scanning electron microscopy (SEM)
The fillers of varying size can easily be distinguished, coated with the resin matrix.
Below: polished and analyzed by atomic force microscopy (AFM) (left) and etched with HF 35% 10s (right), fillers are attacked preferentially and the resin matrix is observed.

Direct versus indirect restoration technique

Resin composites were first developed for direct restorations, so polymerization shrinkage and wear were initially relatively high, causing recurrent caries and timely aging of the restorations, which led to consider them for indirect restorations [54, 74].

Traditionally manufactured composite inlays and onlays are usually stratified with different masses to mimic the optical properties of the tooth. The inlay or onlay may be made by the dentist, as a semi-direct technique, and the dentist often uses composites for the direct technique. It can also be made by a technician. The latter usually uses materials specifically intended to the indirect technique [74, 75].

The first major advantage of indirect composite restorations lies in the fact that the stresses due to polymerization shrinkage are exerted by a small mass of resin composite (the resin cement) compared to a direct restoration entirely made of resin composite [76]. This reduces the risk of post-operative sensitivity (due to tensile stresses on the odontoblastic processes) [77] and seems more favorable biomechanically [75, 78].

The second major advantage over direct composite restorations consists in the ability to maximize the degree of polymerization and thus the mechanical properties of the tooth-restoration entity [78-81].

Polymerization of traditional indirect composites

Initially, indirect composites were light-polymerized. However, unlike direct composites, photo-polymerization could be extended and the strobe light could be directed to all sides of the restoration [82]. Various developments have been proposed to maximize the conversion of C = C bonds of the resin matrix. A post-polymerization heat treatment (80-125 ° C) was first proposed (e.g. now in SR Adoro, Ivoclar-Vivadent and Charisma, Heraeus Kulzer, in which light and heat polymerization are done at the same time) [83-86], then replacing the normal atmospheric conditions by oxygen-free conditions was proposed (especially by substituting air with nitrogen; e.g. in Belleglass and now Premise Indirect, Kerr; or in Sculpture Plus, Pentron laboratory technologies) [77, 82]. Carrying out the polymerization gradually was also proposed (soft start polymerization; e.g. Belleglass NG, Kerr or Cristobal Plus, Dentsply) [87]. Finally, performing the polymerization under pressure was proposed (<10 bars in general; e.g. with Ivomat IP3 Oven, Ivoclar) [74].

Note that the major disadvantage of increasing the conversion rate is reduced potential for polymerization with the resin cement and thus in the adhesive properties of the material.

CAD/CAM contributions

MACHINABLE COMPOSITES

A first machinable composite, whose composition was that of a direct light-cure composite, was commercialized as blocks (Paradigm MZ100, 3M Espe). However, its properties were very close to that of the corresponding direct composite and it will not be marketed for much longer.

Actually, an increase in the inorganic phase can improve the properties of composites. For traditionally manufactured composites (by the direct or indirect technique), the viscosity must remain sufficient to allow the dentist or technician to layer the different masses. Industrial manufacturing of a composite block allows for increasing the filler rate, because the viscosity of the material is no longer a problem. However, fillers still have to be mixed with the matrix, which limits the filler rate (80% by weight in Lava Ultimate, 3M Espe, with approximately 60% of inorganic fillers and 20% of pre-polymerized resin fillers) (Figure 3).

Finally, a composite with a new structure has been commercialized recently. This composite is made of a porous inorganic (ceramic) matrix, infiltrated by resin under very high pressure (Figure 2 and Figure 3). This technique allowed for further increasing the filler rate (75% in volume and 86% by weight in Enamic, Vita). This new material type has also been referred to as a “hybrid ceramic,” “polymer-infiltrated ceramic” or “polymer-infiltrated ceramic-network” material [88, 89].

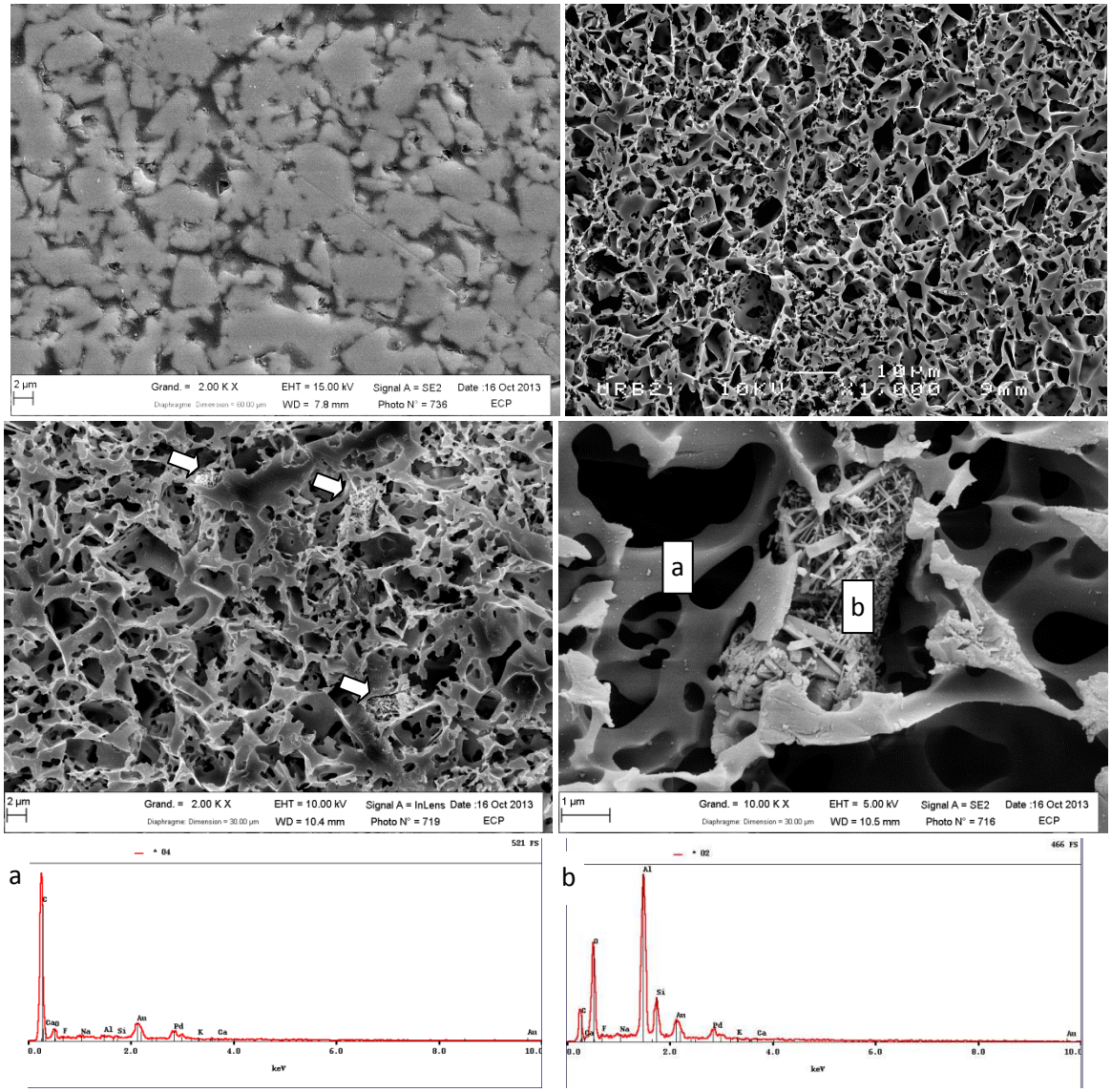


Figure 3. Structure of a polymer-infiltrated ceramic-network composite (Enamic, Vita)
Above: polished (left) and etched with 35% HF 10s (right, the ceramic matrix was removed and the resin network is observed).
Middle: some crystalline clusters (arrows and b) can be observed (left) and magnified (right)
Below: analysis confirms the main remaining network (a) is made of resin (left) and indicates the crystalline clusters (b) contain Al, O and Si (right): they are the beds for the pigments and opacifiers.

Indirect composites: traditional versus CAD/CAM machinable

Table 1 shows some important properties of a traditional composite (Filtek Supreme Ultra, 3M, after which Lava Ultimate was conceived) and two machinable composites (Lava Ultimate and Enamic).

	Modern traditional composite (Filtek Supreme Ultra)	CAD/CAM composite (Lava Ultimate)	CAD/CAM composite (Enamic)
Flexural strength (MPa)	160	200	150-160
Modulus of elasticity (GPa)	11	13	30
K_{IC} (MPa.m$^{0.5}$)	1.7	2	1.5
Volumetric shrinkage (%)	2	-	-

Table 1. Basic properties of traditional versus CAD/CAM machinable composites as published by their manufacturers

This table shows that industrial production improves the mechanical properties of traditional structure composites. The flexural strength of composites is in the lower range of the specification (100-750 MPa). The elastic modulus of the new structure composite is closer to the target set (20 GPa or more). The composites' toughness is similar to that of dentin, whether the composite is traditional or machinable.

Note that thermal expansion coefficients were not reported by the manufacturers for the three materials in this table.

Ceramic inlays and onlays

Ceramic compounds are non-metallic inorganic synthesis solids with ionic or iono-covalent bond. Ceramic materials are ceramic compounds treated with a ceramic process: these materials are prepared by consolidation at high temperature (sintering) of powders that are agglomerated (during layout).

Dental ceramics are mainly composed of oxides (and possibly fluorides) [90]. There are three main categories of ceramics according to their microstructure: glass-based systems, glass-infiltrated crystalline-based systems and polycrystalline solids. [91-93]

The category of ceramics most used to make inlays and onlays is the glass-based systems, which contain silica but also fillers that are usually crystalline. Two different glass-

based sub-categories can be considered and are or have been used to make inlays and onlays: glass based systems with sparse crystals and crystal-reinforced glass-based systems.

This category of ceramics can be obtained traditionally from powder and liquid or with the pressed technique, or through CAD/CAM by machining a block produced industrially.

The two other categories of dental ceramics are used in this indication, but anecdotally; they are usually reserved for other indications.

Glass based systems with sparse crystals

These ceramics are ternary oxides: they are alkaline (Na_2O, K_2O, Li_2O) aluminous (Al_2O_3) silicates (SiO_2). Their structure consists of a glass matrix containing approximately 15-25 vol% of crystalline dispersed fillers, including leucite crystals ($KAlSi_2O_6$), quartz (SiO_2), kaolin ($Al_2Si_2O_6$ $2H_2O$) or felspars: potassium feldspars ($KAlSi_3O_8$: orthoclase or sanidine), sodium feldspar ($Na_2Al_2Si_6O_{16}$: albite) or calcium feldspar ($CaAl_2Si_2O_8$: anorthit) (Figure 4). They also contain modifying oxides (B_2O_3) and oxides for modifying the optical properties (TiO_2, ZrO_2, SnO_2, YO_2) [90, 91, 94]

Figure 4. Natural leucite (left) and albite (right, [95]) crystals

Numerous ceramics in this category are sold, for veneering infrastructures in particular, and can be used to make inlays.

Ceramics are brittle materials with fractures occurring with little or no plastic deformation. The fracture initiates from a defect and then propagates. Initiation occurs when the stress intensity factor at the crack tip (K_I) reaches a critical level (K_{IC}). The fracture propagates from the largest flaw favorably oriented to the tensile stresses and of size greater than a characteristic crack size. Crystals help to deflect, stop or delay the crack propagation; the nature of the crystal, its size and the percentage of crystallization therefore largely affect

the material properties [96]. Larger areas or volumes of stressed material increase the probability of critical flow content and fracture [20].

This subcategory, containing few crystals (and often important porosity), is very fragile. These ceramics can be used for small inlays, but in the context of larger inlays or onlays, which are subject to greater mechanical stress and have a relatively large portion of dentin margins, the next sub-category is preferable [91, 97].

Crystal reinforced glass-based systems

This dental ceramic subcategory is the main one for inlays and onlays. The microstructure of these materials consists of a glass matrix surrounding a second phase of at least 30 vol% crystals that can be feldspar, leucite, lithium silicate, lithium disilicate or zirconia crystals. The material starts as a homogeneous glass. A secondary heat treatment (called “ceraming”) nucleates and grows crystals, which gives this class improved mechanical and physical properties because of the physical presence of the crystals and generation of compressive stress around the crystals.

Heat-pressed crystal-reinforced glass-based systems

These materials are traditionally obtained by pressing (i.e., ceramic injection from a heated glass-ceramic ingot). The equipment needed is relatively inexpensive. This subcategory comprises the following examples:

LEUCITE-REINFORCED GLASS CERAMICS

- IPS Empress Esthetic (Ivoclar) contains 35 to 45 vol% of leucite crystals of 1-5 µm that are formed by surface crystallization (i.e., the crystals grow slowly along the grain boundaries toward the center of the grain) and about 9% porosity.
- Finesse (Denstply), Authentic (Jensen), PM9 (Vita), OPC (Pentron) and CZR (Noritake) are other examples of pressed ceramics that contain leucite crystals [91].

LITHIUM DISILICATE GLASS CERAMICS

The glass matrix of e.max Press (Ivoclar) consists of 65-70 vol% of needle-like interlocked lithium-disilicate crystals ($Li_2Si_2O_5$) of length 3-6 µm and diameter 0.8µm as the main crystalline phase and about 1% porosity [91, 98].

LITHIUM-SILICATE AND ZIRCONIA REINFORCED GLASS-CERAMICS

This is a brand new category. It comprises Celtra Duo (Dentsply/Degudent), which is heat-pressed in a crystallized state.

Machinable crystal-reinforced glass-based systems

In general, blocks are fabricated from starting powders that are mixed with a binder and then pressed into a mold or extruded into a block form. Then, the blocks are transferred to a furnace to remove the binder and sinter the block to full density. Blocks have improved density and mechanical properties as compared with powder/liquid or pressed ceramics because of the standardized manufacturing process [91]. Structurally, the main difference between the structure of machinable and traditional glass-based ceramics is the degree of porosity, which is very low in blocks [91]. Glass-based blocks are generally hard-machined, i.e. the block is sintered before machining [94].

The following machinable crystal-reinforced glass-based ceramics are currently commercialized [91, 99]:

FELDSPAR-REINFORCED GLASS-CERAMICS

- Vitablocs Mark II (Vident) contain a little less than 20% in weight of feldspar polygonal particles, in particular sanidine crystals of about 2-10 µm (Figure 5). Over 20 million restorations have been fabricated for more than 20 years.
- Cerec blocks (Sirona) are very similar: the powder used is the same as that of Vitablocs Mark II.

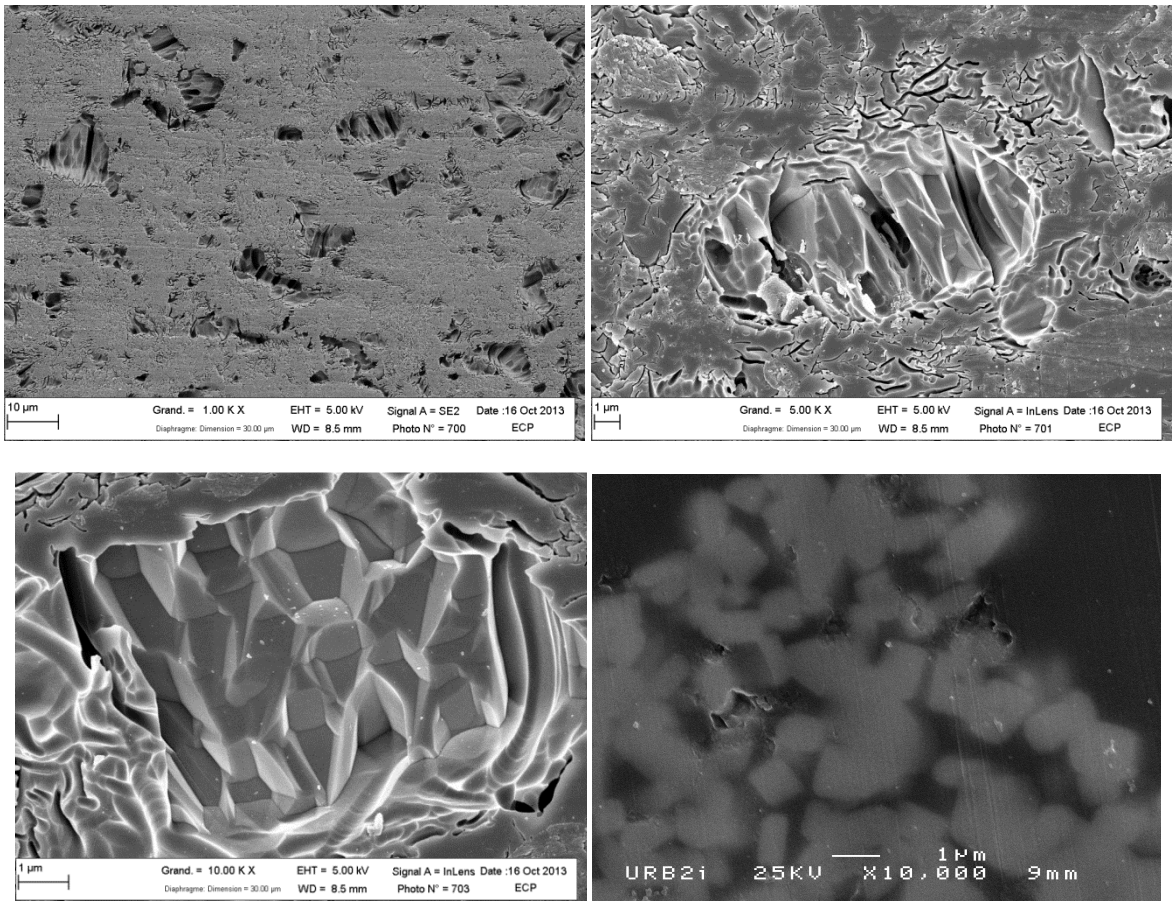
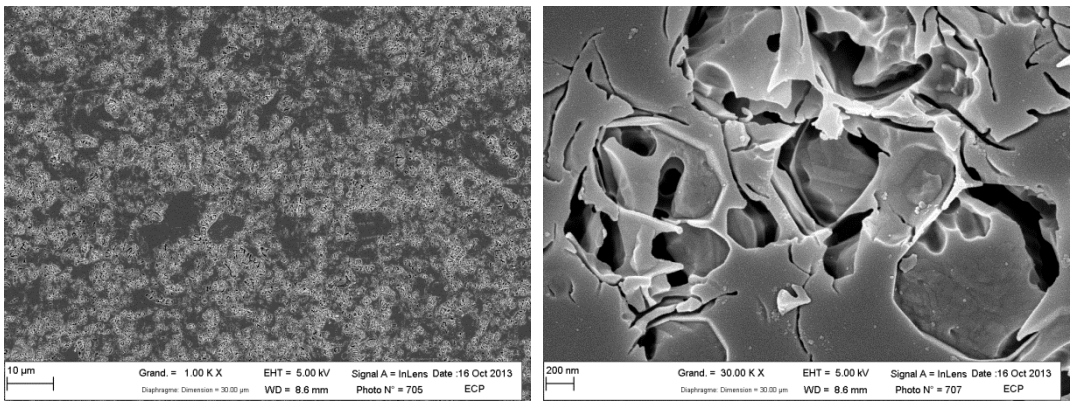


Figure 5. Structure of a machinable glass-ceramic (Mark II)
Above: 3,5% HF etched. Crystals in the glassy matrix (left), magnified crystal with lamellar twinning (right)
Below: 3,5% HF etched, a polygonal crystal can be observed (left), polished to 0.25 µm, large clusters are sometimes observed (right).

LEUCITE-REINFORCED GLASS-CERAMICS

- IPS Empress CAD (Ivoclar Vivadent) is the successor product of ProCAD. The composition is the same as that of IPS Empress Esthetic; its structure is also comparable, except that it contains fewer defects (Figure 6).



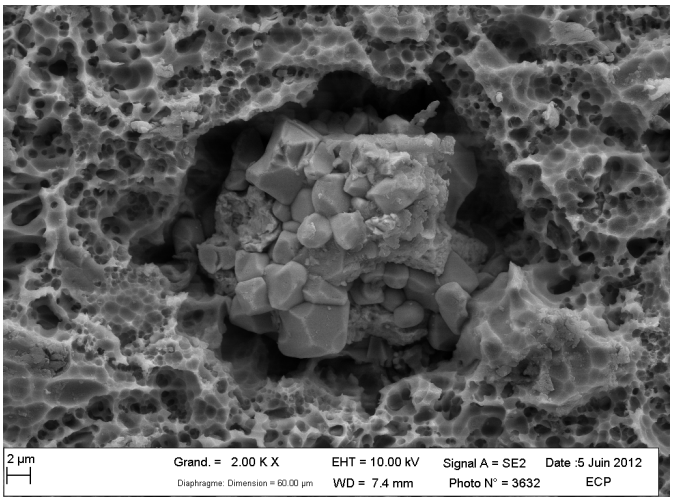
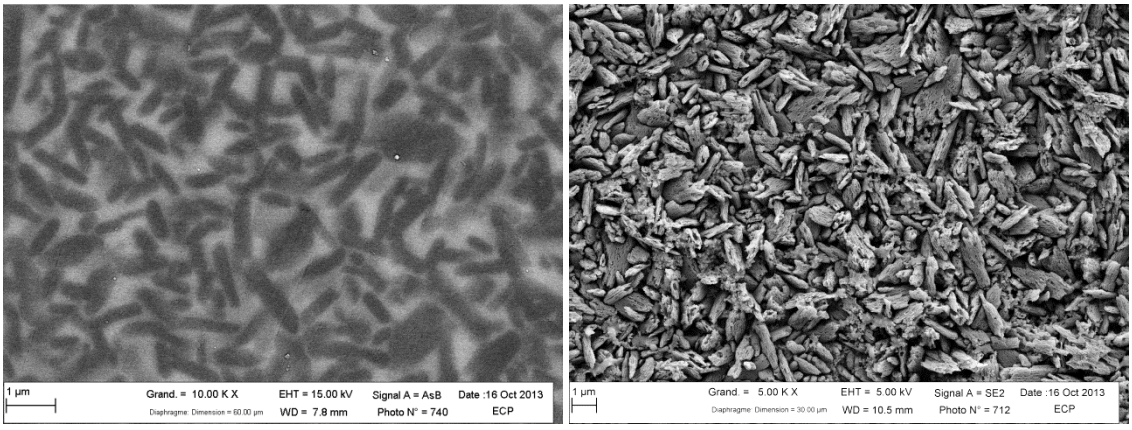


Figure 6. Structure of a leucite-reinforced glass-ceramic (Empress CAD,
above: etched with 3,5% HF for 10s, some lamellar twinning of the leucite crystals can be observed
below: 10% HF etched for 20 s, a large leucite crystals' cluster is observed).

- Paradigm C (3M Espe). It contains approximately 30% leucite crystals.

LITHIUM-DISILICATE REINFORCED GLASS-CERAMICS

- e.max CAD (Ivoclar Vivadent) contains about 70% in volume of lithium disilicate crystals of about 1.5 µm (Figure 7). e.max CAD machinable blocks (Blue blocks, because of added coloring agents) contain approximately 40% lithium metasilicate crystals (Li_2SiO_3) of about 0.5 µm and lithium disilicate crystal nuclei. This structure allows for better machinability (bur wear in particular) of the material. After milling, a heat treatment (840-850°C) in a porcelain furnace transforms the lithium metasilicate into lithium disilicate [94, 98].



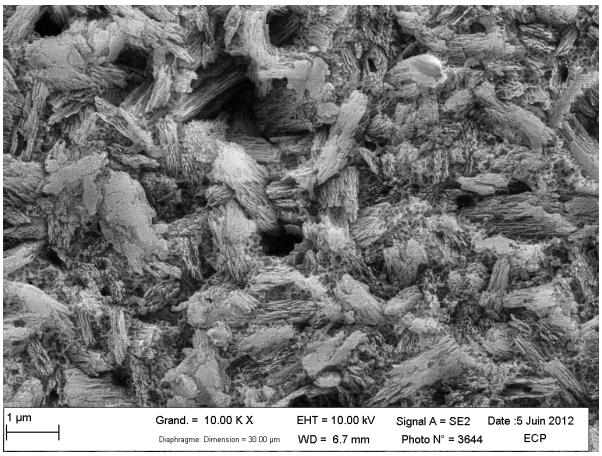


Figure 7. Structure of a lithium-disilicate reinforced glass-ceramic (e.max CAD above and left: polished, above and right: 35% HF etched for 10 s, below: 10% HF etched for 20 s).
Interlocked crystals can be observed, as well as the layered crystallographic structure.

LITHIUM-SILICATE AND ZIRCONIA REINFORCED GLASS-CERAMICS

This new category has just been commercialized. It comprises two materials: Celtra (Dentsply/Degudent) and Suprinity (Vita). They contain 10% in weight of dispersed zirconia. Celtra Duo is processed in a crystallized state while Celtra CAD must be crystallized after milling. Vita Suprinity is delivered in a pre-crystalline state and must be cristallized after milling [100].

Other ceramic categories

Some authors propose to make inlays and onlays with other ceramics. The other two categories that can be considered are as follows:

- glass-infiltrated crystalline-based systems or infiltrated ceramics (In Céram). These ceramics are mainly composed of alumina, sintered in the solid phase and later infiltrated with glass.
- Poly-crystalline solids: alumina and zirconia. These ceramics are sintered in the solid phase; their structure is exclusively crystalline [91].

The disadvantage of these ceramics is that they are more difficult to bond to tooth tissues [101]. In addition, zirconia – a material increasingly used in dental prosthesis – is sensitive to water degradation [102] and has been little evaluated in the context of full-contour restorations [101]. However, these ceramics may have mechanical advantages in certain cavity configurations, especially for large cavities [20].

Traditional versus CAD/CAM ceramics for inlays and onlays

Mechanical and physical specifications

Table 2 shows some important properties of three traditional and three machinable ceramics.

Felspathic ceramics benefit from industrial processing of CAD/CAM blocks as compared with traditional feldspathic restorations in terms of flexural strength and elastic modulus. Blocks contain much fewer defects than traditionally agglomerated powders. However, machining generates surface defects, which could be sites of crack initiation; flexural strength is indeed lower for machined bending bars.

Blocks and ingots of glass-ceramic enriched with leucite have the same composition and therefore if machining generates more defects than pressing, then the restoration obtained in the traditional way could be stronger in the end.

	Traditional feldspathic ceramic	Mark II CAD/CAM ceramic	IPS Empress Esthetic	IPS Empress CAD	IPS e.max Press	IPS e.max CAD
Flexural strength (MPa)	100[a]	150[a], 110[b]	160[a]	160[a]	400[a]	360[a]
Modulus of elasticity (GPa)	65-70	63	62	62	95	95
K_{IC} (MPa.m$^{0.5}$)	1-1.2[d]	1.7[c], 2.2[d]	1.3	1.3	2.75	2.25
Coefficient of thermal expansion (10^{-6}/K)	9-9.5	9.4	16.6 (100-400)	16.6 (100-400)	10.2 (100-400°)	10.2 (100-400°)

Table 2. Mean flexural strength, modulus of elasticity, fracture toughness and CTE of traditional and machinable glass-based ceramics as published by their manufacturers.
[a]Cut with laboratory devices, [b]Milled with dental CAD/CAM device, [c]SENB, [d]Vickers indentation.

With lithium disilicate-enriched glass-ceramics, mechanical properties of e.max CAD should be lower than e.max Press for two reasons: crystals are longer in e.max Press, and machining most probably creates small surface defects or even micro-fissures in e.max CAD. A recent study confirmed this hypothesis by comparing the fracture resistance of the assembly

of a mesio-occlusal-distal-lingual onlay in e.max Press or e.max CAD with a maxillary molar subjected to a compressive force [103].

Other specifications

Regarding technical specifications, it seems that the accuracy of fit of ceramic restorations in the traditional way is higher – at least for now – than that of CAD/CAM restorations. For example, one study compared Mark II CAD/CAM restorations made with the Cerec machine and pressed leucite-reinforced– and lithium-disilicate–reinforced glass-ceramics and found geometrical mean accuracy of 75, 52 and 60 μm, respectively [104]. Note that comparing the marginal adaptation of the same material, obtained in a traditional way or machined, would be better, and that this lesser “accuracy” might not be due to inaccuracy in the CAD/CAM chain but to ceramic chipping during milling (cf. conclusion p.146); technical properties of machinable materials have been studied very little.

Which of the two machinable materials should we choose?

Table 3 shows a short summary of some physical and mechanical properties of machinable composite and ceramics materials compared to those of dental tissues (defined earlier in the specifications).

	Composites		Ceramics			Tooth tissues	
	Lava Ultimate	Enamic	Mark II	IPS Empress CAD	IPS e.max CAD	Enamel	Dentin
Flexural strength (MPa)	200	150-160	150[a], 110[b]	160[a]	360[a]	80	80-250
Modulus of elasticity (GPa)	13	30	63	62	95	70-85	18-20
K_{IC} (MPa.m$^{0.5}$)	2	1.5	1.7[c], 2.2[d]	1.3	2.25	0.7-1	1-2
Coefficient of thermal expansion (10^{-6}/K)	?	?	9.4	16.6	10.2	17	10.5
Material wear (µm/an, µm[e])	48[e]	49[e]	23[e]	41[e]	33[e]	30-50 42[e]	-
Antagonist wear (µm/an, µm[e])	25[e]	29[e]	37[e]	67[e]	61[e]	30-50 49[e]	-

Table 3. Synthesis of the properties of machinable composites and ceramics compared to dental hard tissues
[a]Cut with laboratory devices, [b]Milled with dental CAD/CAM device, [c]SENB, [d]Vickers indentation, [e]Wear quantified by Mörmann [105].

No material fully meets all mechanical and physical specifications for the moment.

Thus, a compromise is necessary and, today, we still do not know whether composite or ceramic should be used for the CAD/CAM manufacturing of inlays and onlays. Yet millions of inlays and onlays have been milled.

Therefore, a comparison of the different machinable materials used for fabricating inlays and onlays was needed. In terms of the *in vitro* study to be described, adhesion is an important physical specification and adherence of indirect compposites and ceramics is not intrinsic; however, machinable materials have never been compared on this aspect so far.

Résumé du chapitre en français

La CFAO est une technologie industrielle récente, développée dans le domaine dentaire depuis les années 1980. Nous pensons, ainsi que de nombreux auteurs, que cette technologie est amenée à se développer pour des raisons pratiques et économiques. C'est pourquoi nous avons décidé de nous intéresser dans ce travail aux inlays-onlays réalisés en céramique ou en composite par CFAO, c'est-à-dire usinés.

Nous avons défini le cahier des charges d'un matériau pour inlays-onlays d'après les propriétés des tissus dentaires (en particulier les tissus durs que l'on cherche à remplacer : l'émail et la dentine). Mécaniquement, ces tissus ont une résistance en flexion de 80 à 250MPa, un module élastique de 15-20 GPa pour la dentine et de 70-85 GPa pour l'émail, une dureté de 350 Hv environ pour l'émail, une ténacité de 1-2 $MPa.m^{0,5}$ pour la dentine et subissent une usure annuelle de 15-30µm. Afin de minimiser le vieillissement de l'assemblage dent-restauration, il est souhaitable que le matériau prothétique se rapproche de ces valeurs. Or, pour l'instant, aucun matériau ne présente toutes ces valeurs ; un compromis est donc nécessaire. Sur le plan des propriétés physiques, les propriétés thermiques importent peu car les composites et céramiques utilisés sont peu conducteurs, effusifs et diffusifs ; en revanche, leurs propriétés adhésives devraient être optimisées et sont mal connues, de même que leurs propriétés biologiques et leur biocompatibilité. Sur le plan technique, il est souhaitable que l'usinage soit facile et produise une restauration adaptée sans générer de défaut, mais ces aspects ont également été peu étudiés.

Nous avons ensuite décrit les différents composites et céramiques permettant de réaliser des inlays-onlays. Différentes évolutions à partir des résines composites utilisées pour la méthode directe ont permis d'améliorer les performances des restaurations en composite indirectes (polymérisation progressive/sans oxygène/thermo-polymérisation/polymérisation sous pression). La CFAO permet d'aller plus loin en augmentant encore les taux de charge et le degré de polymérisation (très haute pression…). Les deux principaux composites usinables actuellement sont le Lava Ultimate (3M Espe) et l'Enamic (Vita), qui a une structure qui diffère des composites traditionnels. Les céramiques les plus adaptées aux inlays-onlays sont les céramiques à matrice vitreuse renforcées par des cristaux, dont les vitro-céramiques enrichies en feldspaths, à la leucite, au disilicate de lithium ou au silicate de lithium et à la zircone, qu'ils soient mis en forme par pressée ou usinés (Mark II, Vita ; Cerec blocs, Sirona ; Empress CAD, Ivoclar ; Paradigm C, 3M ; e.max CAD, Ivoclar ; Suprinity, Vita ; Celtra, Dentsply).

Chapter 2
Composite versus ceramic for inlays and onlays:
systematic review

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Background

Two major classes of materials allow for making aesthetic inlays and onlays. The question examined in this chapter is which of the two materials is most clinically effective.

Because this question concerns therapy, the type of study to best answer it is a systematic review of randomized clinical trials comparing composite and ceramic inlays and onlays in terms of clinical criteria.

We wondered whether such a systematic review had already been published. No study was found by a search of the PubMed, Embase and Cochrane databases. Three reviews of the literature treating part of this problem were published: a 1997 review by Jean-François Roulet dealing with the advantages and disadvantages of aesthetic alternatives to dental amalgam [106] and a 2001 review by Hickel and Manhart updated in 2004 on the longevity of posterior direct and indirect restorations [13, 107].

Two systematic reviews dealt with inlays and onlays. The first concerned CAD/CAM single-unit restorations and reported an estimated 5-year survival rate of 90.6% [29,6-99,2] for composite and 94.2% [89,8-96,7] for ceramic restorations. However, different types of restorations were considered in the latter study and composite restorations were not assessed enough for a comparison [108].

The second systematic review, conducted by the Cochrane Collaboration, "Ceramic inlays for restoring posterior teeth" was published in 2003; it has not been updated and covered only one study comparing ceramic and gold inlays. The Cochrane search filter for clinical trials had not been applied [109].

In France, the High Authority for Health (HAS) published a report in 2009 on "Tooth reconstruction by embedded materials" (« *Reconstitution d'une dent par matériau incrusté »)* [110]. The report indicated "no differential indications between ceramic and composite inlays and onlays except for large-volume restorations where ceramic is preferred", whereas the "composite inlay/onlay has an advantage in case of repair" and finally that studies comparing composite and ceramic inlays and onlays have "short follow-up periods that do not allow for detecting a difference between composites and ceramic inlays and onlays."

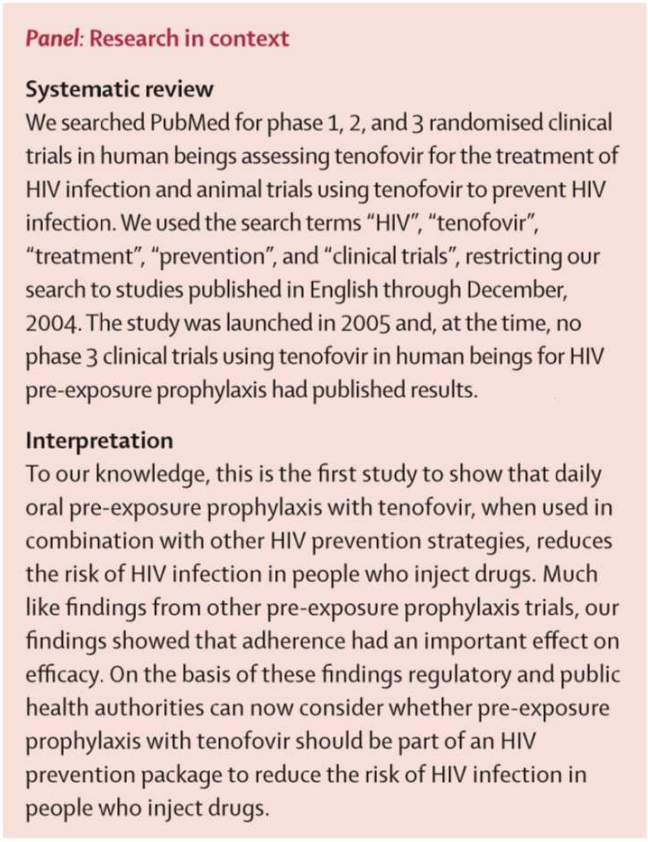
Because no systematic review answered the question posed, we conducted a systematic review of randomized clinical trials comparing composite and ceramic inlays and onlays in terms of clinical criteria.

Summary of the work that was carried out

We performed this work before the clinical trial, which is discussed in the next chapter. However, the study entailed methodological difficulties. In particular, we could not find a search equation that identified all clinical studies evaluating composite and ceramic inlays and onlays because of indexing, which is still often approximate in dental studies: MeSH terms are not always accurate and are rarely used for indexing in PubMed.

Along with the thesis, we worked on updating a Cochrane review entitled "Pulp treatments for extensive decay in primary teeth" [111]. In the end, the review was completely re-written for several reasons: the reasons for inclusion/exclusion in the initial review were not always clear and the review should comply with the latest version of the Cochrane handbook for systematic reviews of interventions [112]. Working with methodologists of the Cochrane Oral Health Group (based in Manchester) and the French Cochrane centre (based in Paris) allowed for increasing our knowledge of the methodology of systematic reviews. As well, the endpoints of these treatments were developed [113].

Upon publication of the trial protocol, to be detailed in the second chapter, we considered that it would be better to base the introduction on a systematic review and make a box section summarizing data from previous trials concerning the same question, as proposed by *The Lancet* in 2005 (cf. Figure 8 below).



***Panel*: Research in context**

Systematic review

We searched PubMed for phase 1, 2, and 3 randomised clinical trials in human beings assessing tenofovir for the treatment of HIV infection and animal trials using tenofovir to prevent HIV infection. We used the search terms "HIV", "tenofovir", "treatment", "prevention", and "clinical trials", restricting our search to studies published in English through December, 2004. The study was launched in 2005 and, at the time, no phase 3 clinical trials using tenofovir in human beings for HIV pre-exposure prophylaxis had published results.

Interpretation

To our knowledge, this is the first study to show that daily oral pre-exposure prophylaxis with tenofovir, when used in combination with other HIV prevention strategies, reduces the risk of HIV infection in people who inject drugs. Much like findings from other pre-exposure prophylaxis trials, our findings showed that adherence had an important effect on efficacy. On the basis of these findings regulatory and public health authorities can now consider whether pre-exposure prophylaxis with tenofovir should be part of an HIV prevention package to reduce the risk of HIV infection in people who inject drugs.

Figure 8. Example of a "Research in context" panel from *The Lancet* [114]

Therefore, we performed a systematic review of randomized clinical trials comparing composite and ceramic inlays and onlays.

Drafting the protocol and registering the systematic review

Search equation

With experience in conducting a Cochrane review, a search equation of randomized clinical trials comparing composite and ceramic inlays and onlays could be defined.

In particular, the Cochrane filter for clinical trials was changed by adding the term "clinical study" because many dental clinical studies are so called, and not "clinical trial" which is sought by the Cochrane method. The final search equation is in Appendix 1.

Data extraction form

The data to extract from trials was defined and a data extraction form prepared (Appendix 2).

Registering the review

Finally, the systematic review was registered in the Prospero register on January 2, 2013 (Appendix 3).

Conducting the systematic review

The search equation was implemented on December 24, 2012.

Reports identified in each of the 3 databases were exported to Endnote, which allowed us to eliminate duplicates; 145 reports were retrieved by the search equation (Appendix 4).

Articles that met the inclusion criteria were searched first on the title, then on the abstract or summary (Appendix 5), and finally on the full text (Appendix 6).

The methodology and format of the tables we had developed for conducting the Cochrane review were followed again for this review.

After completing the selection and data extraction, the Prospero record was updated on March 28, 2013.

Revman 5 software, created by the Cochrane Collaboration, was used to analyze the risk of bias of included studies and create the corresponding figures, as well as for quantitative synthesis of primary endpoint data.

Publication

The article below was written. Before submission, new publications on the subject were searched.

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Review

Clinical efficacy of composite *versus* ceramic inlays and onlays: A systematic review☆

Hélène Fron Chabouis[a,b,d,*], *Violaine Smail Faugeron*[a,c], *Jean-Pierre Attal*[a,b]

[a] *Department of Biomaterials (URB2i, EA4462), Université Paris Descartes, Sorbonne Paris Cité, Montrouge, France*
[b] *Dental Department, Charles-Foix Hospital, AP-HP, Ivry-sur-Seine, France*
[c] *Dental Department, Bretonneau Hospital, AP-HP, Paris, France*
[d] *Ecole doctorale Galilée, Université Paris 13, Sorbonne Paris Cité, Villetaneuse, France*

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ABSTRACT

Objectives. Large tooth substance losses are frequent in posterior teeth because of primary caries or aging restorations. Inlays and onlays are often the minimal invasive solution in such cases, but the efficacy of the composite and ceramic materials used is unknown. We performed a systematic review of randomized controlled trials comparing the efficacy of composite and ceramic inlays or onlays.

Data sources. MEDLINE, Embase and the Cochrane Central Register of Controlled Trials were searched without any restriction on date or language, as were references of eligible studies and ClinicalTrials.gov.

Study selection. Eligible studies were randomized trials comparing the clinical efficacy of composite to ceramic inlays or onlays in adults with any clinical outcome for at least 6 months. From 172 records identified, we examined reports of 2 randomized controlled trials involving 138 inlays (no onlays evaluated) in 80 patients and exhibiting a high-risk of bias. Outcomes were clinical scores and major failures. The 3-year overall failure risk ratio was 2 [0.38–10.55] in favor of ceramic inlays although not statistically significant. The reported clinical scores (United States Public Health Services and Californian Dental Association) showed considerable heterogeneity between trials and could not be combined.

Conclusions. We have very limited evidence that ceramics perform better than composite material for inlays in the short term. However, this result may not be valid in the long term, and other trials are needed. Trials should follow Fédération dentaire internationale recommendations and enhance their methodology. Trials comparing composite and ceramic onlays are needed.

☆ Systematic review registration number: CRD42013003441.

* *Corresponding author at*: Service de biomatériaux (pôle de recherche Clinique), 1 rue Maurice Arnoux, 92120 Montrouge, France. Tel.: +33 1 58 07 67 25; fax: +33 1 58 07 68 99; mobile: +33 6 22 78 72 64.
E-mail addresses: helene.fron@parisdescartes.fr, fronhelene@gmail.com (H. Fron Chabouis).

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1. Introduction

Dental caries is still a common disease worldwide and results in tooth substance loss. Inlay or onlay restorations are widely used to treat moderate Class I and II losses. Inlays and onlays can be made of alloy, composite or ceramic material. However, patients often refuse metallic restorations, so practitioners must choose between the 2 esthetic materials: ceramic and composite.

Many studies have compared these materials *in vitro*. Ceramic inlays and onlays are mainly composed of glass, with some crystals added to increase strength [1]. Composite inlays and onlays are made of a resinous matrix and fillers of different types [2]. Ceramic materials are resistant to compressive forces but are susceptible to tensile stresses and more prone to fracture than are composite materials [3,4]. However, ceramics are harder than composites and more wear-resistant but can induce more wear than usual with the opposing tooth's surface [5,6]. Furthermore, adhesive cement interfaces are made of composite material, so the wear of the interface and restoration material should be closer for composites and marginal integrity could be better [7,8]. Another disadvantage of composites is their resinous matrix and the possible monomer release if it is incompletely polymerized [9].

Although *in vitro* studies generally do not predict *in vivo* results [10–13], few clinical studies have verified these *in vitro* findings concerning the performance of composite and ceramic for inlays and onlays.

Several clinical studies have evaluated ceramic and composite materials separately [8,13–37]. Yet, we can draw no definite conclusions on the best material from these studies. In 1997, Roulet et al. concluded that "very little" was known about the longevity of esthetic inlays. The authors mentioned the difficulty in obtaining a strong bond between the restoration's surface and the tooth for composite inlays [38], but this problem has since been solved [39,40]. In 2001, Hickel and Manhart reported an annual failure rate of 2.3% (range: 0–11.8%) for composite inlays and onlays, as compared with 1.3% (range: 0–7.5%) for ceramic inlays and onlays evaluated in longitudinal studies [41]. In 2004, the same authors reported an annual failure rate of 2.9% (SD 2.6) for composite inlays, as compared with 1.9% (SD 1.8) for ceramic restorations [42]. Note that we have no evidence for linear failure rates of inlays and onlays, so the latter results can be discussed.

Finally, material knowledge has evolved, new materials have been developed, and no systematic review has answered the question posed by practitioners: Is the clinical efficacy of composite or ceramic better for inlay and onlay manufacturing?

We aimed to perform a systematic review of published reports of randomized controlled trials comparing the efficacy of composite and ceramic inlays and onlays for restoring posterior teeth of adults.

2. Methods

The review is registered, and the protocol can be accessed on the Prospero website [43].

Eligible studies were randomized controlled trials comparing the clinical efficacy of composite to ceramic inlays or onlays. Any composite or ceramic material was eligible. Patients had to be adults, treated in any dental care center or practice. The follow-up had to be 6 months or more. We searched MEDLINE, Embase and the Cochrane Central Register of Controlled Trials (Central) without any restriction on date or language. The last search was on December 24, 2012. The full electronic search strategy is in Appendix 1. We searched ClinicalTrials.gov to identify ongoing trials. The references of all eligible trials were checked for other relevant studies.

Two authors independently and in duplicate screened the titles of records retrieved by the search, then screened the selected abstracts to identify studies that potentially met the eligibility criteria. Any disagreements were resolved by discussion and the reasons for exclusion were recorded. The full text of potentially eligible studies was retrieved and assessed for

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eligibility by the same authors. Again, the reasons for exclusion were recorded.

A standardized, pre-piloted form was used to extract data from the included studies for assessment of study quality and synthesis of evidence. Data were extracted on (1) general trial information (publication year, number of patients treated, number of inlays or onlays manufactured, and number of operators); (2) intervention characteristics (rubber dam isolation, base or liner application, inlay/onlay materials and manufacturing technique(s), adhesive and cement), and (3) outcome data (clinical scores [United States Public Health Services (USPHS) or Californian Dental Association (CDA) or Fédération dentaire internationale (FDI) criteria] and restoration failures). The clinical scores are usually ordinal variables that measure the quality of the restoration according to a variety of dimensions. When published, in 1971, the USPHS scale comprised 3 grades (Alfa, Bravo and Charlie: Charlie being pejorative and Alfa being favorable) and 5 items (color match, cavosurface marginal discoloration, anatomic form, marginal adaptation, and caries). A fourth grade (Delta) was later added. The CDA scale is similar (except the grades are Romeo, Sierra, Tango and Victor) [44]. The consensus FDI score, published in 2007, comprises 5 grades (from 1 to 5, 1 being ideal and 5 corresponding to a restoration that needs replacement) and 18 items that comprise the 5 initial USPHS items [45]. Any event that required replacement of the inlay or onlay was defined as a failure. Failure types were also extracted and classified according to failure cause: inlay fracture, tooth fracture, recurrent caries, persisting hypersensibility and endodontic treatment.

The risk of bias for each study was assessed by the Cochrane Collaboration Risk of Bias tool, which includes the following domains: methods for sequence generation and maintaining allocation concealment, blinding, and incomplete outcome data [38,46,47]. Each domain was rated as low, high, or unclear risk of bias. Within-study selective outcome reporting was not assessed because we did not have access to study protocols. Blinding of dental staff (operators and clinical evaluators) is not possible because both materials can easily be recognized by an experienced eye, so this domain was not assessed and the tool was slightly modified to take into account intervention standardization and the risk of bias during clinical outcome assessment. The standardization risk was high if the cavity preparation or the adhesion procedure differed between treatment groups; it was low otherwise and unclear if these aspects were insufficiently or not reported. The clinical outcome assessment risk was low if 2 independent evaluators or 1 evaluator distinct from the operator had completed the clinical follow-up examinations; it was high otherwise and unclear if these aspects were insufficiently or not reported. The source of funding was also extracted.

The unit of analysis was the tooth. For clinical score outcomes, we reported only percentages of restorations assessed with the best grade (i.e., 1 for FDI criteria, A for USPHS criteria, R for CDA criteria). For each item, we estimated risk ratios for the restoration to be assessed with the best grade (considered the event). To take into account patients with missing outcome data, we assumed that the proportion of patients with the best grade was the same in complete cases and in patients with missing outcome data. For the dichotomous failure outcome, the measure of treatment effect was the risk ratio. To allow for an intention-to-treat analysis, we imputed missing outcome data as success.

When a study included multiple composite or multiple ceramic groups, all composites were combined into a single composite group and/or all ceramics were combined into a single ceramic group [48]. We synthesized trials comparing at least one composite and one ceramic with the same outcome (item score or failure) at a given follow-up time. The decision whether or not to combine the results of individual studies depended on the assessment of heterogeneity in forest plots and by I^2 coefficients. Combined estimates and associated 95% confidence intervals were calculated by use of Mantel–Haenszel fixed-effect methods.

3. Results

3.1. *Description of studies*

3.1.1. *Results of the search*

In all, 172 records were identified by a search of MEDLINE, Embase and Central databases (Appendix 2). We discarded 27 duplicates, and thus screened and assessed 145 record titles for eligibility. Finally, 84 abstracts (Appendix 3) and 12 full-text articles were screened: 4 records met all eligibility criteria, but 3 records concerned a single study, so only 2 prospective randomized clinical studies were finally included in the review (Appendix 4 and Fig. 1). For the Fasbinder et al. [49] trial, 3-year results were published in 2005 and for the Thordrup et al. [50] trial, 1-year, 5-year and 10-year results were published in 1994, 2001 and 2005, respectively. We did not identify any additional trial from ClinicalTrials.gov.

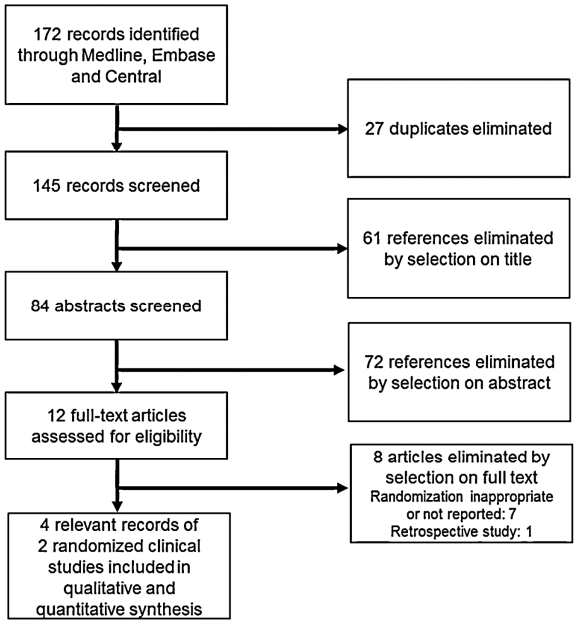

Fig. 1 – Study flow diagram.

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Table 1 – Patient, teeth and intervention characteristics of included studies.

	Fasbinder study	Thordrup study
Trial characteristics		
No. of operators	2	1
No. of centers	1	1
Patient characteristics		
Number	43	37
Gender (% women)	–	81
Age (years)	–	23–69
Teeth characteristics		
Number	80	58
Maxillary/mandibular (%)	55/45	–
Primary/secondary caries	Primary or secondary	Secondary
Cavity type	Occluso-proximal or mesio-occluso-distal	Mesio-occluso-distal
Interventions characteristics		
Base application	No	Yes (Dycal, Caulk and Vitra Bond, 3M)
Composite materials [no. of inlays]	Paradigm MZ100 (3M Espe): 85 wt% nanocrystalline zirconia-silica spherical ceramic fillers; polymer matrix: bisGMA, TEGDMA, patented ternary initiator [40]	Estilux (Heraeus Kulzer): 77 wt% glass particle fillers; polymer matrix: bisGMA, pigments [14] Brilliant D.I. (Coltene): 77–78 wt% glass particle fillers, polymer matrix [15]
Ceramic materials [no. of inlays]	Mark II (Vita): fine particle feldspar ceramic (SiO_2, Al_2O_3, Na_2O, K_2O, CaO, TiO_2, pigments) [40]	Cerec blocks (Sirona): fine particle feldspar ceramic (SiO_2, Al_2O_3, Na_2O, K_2O, CaO, TiO_2, pigments) [15] Vita Dur N (Vita): fine particle feldspar ceramic (SiO_2, Al_2O_3, K_2O, B_2O_3, Na_2O, pigments) [14]
Rubber dam isolation	Yes	No
Adhesive	Single Bond (3M Espe)	Gluma 2 and 3 (Bayer), Durabond resin
Cement	Rely X ARC (3M Espe)	Cerec Dual Cement (Kulzer)

3.1.2. *Characteristics of trials, patients, teeth and interventions*

The 2 trials investigated 138 teeth for 80 patients. Characteristics of each trial are presented in Table 1. In both trials, patients had low caries risk (Fasbinder et al. "scored all enrolled patients as having a low caries risk" while "patients with [. . .] high caries progression" were excluded in Thordrup's study), all teeth were vital at inclusion and all restorations were inlays; no onlay was evaluated.

The Fasbinder trial was two-arm; all inlays were direct (chairside) CAD–CAM manufactured, with the Cerec 2 unit. Cavity preparation involved butt joint margins (without bevels) and a wall divergence of 6°–8°.

The Thordrup trial was four-arm: Cerec and Brilliant D.I. inlays were directly manufactured (by the operator, with the Cerec Cos 2.0 for Cerec inlays) and Vita Dur N and Estilux inlays were indirectly manufactured (by a dental technician). Margins and wall divergence were not detailed, but divergence was greatest for the Brilliant D.I. composite and least for the Cerec. A noneugenolic temporary filling (Fermin, Detax dental) was placed between visits for indirect inlays.

3.2. *Risk of bias of trials*

The risk of bias for each study is in Fig. 2; risk of bias tables are in Appendix 5. The risk of bias was high overall for both studies. The random sequence generation was not reported in either study. For the Thordrup study, the randomization was mentioned in the 10-year report but not in the 1- and 5-year reports. The allocation was concealed only in the Fasbinder study. Cementation standardization was correct in both studies, but preparation was standardized only in the Fasbinder study. Patients were not blinded in the Thordrup study and no information was given for the Fasbinder study. Concerning clinical outcome assessment, the risk of bias was low in the Fasbinder study and unclear in the Thordrup study because the process differed between assessment times. Radiographs were taken in the Thordrup study, but the report gave no information concerning radiograph assessment; no radiographic

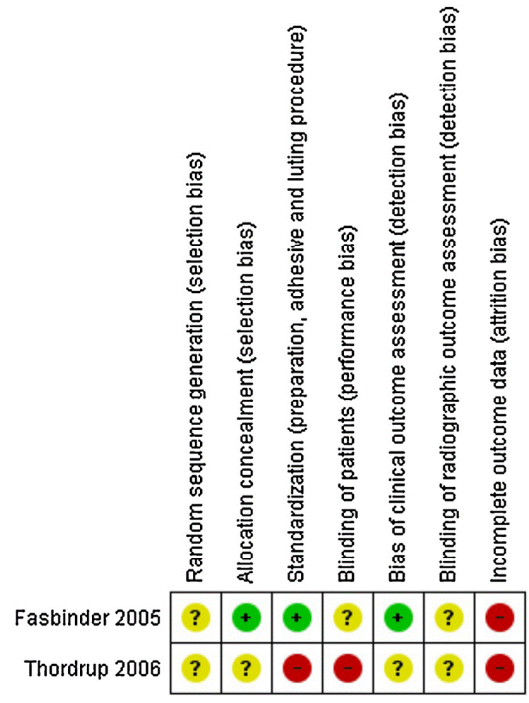

Fig. 2 – Risk of bias of included studies (by the Cochrane Collaboration Risk of Bias tool).

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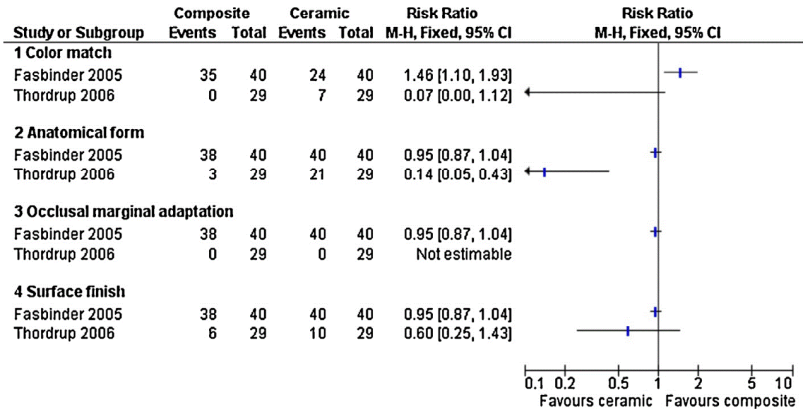

Fig. 3 – Forest plot of the risk ratio for composite or ceramic inlays assessed by the best grade for 4 common items. Events correspond to inlays assessed by the best grade according to the criteria used in the study (A for United States Public Health Services in the Fasbinder study; R for California Dental Association in the Thordrup study).

examination was reported for the Fasbinder study. Both studies exhibited attrition bias according to the Cochrane's Risk of Bias tool. The Fasbinder study was supported by Septodont and 3M. The source of funding was not mentioned for the Thordrup study.

3.3. *Efficacy of ceramic versus composite inlays and onlays*

In the Fasbinder study, 37 patients received 2 inlays, and 6 patients each received 1 inlay. In the Thordrup study, 17 patients received 2 inlays and 20 patients each received 1 inlay. Pairing of data needed to be taken into account in the analysis, but intra-patient correlation was not taken into account and patient data were not reported in either trial, so we could not reanalyse data appropriately.

The duration of follow-up was 3 and 10 years in the Fasbinder and Thordrup trials, respectively. Clinical outcome was assessed at baseline, 6 months, and 1, 2 and 3 years in the Fasbinder trial and at baseline, 6 months, and 1, 3, 4, 5 and 10 years in the Thordrup trial.

3.3.1. *FDI/USPHS/CDA score*

In the Fasbinder trial, clinical outcome assessment of inlays involved the modified USPHS criteria. The trial evaluated color match, margin discoloration, anatomical form, margin finish, marginal adaptation, surface finish, cusp/tooth fracture, caries, restoration fracture and proximal contact. Postoperative sensitivity was evaluated once a week by telephone interview. In the Thordrup trial, clinical outcome assessment of inlays involved the CDA criteria. The trial evaluated color match, anatomical form, marginal adaptation, surface finish and proximal contact. These criteria were reported only in the 1- and 5-year articles. Proximal contact grades were not reported for either study.

The number of events (restorations that received the best grade) by the 4 criteria that were reported by both studies is in Fig. 3. The Fasbinder study reported 3-year grades and the Thordrup study 5-year grades (3-year R percentages were reported but not the number of patients with missing outcome data).

The color match risk ratio was statistically in favor of composite inlays in the Fasbinder study; in the Thordrup study, the color match risk ratio appeared in favor of ceramic inlays although this was not statistically significant. The anatomical form risk ratio was in favor of ceramic inlays in both studies (without statistical significance in the Fasbinder study and with significance in the Thordrup study). The marginal adaptation risk ratio was not significantly in favor of ceramic inlays in the Fasbinder study and the risk ratio was not estimable in the Thordrup study (no inlay was assessed with an R rating). The surface finish risk ratio was in favor of ceramic inlays in both studies but was not statistically significant.

Thus, for all 4 criteria except color match, ceramic inlays performed insignificantly better than composite inlays.

Because of the heterogeneity in the definition of the outcomes and the considerable statistical heterogeneity in the 4 common item grades (color match: $I^2 = 86\%$; anatomical form: $I^2 = 99\%$; surface finish: $I^2 = 74\%$), the clinical scores could not be combined.

3.3.2. *Failure*

Failures, with their type and the time they occurred, are described in Table 2.

In the Fasbinder study, 40 composite and ceramic inlays were fabricated at baseline. After 3 years, 2 composite inlay failures (symptomatic partial tooth fractures) occurred, for a 95% success rate after 3 years; 1 ceramic inlay failure (fracture) occurred after 3 years, for a 97.5% success rate. The 3-year failure risk ratio was thus 2 [0.19–21.18] in favor of ceramic inlays although not statistically significant.

In the Thordrup study, 29 ceramic and composite were fabricated at baseline. After 3 years, 2 composite inlay failures (1 recurrent caries and 1 persisting hypersensitivity) occurred, for a 93.1% success rate; 1 ceramic inlay failure (fracture) occurred, for a 96.5% success rate. The 3-year failure risk ratio was thus 2 [0.19–21.86] in favor of ceramic inlays although not statistically significant.

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Table 2 – Types of failure of composite and ceramic inlays and failure times for included studies.

Study and material (*N*)	Failure type	No. of failures	Failure time (years)
Fasbinder (80)			
Composite (40)	Symptomatic partial tooth fracture	2	2; 2
Ceramic (40)	Inlay fracture	1	3
Thordrup (58)			
Composite (29)	Inlay fracture	1	6.5
	Caries	2	1; 5
	Persisting hypersensitivity	1	2
	Endodontic treatment	1	8
Ceramic (29)	Inlay fracture	5	1; 4; 4.5; 8.5; 9.5
	Caries	2	4.5; 8.5

After 5 years, 3 composite failures occurred, for an 89.7% success rate, and 4 ceramic failures occurred, for an 86.2% success rate. The 5-year failure risk ratio was thus 0.75 [0.18–3.06] in favor of composite inlays although not statistically significant. After 10 years, 5 composite failures occurred, for an 82.8% success rate, and 7 ceramic failures occurred, for a 75.9% success rate. The 10-year failure risk ratio was thus 0.71 [0.26–1.99] in favor of composite inlays although not statistically significant. Note that only 19 (65.5%) composite and 22 (75.9%) ceramic inlays were followed up at 10 years, for success rates of 73.7% for composite inlays and 68.2% for ceramic inlays and a failure risk ratio of 0.83 [0.31–2.18] if the analysis was not by intention to treat.

Fig. 4 shows the forest plot for 3-year failure risk ratios. Because visual examination of the forest plot and the null I^2 indicated low heterogeneity [50], the 3-year failure risk ratios could be combined. The resulting overall 3-year failure risk ratio was 2 [0.38–10.55] in favor of ceramic inlays although still not statistically significant. The overall 3-year success rate was 94.2% for composite inlays and 97.1% for ceramic inlays.

Most failures were inlay fractures for ceramic inlays; 2 occurred in the first 3 years, for a 2.9% fracture rate for ceramic inlays. Failures were more varied in the composite group (secondary caries, persisting hypersensitivity).

4. Discussion

This systematic review examined reports of 2 randomized controlled trials comparing the efficacy of composite and ceramic inlays for restoring posterior teeth because of primary caries or aging restorations. The 3-year clinical scores showed heterogeneity between the studies. Color match results favored composite inlays in the Fasbinder study and ceramic inlays in the Thordrup study. Materials layered by a laboratory technician yielded more esthetic restorations. In both trials, ceramic inlays showed better anatomical form and surface finish although not statistically significant. This finding could be expected in light of the wear behavior of ceramic materials, which usually wear less than composite materials [6]. Occlusal marginal adaptation was not significantly better for ceramic than composite inlays in the Fasbinder study but was significantly better for composite than ceramic inlays after 3 years in the Thordrup study, which was expected by the authors because the wear of the adhesive luting material should be closer to composite than ceramic material [7,8]. However, cement wear seems to slow once a small interfacial gap has been created, thus preventing the cement from further abrasion. Proximal contacts were evaluated in both studies but were reported for neither. Other items were evaluated in only one of the trials. In the Fasbinder trial, almost all grades evaluating the clinical outcomes were optimal, but the Thordrup trial featured many intermediate grades: the considerable heterogeneity in grades attributed to the restorations between these 2 trials outlines the need for calibration of assessment criteria [52].

Failures necessitating inlay replacement were well reported for both trials. Thus, we could combine failure data for each material because of the low heterogeneity; the resulting overall 3-year failure risk ratio was 2 [0.38–10.55] in favor of ceramic inlays. Therefore, we provide some evidence that ceramic inlays perform better than composite inlays in the short term for this outcome. However, the risk ratio in the Thordrup study was 0.75 [0.18–3.06] after 5 years and 0.71 [0.26–1.99] after 10 years and therefore in favor of composite inlays although still not statistically significant. This finding may be due to ceramic fatigue with time, because most failures affecting ceramic inlays were fractures and occurred after 3 years. The only composite inlay fracture, although possibly occurring at random, occurred after 6.5 years in the "direct" composite group; direct composite restorations are generally considered materials less mechanically resistant than indirect CAD–CAM or laboratory-manufactured composites [53–55].

Our review contains some limitations. First, the 2 included studies were small in size, which means that only 80 patients with 138 restorations were analyzed in the review and subsequent meta-analysis. Second, included trials had methodological limitations. Although both trials were small sized and the main prognostic factors (such as tooth or cavity type) could have been taken into account at the time of randomization to enhance the similarity of groups, the random sequence generation was not detailed for either study [56]; in the Thordrup trial, the allocation description was unclear and the quality of the randomization can be questioned. Neither study entailed operator or clinical assessor blinding, because an experienced dentist's eye can easily distinguish ceramic and composite inlays; patient blinding can be difficult in this situation. Because the trials were open-labeled, recall evaluations could be completed by at least one evaluator distinct from the operator(s), which was the case in the Fasbinder study but not in the Thordrup study, at least during the 10-year follow-up. In all, 11.25% inlays were lost to follow-up after 3 years in the Fasbinder study, and 10.3% inlays were

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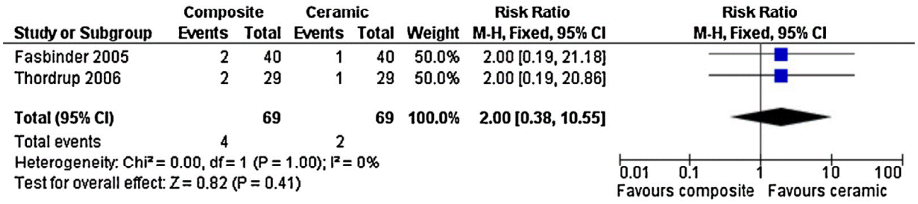

Fig. 4 – Forest plot of the risk ratios for 3-year failure rates of composite and ceramic inlays.

lost to follow-up after 10 years in the Thordrup study, so risk of attrition bias seemed lower in the Thordrup than Fasbinder study. As compared with other operative trials in dentistry, the follow-up seemed acceptable in both studies. The protocol was not publicly available for either study but this was not required in dental research when both studies started. However, both the USPHS and the CDA criteria include color, anatomic form and marginal characteristics (adaptation, discoloration and caries); all of these items are reported in the Fasbinder trial, so the risk of selective reporting seems low; marginal discoloration was mentioned in none of the three Thordup trial reports, which may suggest a risk of selective reporting.

Although the Fasbinder study was supported by Septodont and 3M, the study did not report extraordinary findings in favor of the 3M Paradigm composite material. Because of some methodological limitations at the study level, the risk of bias was high according to the Cochrane Risk of Bias tool, but some limitations were inherent to the research and period when the studies were conducted. Third, clinical limitations were limited. No base or liner was used in the Fasbinder study, so cavity preparation was probably less preservative than in the Thordrup study, which used RMGI in undercuts. However, the Thordrup study did not use a rubber dam and modified cavity preparation depending on the inlay material used as opposed to the Fasbinder study. Finally, consensus outcomes for evaluating dental restorations are now the FDI criteria, but these criteria were not available when both studies started. However, the former criteria (CDA and USPHS) were incompletely reported and incorrectly analyzed for both studies because only the best scores (R for CDA and A for USPHS) were reported. Yet, all failures necessitating inlay replacement were reported, as was the time they occurred, which allowed for combining data for failures and calculating overall risk ratios. Some failures may have been insufficiently reported, especially in the Thordrup study, because some evaluations were performed by the patient's practitioner and not the researchers. However, this situation occurred only for the 10-year report, so it did not affect the 3-year results that were synthesized in this review. Finally, neither the Fasbinder nor the Thordrup reports mention evaluator training, although most recommendations emphasize its importance. Inter-examiner agreement could give an idea of such training; in the Fasbinder study, the 2 examiners reached a consensus, and inter-examiner agreement is not reported; in the Thordrup study, inter-examiner agreement was reported in the 1-year report, ranged from 38 to 100% and was rather poor for marginal adaptation (38–71%), which could indicate an absence or a lack of evaluator training.

The risk of bias at the outcome level seems low, because both studies accurately reported all failures. Failure data were combined because inconsistency was low and estimates were close, so we observed no statistical heterogeneity [51]. Some clinical heterogeneity clearly existed though. However, concerning the groups compared, all ceramics evaluated were feldspathic; composite materials were not that different either: Brilliant and Estilux composites have a similar proportion of fillers, Paradigm was slightly more filled and comprised nanofillers but its fabrication process was still close to that by a dental technician (it was not polymerized under high temperature or pressure as in current composite blocks). Furthermore, both studies were conducted approximately in the same decade (from 1993 to 2004). Other clinical parameters differed between studies and could be confounding factors. First, 3 different techniques were used: "direct" manufacturing, traditional laboratory manufacturing and CAD–CAM (Cerec) manufacturing. Second, adhesive, cement, liner and dental dam use was the same at the study level but differed between the 2 studies. Still, adhesive cement was used in both studies, which is favorable because adhesive luting has shown better results than resin-modified glass-ionomer luting both *in vitro* [57] and clinically [33,34]. Third, other unreported variables that may influence inlay failure include tooth type [58,59], cavity type [60,61] and situation.

However, the 97.1% success rate observed after 3 years for ceramic inlays seems in line with the literature. Success rates of 97% (ProCad [16]), 97.5% (IPS-Empress [62]), 98% (Cerec [63]) and 100% (eMax Press [17]) were reported after 2 years; 97% (Vita Mark II and Dicor [27]) and 100% (Empress [58]) after 3 years; 94% (Cergogold [21]), 95% (IPS Empress 2 [28]), 93% or 96% (IPS Empress [64,65]) after 4 years; and 92% (Cerec, Mirage and Empress [66]) and 94% (Cerec [67]) after 5 years. Manhart calculated an annual failure rate of 1.9% for ceramic restorations and 1.7% for CAD–CAM ceramic restorations, which corresponds to a 94.3% to 94.9% success rate after 3 years [42]. The 94.2% success rate we observed after 3 years for composite inlays also seems in line with the literature. Dukic reported a 100% success rate for Grandio and Admira restorations after 3 years [13] and Manhart et al. [58] found 89% of composite (Tetric) inlays to be clinically excellent or acceptable after 3 years. Xu et al. [37] reported a 91% success rate for composite (Targis and direct composite) inlays after 3 years. Manhart et al. [42] calculated an annual failure rate of 2.9% for composite inlays, for a 91.3% success rate after 3 years.

However, the 10-year success rates (75% in the composite group and 71% in the ceramic group) reported in the Thordrup study are lower than those generally reported. For IPS Empress

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inlays, Kramer et al. reported an overall success rate of 90% [19] or 92% [20] after 8 years. For Vita Mark II and Dicor ceramic inlays, Pallesen and van Dijken reported a 90% success rate after 8 years [27]. For Cerec inlays, Posselt and Kerschbaum [29] reported a 95.5% success rate after 9 years while Sjogren et al. [31] reported a 89% success rate after 10 years.

Concerning failure types, inlay fracture was the most frequent, especially for ceramic inlays. The 2.9% ceramic inlays fracture rate after 3 years was again in line with the literature. Molin and Karlsson observed an 8% fracture rate after 5 years (Cerec, Mirage and Empress, [66]); Pallesen and van Dijken observed a 3.1% fracture rate after 3 years and a 9.4% fracture rate after 5 years (Vita Mark II and Dicor, [27]); Sjogren et al. observed a 1.5% fracture rate after 2 years, a 4.8% fracture rate after 5 years and a 6.6% fracture rate after 10 years (Cerec, [31,63,67]). Studer et al. observed a 2.3% fracture rate after 2 years (IPS-Empress, [62]). Other failures were observed in only one patient during the first 3 years of follow-up common to both included studies.

At the review level, our study contains a few limitations. The chosen minimal follow-up duration (6 months) for inclusion was shorter than that recommended by the FDI, but few studies for inclusion were expected after the exploratory searches. The chance that eligible studies were not identified by the search is low because we searched 3 major databases with no restriction on language or date, all full texts could be retrieved, and we checked the reference lists of included reports. The results of this review rely on the results reported, and we would have preferred to analyze original data, but we tried to contact the authors of both studies and obtained no information; however, each patient in this review received an average of 1.7 restorations, so that the results obtained with the tooth as the unit of analysis should not be too biased by intra-patient correlation. We did not examine minor failures necessitating repair although they were reported for the Thordrup study, because they were not reported by Fasbinder and insufficient data could be analyzed. However, such failures should be registered in future trials and analyzed in a later stage, because repair is a solution for preservative dentistry. Finally, we had planned to assess a possible publication bias by producing a funnel plot of effect estimates against their standard errors if at least 10 trials were included in a meta-analysis. Since this was not the case, identifying and discussing a publication bias is awkward. Because most studies are supported by industries in restorative dentistry, such a bias cannot be excluded. Nonetheless, industries who want to sell a new indirect restorative material seem to have other solutions to avoid potential unfavorable results of a comparative study: for example, this study identified many studies where the adhesive cement or some other aspect of the procedure was randomized but not the restorative material itself.

Finally, thousands of patients are treated with inlays and onlays each year, and this type of restoration is often indicated because it is minimally invasive as compared with a crown. However, only 2 randomized trials have compared composite and ceramic material for manufacturing inlays. We lack clinical information about the material to use for onlays or endodontically treated teeth, and the prognostic factors that influence the choice of material have never been confirmed.

An ongoing trial, CEramic and COmposite Inlays Assessment (CECOIA), may provide some answers to these questions. The trial will compare ceramic and composite inlays and onlays, include 400 patients undergoing treatment from 3 institutional and 5 private dental practitioners and take into account some of the main prognostic factors (inlay/onlay, premolar/molar, vital/non-vital, operator) [68]. Other trials evaluating other materials in other clinical situations are needed. We recommend that all future studies use FDI consensus criteria to assess inlay or onlay failure [45] and that they maximize assessors' calibration, report results of all scores and follow up patients for at least 5 years (although difficult). Missing data should be treated for intention-to-treat analysis. In terms of public health, future studies should anticipate data sharing so that the scientific evidence is obtained faster and the choice of material for inlays and onlays will no longer depend on practitioners' beliefs or *in vitro* results. Finally, new promising materials are now available and should be evaluated; CAD–CAM composite blocks seem to have the advantages of composites as well as limited monomer release and thus little expected toxicity and hydrolysis aging. However, how this enhanced biocompatibility compares with that of ceramics is unknown. Finally, composite and ceramic onlays have never been compared in a randomized controlled trial, although the behavior expected by *in vitro* studies differs from that of inlays and these restorations are the choice for minimally invasive dentistry in cases of large coronary substance loss.

5. Conclusions

This systematic review examined results of 2 randomized controlled studies comparing the efficacy of composite and ceramic inlays. We found an overall 3-year failure risk ratio of 2 [0.38–10.55] favoring ceramic inlays. The clinical scores (USPHS and CDA) reported in these studies showed considerable heterogeneity between trials and could not be combined. Although we provide some evidence that ceramic inlays perform better than composite inlays in the short term, this review included only 2 randomized clinical studies and 138 restorations and the 3-year result may not remain in the long term.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at http://dx.doi.org/10.1016/j.dental.2013.09.009.

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Supplementary information

The tables needed to assess the risk of bias of the randomized clinical trials included in this systematic review, performed by use of Revman 5, are in Appendix 7.

Perspective

The quantitative synthesis of failure data conducted in this systematic review could be useful to discuss the results from the Cecoia trial (described below), perhaps by Bayesian analysis: they would help construct the Bayesian prior.

Résumé du chapitre en français

La question à laquelle nous avons tenté de répondre dans ce chapitre était : le composite ou la céramique est-il plus efficace cliniquement pour réaliser des inlays-onlays ? La meilleure méthodologie permettant de répondre à cette question est une revue systématique des essais randomisés. N'ayant trouvé aucune revue systématique sur ce sujet, nous avons décidé de réaliser une telle revue.

Nous avons défini les critères d'inclusions : les essais randomisés comparant l'efficacité clinique d'au moins une céramique et au moins un composite pour la réalisation d'inlays ou d'onlays chez des adultes suivis pendant au moins 6 mois seraient inclus. Un formulaire d'extraction de données a été conçu ; des données générales sur l'essai seraient relevées, ainsi que les scores cliniques éventuels (USPHS, CDA ou FDI) et les types et nombres d'échecs. Une équation de recherche a été définie pour les bases de données Medline, Embase et le registre central Cochrane des essais cliniques. Celle-ci a été mise en œuvre en Décembre 2012.

172 études ont été obtenues. La sélection a été faite sur le titre, puis sur le résumé par deux personnes indépendantes ; un consensus a été trouvé pour les cas de discordance. Le formulaire d'extraction de données a été rempli pour les études sélectionnées sur le résumé. Au final, quatre publications concernant deux essais cliniques répondaient aux critères d'inclusion. Ces deux essais publiés, totalisant 138 inlays chez 80 patients, présentaient un risque de biais élevé selon les critères définis par la Fondation Cochrane. Les scores d'évaluation cliniques étaient trop hétérogènes pour qu'une synthèse quantitative puisse être envisagée. Notons simplement que la forme anatomique et l'état de surface étaient en faveur de la céramique dans les deux études. En revanche, les échecs étaient bien décrits et une méta-analyse a été réalisée. Celle-ci a montré que les inlays en céramique entrainaient dans ces études moins d'échecs à court terme (rapport de risque d'échec à 3 ans : 2 [0,38-10,55] en faveur de la céramique) mais ce résultat pourrait ne pas être valable à long terme. Notons qu'aucun essai randomisé n'a comparé des onlays en composite et en céramique ou n'a comparé ces deux matériaux pour des dents dépulpées.

Des essais à faible risque de biais sont ainsi nécessaires en ce que concerne la comparaison des inlays-onlays en composite et en céramique, en particulier sur les dents dépulpées, pour pouvoir répondre à la question posée avec un bon niveau de preuve.

Chapter 3
Composite versus ceramic for CAD/CAM inlays and onlays: randomized controlled trial

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Background

We have previously shown by a systematic review that very few clinical trials have compared composite and ceramic for manufacturing inlays and onlays, that the trials conducted have relatively high risk of bias and that the number of inlays and onlays evaluated in these trials was low.

Therefore, our second objective was to design and implement a randomized clinical trial comparing composite and ceramic for inlays and onlays.

This work was begun for a Master's thesis. In this context, a draft protocol focused on different methodological aspects that were more-or-less specific to nonpharmacological dental clinical trials: the main outcomes, sample size, recruitment and follow-up of subjects and the choice of treatment allocation method. Regarding this last aspect, a program tailored for the planned clinical trial with the Visual Basic for Applications (VBA) software was used. This program generated the number of patients determined by the sample size, allocated them a treatment with two most classic randomization methods (stratification and minimization) and allowed for comparing the performance of these two methods in terms of predictability for the investigator and balance between the two treatment groups. However, this program could not be used for other clinical trials because it was adapted to the specific characteristics of the planned trial. So a second program was written to compare stratification and minimization for different types of clinical trials, among them dental nonpharmacological clinical trials. The first part of this chapter discusses the choice of the randomization method and this program.

In the meantime, we conducted the various stages of the trial, which led to a modified protocol that had been published and to the recruitment and treatment of patients. These steps are described in the second part of this chapter.

Trial planning and randomization method choice

Conducting a clinical trial starts with designing it. The choice of the randomization method is one essential aspect, for dental non-pharmacological trials in general and for trials comparing inlay and onlay materials in particular. This choice is even more true because blinding often cannot be implemented or only partially. In this investigation, composites can usually be easily distinguished from ceramics by a dentist practicing these types of restorations; therefore, blinding could not be implemented in the planned trial (operators and evaluators would be able to distinguish between composites and ceramics).

In addition, when the trial sample size is not very large, the major known prognostic factors must be considered at the time of randomization to obtain treatment groups truly comparable (e.g., equivalent numbers of non-vital teeth in the "composite" and "ceramics" groups of our trial evaluating inlays and onlays). The two most common methods to consider these factors are stratification and minimization. The allocation sequence can be defined in advance for stratification, whereas minimization is a dynamic method and the treatment allocated depends on the characteristics of the patients already included (for more information about stratification or minimization, see publication below).

Summary of the work that was carried out

Definition of the program's specifications

Definition of trial parameters to be considered

We first specified the parameters of a trial that may vary and should be considered to simulate the allocation of patients by stratification or minimization:

- trial sample size (number of subjects required). In the protocol, the sample size required for our trial is 358.
- number of factors to be considered in the stratification or minimization. In the scheduled trial, four factors were considered in light of the parameters identified in the literature as influencing the success of inlays and onlays: the operator and the

fact that the tooth to be treated is a premolar or a molar, vital or not, and the restoration to be made is an inlay or an onlay.

- number of levels that each factor can take. In the planned trial, the operator factor could take 7 levels: 7 operators would make inlays and onlays, and the 3 other factors had 2 levels.
- the sample size proportion expected in each level for each factor. For our trial, we estimated the following proportions: 18.75% of the subjects in each of the two university hospitals and 12.5% for each of the 5 private practitioners, 50% of inlays and 50% of onlays, 70% molars and 30% premolars, 80% vital teeth and 20% non-vital teeth.

Defininition of the randomization parameters to be considered

We listed the stratification and minimization parameters that can be modified:

- For stratification: the number of blocks.
- For minimization: the proportion of random allocations and the possible inclusion of the treatment as a minimization factor.

Definition of criteria for comparing different randomization methods

We then defined the outcomes, that is, the parameters for which we wanted to compare the different randomization methods. Four major parameters have been described in the literature.

1. ALLOCATION PREDICTABILITY FOR THE OPERATOR

For the investigator/operator not to be influenced at enrollment, the person must not know which treatment (here composite or ceramic) will be allocated to the patient. Predictability must be minimized, especially when blinding cannot be implemented.

2. BALANCE BETWEEN TREATMENT GROUPS

In our case, we wanted the "composite" and "ceramic" groups to be as close as possible. Indeed, group imbalance results in loss of power.

3. BALANCE BETWEEN TREATMENT GROUPS IN PROGNOSTIC LEVELS

To ensure validity of the results and the statistical analysis and for subgroup analysis, the method should not involve prognostic groups with no or very few subjects. For example, among non-vital teeth, we wanted almost as many composite and ceramic inlays and onlays.

4. POWER

Power available for the statistical analysis of the primary endpoint can be taken into account for the choice of the allocation method.

CHOOSING BETWEEN THESE 4 PARAMETERS

We implemented the first 3 parameters in our software. The last parameter -- power -- was not retained because it would necessitate having data (pre-study or similar trial published) or simulating primary endpoint data for each patient. On the one hand, outcomes can take many forms, which would have greatly complicated the program. On the other, for many dental trials to date, speculating on the success of the treatments compared seemed unreliable. For the trial considered, the systematic review showed that only 2 trials compared composite and ceramic inlays and onlays and used outcomes different from those chosen and also evaluated different materials; their results could therefore not be used for power comparison.

CALCULATION OF PREDICTABILITY

We consulted the literature to determine how many allocations an investigator could remember. The values most frequently found were 1, 3, 5, or all allocations.

Technical specifications

We considered that investigators should be able to choose the number of simulations to be performed so that they can adapt the latter to the computational capabilities of his computer and to the complexity of the trial considered.

Implementation: programming

After this preliminary work, we created the program with Excel and Visual Basic for Applications (VBA) software, trying to clarify the different components of the code so that it can evolve. Of course, the program was debugged and verified step by step.

Publication

For the publication, we initially used the example of the trial being planned. However, because the trial was rather complex (high number of subjects and number of prognostic levels), comments from reviewers eventually led us to choose a simple trial (trial 0, recruiting

50 subjects and taking into account 1 prognostic factor and 2 operators) to illustrate our program.

The article, as it was published, is presented below.

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ORIGINAL ARTICLE

Randomization in clinical trials: stratification or minimization? The HERMES free simulation software

Hélène Fron Chabouis · Francis Chabouis · Florence Gillaizeau · Pierre Durieux · Gilles Chatellier · N. Dorin Ruse · Jean-Pierre Attal

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Abstract
Objectives Operative clinical trials are often small and open-label. Randomization is therefore very important. Stratification and minimization are two randomization options in such trials. The first aim of this study was to compare stratification and minimization in terms of predictability and balance in order to help investigators choose the most appropriate allocation method. Our second aim was to evaluate the influence of various parameters on the performance of these techniques.
Materials and methods The created software generated patients according to chosen trial parameters (e.g., number of important prognostic factors, number of operators or centers, etc.) and computed predictability and balance indicators for several stratification and minimization methods over a given number of simulations. Block size and proportion of random allocations could be chosen. A reference trial was chosen (50 patients, 1 prognostic factor, and 2 operators) and eight other trials derived from this reference trial were modeled. Predictability and balance indicators were calculated from 10,000 simulations per trial.
Results Minimization performed better with complex trials (e.g., smaller sample size, increasing number of prognostic factors, and operators); stratification imbalance increased when the number of strata increased. An inverse correlation between imbalance and predictability was observed.
Conclusions A compromise between predictability and imbalance still has to be found by the investigator but our software (HERMES) gives concrete reasons for choosing between stratification and minimization; it can be downloaded free of charge.
Clinical relevance This software will help investigators choose the appropriate randomization method in future two-arm trials.

Keywords Random allocation · Minimization · Stratified randomization · Randomized controlled trials · Simulations · Predictability

H. Fron Chabouis (✉) · J.-P. Attal
Sorbonne Paris Cité, Faculté de chirurgie dentaire, Biomaterials department (URB2i, EA4462), Clinical Research Unit, Université Paris Descartes, 1 rue Maurice Arnoux, Montrouge 92120, France
e-mail: helene.fron@parisdescartes.fr

F. Chabouis
Master MASEF, Université Paris Dauphine, Place du Maréchal de Lattre de Tassigny, Paris 75775, France

H. Fron Chabouis · J.-P. Attal
Service d'odontologie, APHP, Hopital Charles Foix, Ivry-sur-Seine 94200, France

H. Fron Chabouis
Sorbonne Paris Cité, Ecole doctorale Galilléc, Université Paris 13, Villetaneuse 93430, France

F. Gillaizeau · P. Durieux · G. Chatellier
APHP, HEGP; INSERM, UMR S872/20, Paris 75015, France

N. D. Ruse
Biomaterials, University of British Columbia, Vancouver, Canada

Published online: 01 March 2013

Introduction

A good randomized controlled trial is needed to support the correct prescription of a treatment or a medical procedure to a patient [1]. However, in operative dentistry, as in many other surgical specialties like orthopedics, many technical difficulties complicate the design and conduct of clinical trials [2, 3]. Operative protocols are often long, and therefore expensive, making it difficult to include many patients; operative parameters (such as the instruments used, the

operator himself, etc.) can vary, and it is difficult to carry out a double-blind trial, as the operator generally cannot be blinded during the procedure.

When a clinical trial cannot be blinded, the protocol and randomization have to be faultless and well documented [4]. Randomization should be carried out as late as possible so that treatment knowledge does not influence the operator's actions upstream [5]. It should take into account low recruitment, absence of blinding, and operative parameters. When there is limited recruitment, the first aim of the randomization is to obtain a good balance between the treatment or procedure groups being compared [6] in order to optimize estimation of treatment effect and power. Secondly, to overcome absence of blinding, the allocations should not be predictable [7]. Lastly, the parameters which may influence the treatment effect estimate (which are also called "prognostic factors") should be considered. Only a limited number of main prognostic factors should be accounted for at the time of randomization [8–13]. If these factors are well distributed between groups, it is possible to attribute the effect observed to the evaluated treatment or procedure rather than to these factors [14, 15]. Taking the main prognostic factors into account is especially important when few patients are included (<200 patients per trial arm) [16, 17], when the trial is open-label, when subgroup or intermediate analyses are planned, or when the trial is aiming to demonstrate equivalence [18–20].

Most dental trials fall within the above-mentioned types of trials and therefore, stratified blocked randomization or minimization should be implemented; these are the two traditional techniques which achieve the randomization aims described above [21]. Other techniques have been described, but they are more sophisticated and thus more difficult to implement (e.g., Efron's biased coin design [22], Wei's urn design [23], Soares and Wu's big stick design [24], Signorini's dynamic balanced allocation [25]).

Stratified blocked randomization consists of generating blocks of treatment allocation (e.g., a block of 4: "ABBA", meaning the first patient receives treatment A, the second treatment B, etc.). Blocks can be of varying size, but one block contains an equal number of treatments A and B in order to achieve balance between groups. The order of treatments within a block is randomly generated. A randomization list (which is a block series) is generated for each stratum of patients which contains patients whose prognostic factors are all identical [21]. Stratification is the procedure recommended by regulatory bodies [15]. It works quite well when only a few prognostic factors must be taken into account.

Minimization is a dynamic method that minimizes the imbalance between the number of patients in each treatment group over a number of prognostic factors [26]. The treatment allocated to the next participant depends on the characteristics of the patients already enrolled [5]. Minimization can take into account many factors [27], but it is not recommended by the regulatory bodies. The first method described (by Taves [28] and by Pocock and Simon [29]) was completely deterministic. Thus, the method was considered to be a potential source of bias since operators might be able to predict all the allocations, especially in monocenter and industry-supported trials. Although some authors have proposed introducing some randomness to the minimization [29, 30], authorities still require the use of this method to be justified [10, 15].

Different suggestions have been put forward to help in the effective choice between the two methods. For minimization, the proportion of random allocations recommended ranges from 5 to 30 % depending on the author or the recommendation [30, 31]. It has been generally considered that minimization could easily deal with 10 prognostic factors [27] and Rovers et al. stated that the expected number of patients in each subcategory should be greater than five, to prevent empty cells [17]. For stratification, two recommendations have defined the maximum number of strata: Therneau suggests that the number of strata be less than half the sample size [27], while Kernan et al. suggests keeping the number of strata S below $N/(B\times 4)$, where N is the sample size and B is the block size [20]. However, the choice of the block size and the proportion of random allocations included depend on other clinical trial parameters. Statisticians have therefore suggested using computer simulations to choose the allocation method best suited for the proposed trial [32, 33].

Some authors have used simulated data to compare both methods in terms of balance between treatment arms [27, 29], balance within a factor and within strata [25, 34], and statistical analysis (e.g., performance of conventional model-based statistical inference [33], estimated treatment effect, size of the rejection region, and power [35]). Recently, Zhao et al. compared many designs in terms of imbalance and correct guess probability, but stratification and minimization were not among the designs compared [36]. Real clinical data have also been used to conduct a posteriori simulations and compare randomization methods in terms of balance [37], statistical power [32], and nominal significance level [38]. Brown et al. compared deterministic minimization to minimization incorporating various random elements in terms of prediction rates and balance [30]. However, comparisons between stratified blocked randomization and minimization in terms of predictability and balance are missing.

The aim of this study and of the HERMES software we created was to compare stratification methods (with various block sizes) and minimization methods (including more or less randomness), to analyze the effect of various parameters of clinical trials on this choice (sample size, number of prognostic factors, and operators), and to therefore, provide guidance for future investigators. To compare the methods, we computed an indicator of balance between treatments and an indicator of predictability for operators. Specifically,

we wanted to choose the optimal method to randomize 358 patients between two groups in a trial comparing ceramic and composite to make inlays/onlays (CECOIA trial, NCT01724827, www.cecoia.fr), while taking into account four prognostic factors (pulp vitality, inlay or onlay, premolar or molar, and operator). We wrote an initial computer simulation program that answered this question. We then wrote a second program (HERMES)[1] that can be applied to other studies, in order to help future clinical trial investigators choose the most suitable randomization method.

Materials and methods

A computer simulation program was coded with Visual Basic for Applications and Excel software. It allocated one of two treatments to patients simulated according to their expected characteristics. Various randomization methods could then be compared in terms of balance between groups and predictability for the operator.

The "Simulation" tab of the Excel interface allowed us to enter the following clinical trial parameters: number of patients to be included; number of simulations to be performed; number of prognostic factors to take into account, associated with the number of levels or values that could be taken by each factor; proportion of patients expected in each prognostic level; number of operators; and the parameters of the allocation methods to be tested.

In order to clarify the minimization and stratification, consider the following simple example of a trial including 10 patients. Two factors were identified: factor 1, with levels, *a* and *b* (e.g., for a surgical trial this could be "smoker" or "non-smoker"); and factor 2, with three values, *a*', *b*', and *c*' (e.g., the three operators in the trial). The study investigators were expecting 50 % *a* and 50 % *b* for factor 1, and 20 % *a*', 30 % *b*', and 50 % *c*' for factor 2. The software randomly generated the patients listed in Table 1, taking into account these expected proportions.

Minimization was coded as described by Pocock and Simon [29]. In our example, the allocation of the first patient was completely random. Suppose treatment A was assigned. The numbers then obtained for treatments A and B are shown in Fig. 1. If treatment A was assigned to the second patient, the sum of squared imbalances would be $2^2+1^2+1^2=6$, whereas it would be $1^2+1^2=2$ if treatment B was assigned (see Fig. 1). Therefore treatment B, which minimized the sum of squares, was assigned to the second patient by minimization.[2] This is a fully-deterministic minimization, where allocations depend solely on the characteristics of already-included patients. The allocations for the 10 patients are listed in Table 1.

It is also possible to introduce some randomness so that the minimization is less predictable. Thus, according to the percentage $X \in [0-50\ \%]$ of randomness chosen, the treatment allocated will be the one dictated by minimization in $(100-X)$ % of cases, and the other treatment will be allocated in X% of cases. This was programmed in a simple way by generating a random number U according to the uniform distribution on [0, 1]. The allocation was then made depending on $U \leq X$ or $U > X$. For example, in the case of randomization with 30 % randomness (X=30 %), B was the treatment that minimized the sum of squared imbalances for patient 5. The random number generated was 0.23. As this is less than 0.3, treatment A was finally assigned (see Table 1). Finally, it was also possible to introduce the treatment (A or B) as a factor in the minimization, in order to keep a better balance overall.

For the stratified blocked randomization, a blocked randomization list was generated for each stratum. The strata number was equal to the product of the number of levels of each factor (here, 2 levels for factor 1 × 3 levels for factor 2=6 strata). Initially, one block was generated by the software for each stratum (see Table 2). Then, a new block was generated for all strata each time a randomization list had been entirely allocated. Take the example of randomization in blocks of two: the program assigned the first patient (*a*, *b*') the first treatment on the corresponding randomization list (*a*, *b*'), here treatment B (see Table 2), and so on (see results in Table 1). For this 10-patient trial, it was not necessary to generate additional blocks. Similarly for randomization in blocks of four, the first patient (*a*, *b*') was assigned treatment A (see Table 2), and the following allocations are shown in Table 1.

Indicators used

For each set of patients, an imbalance indicator was calculated, which corresponded to the absolute value of the difference in numbers between treatments A and B, divided by the number of patients included (to allow comparison of the balance of one trial with another). The imbalance indicators of the various randomization methods, using our example, are listed in Table 1. An indicator of the within-factor imbalance was computed; it was the mean imbalance within prognostic factor levels. Each prognostic level imbalance was the absolute value of the difference in numbers between treatments A and B, divided by the number of patients included in the prognostic level.

Predictability was computed by operator (or center). We adopted four different methods to mimic how operators may predict treatment allocation: 1, prediction based upon knowledge of the last allocation only; 3, the last 3; 5, the last 5; or all, the operator had written down or had access to all his allocations [30, 40, 41]. Consider our example again, with *a*', *b*', and *c*' indicating the three operators, who have remembered only

[1] This software can be downloaded at the following address: chabouis.fr/helene/hermes

[2] We could also do a simple sum of the absolute imbalance values, but this method allowed us to penalize more serious imbalances. [39]

Table 1 Characteristics of the 10 patients randomly generated by the program and treatments allocated to them by the various randomization methods, final numbers, and balance indicators

Patient	Factor 1	Factor 2	Deterministic minimization	Minimization with 30 % randomness	(Random number generated)	Stratified randomization (block size: 2)	Stratified randomization (block size: 4)
1	*a*	*b*'	A[a]	A[a]		B	A
2	*a*	*c*'	B	B	0.61	B	A
3	*b*	*c*'	A	A	0.32	A	A
4	*a*	*b*'	B	B	0.52	A	B
5	*b*	*a*'	B	A	0.23[b]	B	A
6	*a*	*a*'	A	B[a]		A	B
7	*b*	*b*'	B[a]	B	0.68	B	B
8	*b*	*c*'	A	B	0.92	B	A
9	*b*	*b*'	A	A	0.41	A	B
10	*a*	*c*'	B	A	0.56	A	A
Number of treatments A			5	5		5	6
Number of treatments B			5	5		5	4
Imbalance indicator			0	0		0	0.2[c]

[a] Allocated at random because the sums of squared imbalances were the same for this patient

[b] This patient did not receive the treatment allocated by minimization, because the random number drawn was less than 0.3

[c] |6–4|/10=0.2

their last allocations, which were generated by deterministic minimization. Predictability was calculated from the second inclusion. The operator predicted that his new patient would receive the treatment other than the previous allocated one. Thus operator *b*' predicted his second patient would receive treatment B, since his first had received treatment A (see Table 3). His second patient did receive treatment B.

Numbers after inclusion of patient 1 (a, b')

Factor	Class	Treatment A	Treatment B
1	a	1	0
	b	0	0
2	a'	0	0
	b'	1	0
	c'	0	0

Numbers if treatment A is allocated to patient 2 (a, c')

Factor	Class	Treatment A	Treatment B	Imbalance
1	a	2	0	2
	b	0	0	0
2	a'	0	0	0
	b'	1	0	1
	c'	1	0	1

[a]imbalance =| treatment A –treatment B|

Numbers if treatment B is allocated to patient 2 (a, c')

Factor	Class	Treatment A	Treatment B	Imbalance
1	a	1	1	0
	b	0	0	0
2	a'	0	0	0
	b'	1	0	1
	c'	0	1	1

Fig. 1 Treatment allocation to patient 2 by minimization. Numbers after inclusion of patient 1 (*a*, *b*'), Numbers if treatment A is allocated to patient 2 (*a*, *c*'), Numbers if treatment B is allocated to patient 2 (*a*, *c*')

However, he predicted his third patient would receive treatment A whereas he was allocated treatment B, and so on.

The predictability indicator was calculated as the sum of cases where operators correctly guessed the treatment allocated to their patients, divided by the number of guesses. For our example, predictability indicators of each allocation method are shown in Table 3. If the operator remembered 3, 5, or all of his inclusions, he predicted his next patient would receive the treatment that was least affected among the latter.

The number of simulations was the number of samples (like the one in Table 1) simulated. Several minimization and/or stratification methods can be used on each sample. The simulations were activated by the "Launch" button on the "Simulation" tab of the Excel interface. The mean and standard deviation of the indicators of balance and predictability were calculated and these results appeared after a few seconds on the "Results" tab of the Excel interface.

Table 2 Randomization lists generated for each stratum for the stratified randomization in blocks of 2 (upper side) and blocks of 4 (lower side)

	a	*b*
a'	AB	BA
b'	BA	BA
c'	BA	AB
	a	*b*
a'	BABA	ABBA
b'	ABAB	BBAA
c'	AABB	AABB

Table 3 Calculation of the predictability indicator if the operator remembered his last allocation only

	Patients	Deterministic minimization	Minimization with 30% randomness	Stratified randomization (block size : 2)	Stratified randomization (block size : 4)
Operator a'	5, 6	BA	AB	BA	AB
Operator b'	1, 4, 7, 9	ABBA	ABBA	BABA	ABBB
Operator c'	2, 3, 8, 10	BAAB	BABA	BABA	AAAA
Predictability indicator		5/7 = 71%	6 /7 = 86%	7/7 = 100%	2/7 = 29%

In green: operator predicted the treatment actually allocated. In red: operator guessed wrong and the treatment other than the one he had predicted was allocated

Results

The software developed provides access to the predictability and balance of a given randomization method. To present the results, we chose a reference situation (Trial 0), which we varied depending on the number of patients included, the number of selected prognostic factors, the number of operators, and the distribution of subjects within factors (Table 4). We performed 10,000 simulations for each trial. (Appendix 1).

Trial 0

Predictability and balance results for Trial 0, according to the method of randomization selected, are shown in Table 5. Overall imbalance and within-factor imbalance increased when minimization included more randomness (i.e., when X increased), and when the block size increased for stratification. Predictability decreased as minimization included more random allocations or as the block size increased for stratification. Predictability increased when the operator remembered more allocations and it was maximal if he had written down all his allocations (Table 5). We then considered the situation of the operator remembering his last five allocations, because this seemed to be the most likely situation to occur in real-life practice [40].

Influence of parameter variation on predictability and imbalance in trial 0

Sample size

The graphs in Fig. 2 show the effect of the number of patients. For a given randomization method, when the number of patients included increased, the imbalance decreased, as did predictability. For a small trial (cf. Trial 1), the properties of the various methods differed greatly.

Number of prognostic factors

The graphs in Fig. 3 show the effect of the number of prognostic factors. For stratification, the imbalance increased greatly

Table 4 Characteristics of simulated trials (patients, factors, frequencies, operators, and strata)

Simulated trial	Number of patients (*N*)	Number of factors	Distribution of subjects within factors	Number of operators	Percentage of patients per operator	Number of strata (S)	Maximum block size (B)[a]
0	50	1	40/60 %	2	50/50 %	4	3.7
1	30	1	40/60 %	2	50/50 %	4	1.9
2	100	1	40/60 %	2	50/50 %	4	6.2
3	50	2	40/60 %, 30/70 %	2	50/50 %	8	1.6
4	50	5	[b]	2	50/50 %	192	0.06
5	50	1	40/60 %	1	100 %	2	6.2
6	50	1	40/60 %	4	[c]	8	1.6
7	50	1	10/90 %	2	50/50 %	4	3.7
8	50	1	10/90 %	2	10/90 %	4	3.7

[a] Kernan rule: $B=N/(S\times 4)$

[b] Factor 1, 40/60 %; factor 2, 20/80 %; factor 3, 10/90 %; factor 4, 20/30/50 %; factor 5, 20/20/30/30 %

[c] 15/25/30/40 %

Table 5 Imbalance and predictability indicators of Trial 0 for various randomization methods

Randomization method	Predictability						Imbalance		Within factor imbalance	
	Operator remembered last allocation		Operator remembered last 5 allocations		Operator remembered all previous allocations					
	Mean %	SD %	Mean %	SD %	Mean %	SD %	Mean %	SD %	Mean %	(Min, Max) %
Minimization										
- Deterministic	73.8	5.5	75.3	5.7	95.4	4.5	0.6	1.4	2.3	(0.0, 14.3)
- Deterministic+T[a]	73.8	6.5	72.5	6.5	89.9	7.2	0.1	0.6	2.5	(0.0, 14.3)
- *X*= 0 %	66.8	6.9	69.7	6.3	84.8	7.3	1.3	2.0	3.0	(0.0, 23.1)
- *X*=20 %	60.5	7.3	63.9	7.0	75.1	8.6	2.0	2.4	4.2	(0.0, 41.2)
- *X*=30 %	56.4	7.4	59.1	7.1	65.9	8.7	3.4	3.5	6.3	(0.0, 64.7)
- *X*=30 %+T[a]	56.5	7.5	58.5	7.3	64.2	9.3	2.9	3.2	6.9	(0.0, 57.9)
Stratified randomization										
- Block size: 2	62.6	5.9	67.4	5.6	79.7	5.7	1.9	2.1	3.2	(0.0, 14.3)
- Block size: 4	56.1	7.0	61.1	6.1	71.0	6.0	2.7	2.6	4.2	(0.0, 25.0)
- Block size: 6	54.1	7.0	58.2	6.2	66.5	5.8	3.4	3.0	5.1	(0.0, 33.3)

[a] +*T* minimization including treatment as a minimization factor

when the number of prognostic factors increased, as the number of strata increased more quickly. However, imbalance increased slightly for minimization as its predictability decreased.

Number of operators

The graphs in Fig. 4 show the effect of the number of operators. Imbalance increased with the number of operators. An increasing number of operators had a negative impact on both methods, but affected stratification more.

Subject distribution between prognostic factors

The graphs in Fig. 5 show the effect of a more or less unequal distribution of subjects between prognostic levels. Unequal distribution of subjects favored minimization (cf. Trial 0 vs. Trial 7).

Note that including treatment as a minimization factor almost always improved the two indicators (balance and predictability) simultaneously, except when there was only one operator (Trial 5) or when the number of subjects was poorly distributed between operators (Trial 8). Finally, note that in our examples, imbalance was always minimal for a deterministic minimization including treatment as a minimization factor (Table 5, Figs. 2, 3, 4, and 5).

Discussion

In this study, we applied computer simulation of stratification and minimization randomization techniques to a balanced two-arm study model, with the aim of discerning which technique was most appropriate. We found that there

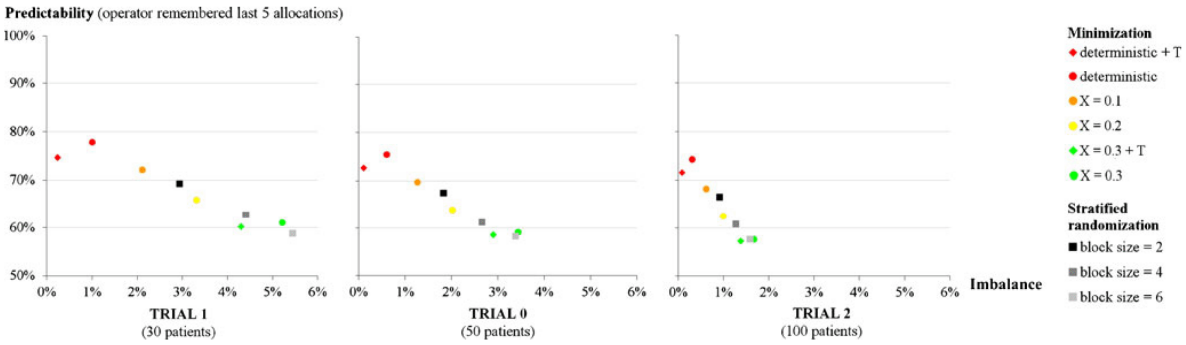

Fig. 2 Effect of change in sample size on imbalance and predictability indicators of various randomization methods (operator remembered his last five allocations)

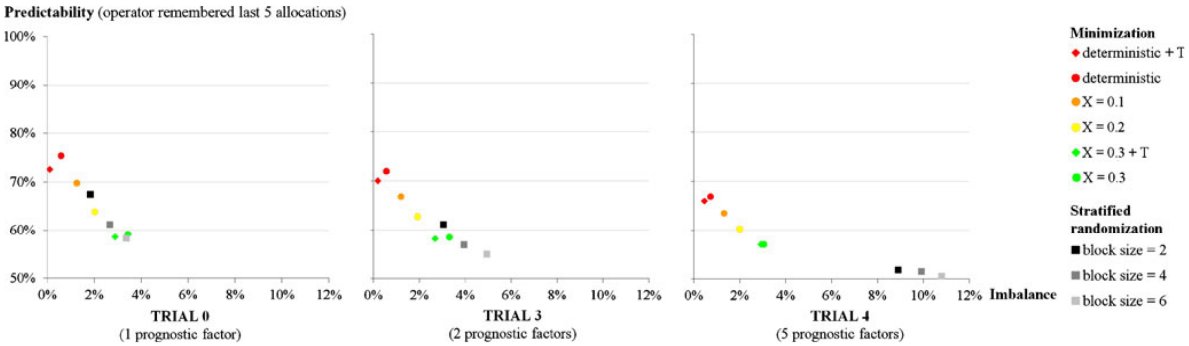

Fig. 3 Effect of the number of prognostic factors on imbalance and predictability indicators of various randomization methods (operator remembered his last five allocations)

was remarkable adaptability in the minimization, and inverse correlation between predictability and balance.

Choosing the right randomization method is important because it will affect the results of the clinical trial in terms of balance between groups, of predictability for the operator, and in terms of statistical analysis. Some rules, such as Kernan's rule [20], already exist to help investigators make that choice. However, we saw, for example on Fig. 5, that Trial 0 was more favorable to stratification than Trial 8, although Kernan's index was the same for both methods (3.7, Table 4). These rules, thus, lack subtlety in the choice of the randomization method because many other parameters can vary within a trial and influence the decision (e.g., the number of subjects, the number of prognostic factors to consider, the number of operators, and the distribution of subjects between factor levels). For this reason, statisticians have suggested performing simulations. However, up until now, investigators have not had freely-available simulation tools; this situation prompted us to create the HERMES software.

The first main result emerging from our study is that minimization was more adaptable and worked better in complex cases. This result confirms those of previous studies [9, 27, 35, 37, 38]. When the number of patients decreased or when the number of prognostic factors or the number of operators increased, the imbalance of stratification increased much more than that of minimization.

The second main result is that there was generally an inverse correlation between predictability and imbalance: when a less predictable method was wanted, its imbalance increased and vice versa. This idea has been mentioned or suggested by some authors [33, 38] but not as clearly demonstrated [30] until recently [36]. A trade-off between predictability and imbalance is therefore necessary as the perfect method (i.e., 0 % imbalance and 50 % predictability) does not exist.

This trade-off highlights a limitation of our study: although the software computed the predictability and imbalance of various methods, choosing the best method would still often be difficult. The imbalance–predictability graphs are helpful because various methods can be compared in terms of these two properties simultaneously; a method whose marker is located at the lower left of another is better. However, choosing the best method is less obvious. Analysis approaching that

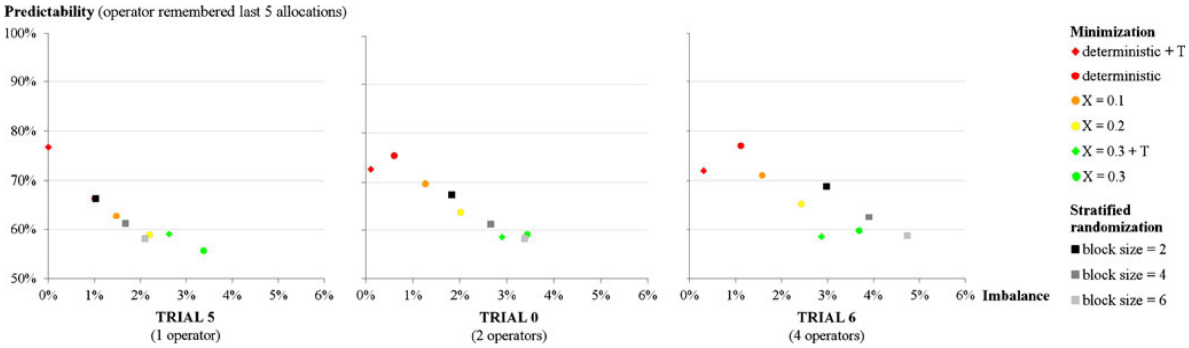

Fig. 4 Effect of the number of operators on imbalance and predictability indicators of various randomization methods (operator remembered his last five allocations)

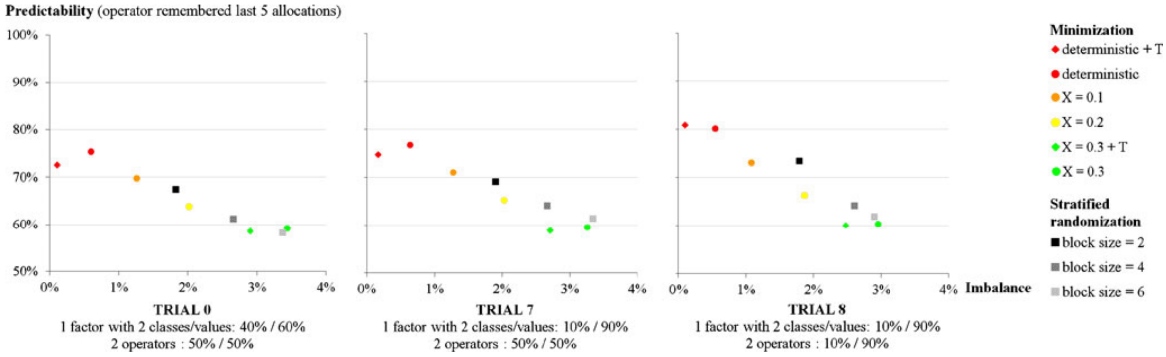

Fig. 5 Effect of subject distribution between classes/values of prognostic factors on imbalance and predictability indicators of various randomization methods (operator remembered his last five allocations

of receiver operating characteristic curves would make us choose the method closest to the origin of the graph [42]. However, the graph is modified by the scale attributed to imbalance and predictability. Ultimately, the choice of the best method on the graph will depend on the trial; predictability is a less fundamental criterion for a double-blind trial than it is for an open-label trial, whereas balance will be less critical if a large difference in effect size between treatments or procedures being compared is expected.

For example, for Trial 0, in the case of a double-blind trial, we may decide to perform a deterministic minimization with the treatment as a minimization factor. If it were an open-label trial, we would prefer a minimization with a random factor of X=10 or 20 % or even more. Note that for this trial, stratification by blocks of two was not far below these minimizations. We could therefore, decide in this case to adopt block stratification because it provides several advantages: it is easier to implement [20, 43] (the sequence can be generated in advance [44]), it is recommended by the authorities, and it allows all interactions that may exist between factors to be taken into account. This latter factor weakens it when many factors must be considered, because some intersections have very few patients. However, it is also a strong point if interactions between prognostic factors are suspected or if subgroup analyzes are planned [34].

The generalizability of our program is limited in two ways. Firstly, it does not take into account possible interactions between prognostic factors at the time of patient simulation. However, these interactions can rarely be quantified before the start of a dental trial. If significant interactions between factors are suspected, the results of stratification should be compared to those of a minimization, taking into account these interactions. For example, if an interaction is suspected between factor 1 with 2 levels (*a* and *b*) and factor 2 with 3 levels (*a*', *b*', and *c*'), patients can be simulated (as if the interaction existed) by 6 levels of minimization (*aa*', *ab*', *ac*', *ba*', *bb*', and *bc*'), instead of by the 5 levels which a minimization without interaction would have included (*a*, *b*, *a*', *b*', and *c*').

Secondly, we restricted the comparison of the different randomization methods to the case of a trial with two balanced arms. However, we wrote the program in Visual Basic for Applications so that the code is accessible and can be changed, if necessary, to adapt it to a wide variety of clinical trials.

A final limitation of our work is that it compared different methods of stratification and minimization on criteria of balance and predictability, but not on the statistical analysis of results. However, to do so would require making assumptions about trial outcomes. This would not be straightforward in our field, and we believe that existing data are preferable for such comparisons. Conclusions regarding the consequences of the randomization method on the statistical analysis obtained on real datasets can be found in Appendix 2.

In conclusion, the HERMES software does compare stratification and minimization in terms of predictability and balance, but it does not entirely solve the choice of the most suitable method for a trial. The right compromise between predictability and imbalance remains to be found, but the software helps to justify this choice based on concrete reasoning. It is available for free download at this internet address: chabouis.fr/helene/hermes.

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Conflict of interest The authors declare that they have no conflict of interest.

Appendix 1

Justification for the number of simulations (10,000) carried out in this study

We aimed to estimate the expected value of a random variable (predictability or imbalance) with n independent realizations (simulations were independent) and identical distribution (patients were simulated in the same proportions). Our indicator was therefore the estimator of the random variable's expected value. According to the central limit theorem, we know that the standard deviation of our estimator was $\sqrt{\frac{Var(X)}{n}}$, where n is the number of simulations (here 10,000).

Taking Trial 0 as an example, the precision of our imbalance indicator for deterministic minimization (whose estimated expected value was 0.597 %) was 1.42 %/$\sqrt{10,000}$, which is 0.0142 %.

The 95 % confidence interval of our imbalance indicator was therefore $0.597 \pm 1.96 \times 0.0142$, or [0.569 to 0.625]. This level of precision seemed acceptable to compare these methods, and is the reason why we presented the results with one digit after the decimal point.

Appendix 2

How the allocation method impacts the analysis of resulting data

Type of analysis

Tests of statistical inference are based on the assumption of random assignment to treatment and control groups. Only simple randomization has this property, so that distorted p values and concerns over the validity of the analysis surround not just minimization but all other allocation methods [39]. However, the disadvantage of adaptive methods like minimization is that the correct analysis is complex and not clearly worked out [39, 44]. In fact, minimization achieves balance only among the marginal distribution of the strata [25]. Where the outcome measure is a continuous variable, various authors recommend that adjustment should be made for factors in the minimization using analysis of covariance [28, 32, 45]. Several other authors recommend using permutation tests to analyze trials where minimization has been used [43, 46]; however, because these tests are not straightforward in practice and seem to make little difference to the results obtained, some authors believe permutation tests are unnecessary and that a classical analysis will usually yield satisfactory conclusions provided that minimization factors are used as covariates in the analysis [8, 9, 11, 12]. Some authors consider that the nominal significance level in that case should be adjusted [32, 35, 45], whereas Hagino et al. believe this is unnecessary [38]. For both stratified randomization and minimization, the collapsibility of the data should be checked, and if it depends on the statistic used, the tenuousness of the conclusions should be noted [47].

Inclusion of randomization covariates in the analysis

Although scientists may find the results of simple, unadjusted treatment comparisons with demonstration of good balance of important factors more convincing than the results of a covariate analysis, there is a consensus that the prognostic factors included in the randomization scheme should be taken into account in the analysis, not just for minimization [12, 32, 46, 48, 49] but also for stratification [50]. The p value for a difference between endpoint rates in treatment groups would be otherwise overestimated [18, 38, 51].

Effect on the nominal level and the power of the test

Authors in favor of stratified randomization put forward its value in reducing the risk of type I error [20] and increasing power [52], but this advantage is controversial. Some authors believe that both stratification and minimization procedures produce comparable improvements in reducing type I and II error [35]. Tu et al. found that minimization procedures were inferior to stratified allocation in reducing the two types of error, due to existing interactions between covariates [48]. However, other simulations have given opposite results [32, 35, 38].

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Supplementary information

Appendix 8 shows the windows of the Excel program that the investigator can use. The "Homepage" window provides some explanation on how the program works. The "Simulations" window allows the investigator to enter the characteristics of the trial planned, to choose the parameters of the stratification and minimization to compare and to launch simulations (if all boxes are correctly filled). The "Results" window displays the results, that is, the predictability and balance of each method.

Appendix 9 shows the lines of the underlying Visual Basic code that performs the simulations.

Trial implementation and protocol

After the trial was planned, it had to be implemented. This required funding and so we started with answering a call for proposals.

Summary of the work that was carried out: call for proposals and project appraisal

Answer to a call for proposals

In January 2011, we responded to a call for proposals from the national hospital clinical research program (Programme Hospitalier de Recherche Clinique: PHRC). The following documents were submitted:

- The protocol: adapted and revised from the draft protocol issued for the Master's thesis, by adding the technical and regulatory aspects, a provisional budget (Appendix 10) and the commitment of industrial partners to provide the materials.

- The additional document requested (Appendix 11), the curriculum vitae of the investigators and their five main publications.

In June 2011, the project was accepted and the reviewers made some comments; these comments were taken into account in a revised protocol.

Project instruction

The project instruction then began. A clinical study coordinator (coordinatrice d'étude clinique: CEC), a statistician and a data manager were assigned to our project by the managers of the Clinical Research Unit (Unité de recherche clinique: URC). We were also assigned a project coordinator at the Department of Clinical Research and Development (DRCD) of Assistance Publique-Hôpitaux de Paris (AP-HP). With the URC team, we revalidated the scientific aspects and began to prepare and organize patients, imaging, and medical device circuits (which were validated once we obtained the funds).

Types of clinical research, regulatory bodies and compliance with research principles

To better understand the steps taken to implement the trial designed, Figure 9 describes the regulatory authorities that should be informed for each type of clinical research project [115]. These bodies ensure that the research meets the following essential principles [116]:

- Research foundation principles
    - Importance of cognitive prerequisites: Research must take into account the latest scientific knowledge; it must be original without harming patients, and any research on human beings must have previously been subject to an animal experiment.
    - Researchers competence principle: the French law only allows doctors/dentists who have had training and experience with the research subject to conduct such research.
    - Principle on the purpose and conditions for conducting clinical research: the research should aim to improve the scientific knowledge of humans and how to improve the human condition without the interest of science or society overriding the interest of people. Research must maintain a balance between the expected benefit and the risk involved. Research should be conducted under conditions that ensure scientific rigor and security.
- Principles for the respect of a strict method while conducting research
- Principles for the consent of the subjects included in the research
- Special cases of research conducted on certain categories of persons (pregnant women, children etc.).

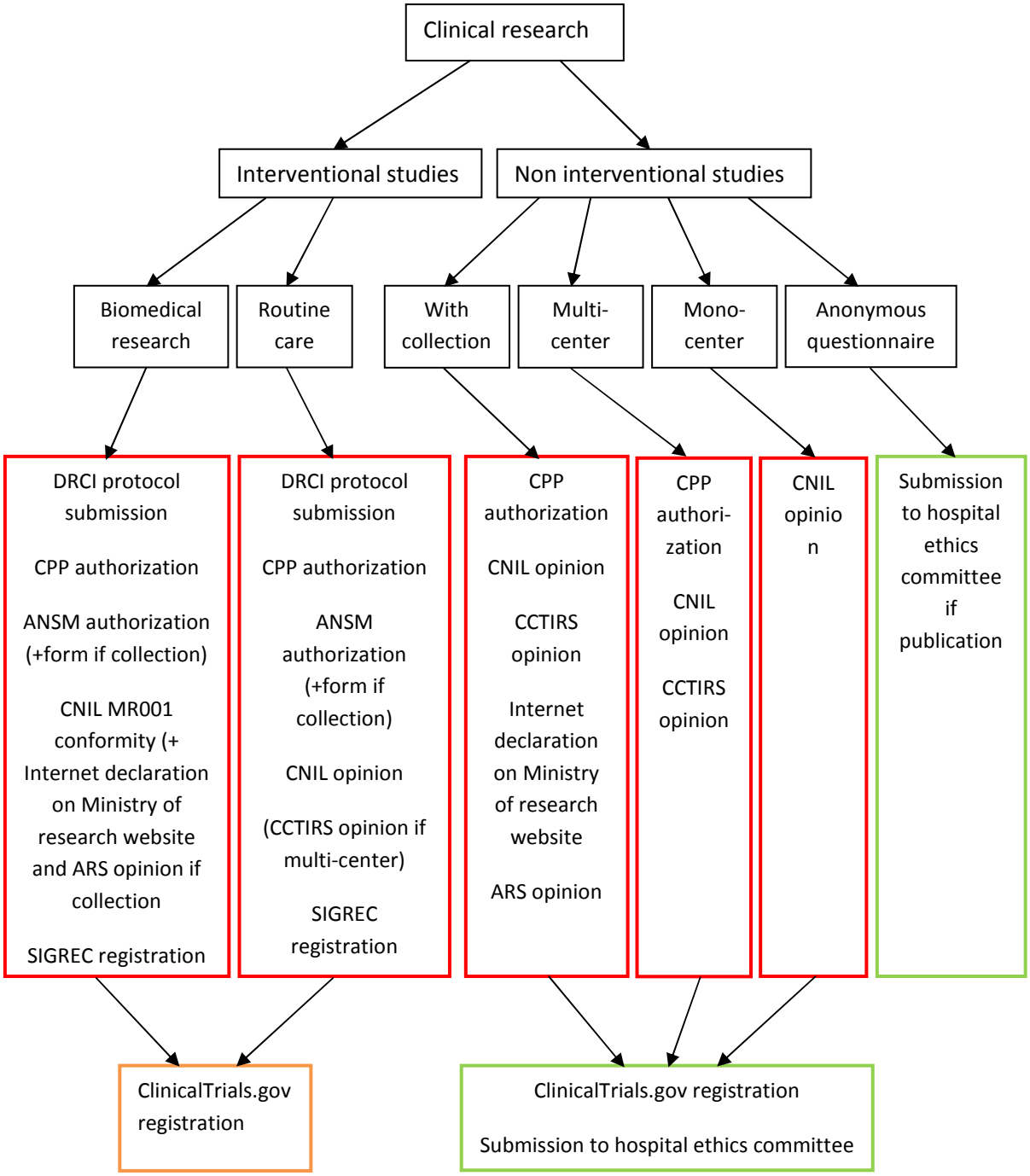

Figure 9. French regulatory bodies that should be informed depending on the clinical research type
Mandatory, recommended, or optional procedure.
DRCI: Direction for clinical research and innovation; CPP: Persons protection committee; ANSM: National agency for the security of medicines and health Products; CNIL: National commission for informatics and freedom; SIGREC: national software for the administrative management and the monitoring of inclusions in clinical trials; CCTIRS: Advisory Committee on information processing in the field of health research; ARS: Regional health agency.

Classification of the research as routine care or biomedical research

The trial we wanted to conduct was interventional. In France, interventional studies can be classified as "routine care" or "biomedical research".

"ROUTINE CARE" INTERVENTIONAL CLINICAL STUDIES

This category concerns projects in which the intervention changes current practice in a minimally invasive way (e.g. randomization or harmless examination). Specifically, the definition of the Code for Public Health (Code de la Santé publique) is as follows:

> The research:
>
> aims "to assess routine care, other than those on drugs, when all procedures are performed and products are used in the usual way but specific monitoring arrangements are set by a protocol" [117],
>
> "the objective is to evaluate actions, action combinations or medical strategies for prevention, diagnosis or treatment that are common practice, that is to say covered by a professional consensus, in accordance with their instructions. "[118],
>
> and in which: "The specific monitoring implemented in this research implies only negligible risks and constraints for the person who participates in the research." [118]
>
> EXCEPT the following situations which correspond to biomedical research:
>
> Research that focuses on techniques or strategies innovative or considered obsolete;
>
> Research that focuses on the evaluation of an innovative combination of actions or products, even if each of them - taken individually - is commonly used;
>
> Research on a comparison of medical strategies, when one of these strategies can, in the state of knowledge, be considered superior to the other in terms of safety and efficiency [118].

"BIOMEDICAL RESEARCH" INTERVENTIONAL CLINICAL STUDIES

This category involves projects for which the intervention changes current practice in an invasive way (e.g., medication intake, medical device insertion or constraining examination). Specifically, the definition of the Code for Public Health is as follows:

> Research arranged and practiced on human beings for the development of biological or medical knowledge are permitted under the conditions laid down in this book and are hereinafter referred to by the terms “biomedical research” [117].
>
> EXCEPT two types of research covered by other texts: non-interventional research and “routine care” research.

CHOOSING BETWEEN "ROUTINE CARE" AND "BIOMEDICAL RESEARCH" IN THE CASE OF CECOIA

Initially, we considered that composite and ceramic inlays and onlays fell within the "routine care" category because they were a combination of common practice dental procedures, and the CAD/CAM technology used in the trial had been authorized and marketed for a long time in France.

However, in view of the tripartite meeting described below, the DRCD asked us to show that the number of composite and ceramic inlays and onlays made annually in France was close, to justify a minimally invasive randomization. We then contacted a dozen large dental laboratories, and only one of them was making ceramic inlays and onlays.

We were not concerned with collections declaration because these declarations relate to biological samples, and the only collection in our trial involved impressions and plaster replicas.

The different risk levels in "biomedical research" (involving medical devices in particular)

Biomedical studies are divided into four categories (the classification of medical devices is described p.76):

- A: low or negligible predictable risk. This category includes in particular clinical investigations on the following:
  - Medical devices (MDs, Dispositifs médicaux/DM in French) marked "CE" of class I, IIa or IIb in current practice
  - MDs marked "CE" of class I
- B: predictable risk similar to that of usual care. This category includes in particular clinical investigations on the following:
  - MDs marked "CE" of class IIa, IIb or III in current practice with short follow-up on use but without demonstrated efficiency
  - MDs marked "CE" of class IIa used off indication
  - Class I MDs that are not marked "CE" except if they are invasive or active.
- C: high predictable risk. This category includes in particular clinical investigations on the following:
  - MDs marked "CE" of class III with short follow-up on use
  - MDs of class IIb in research context

- D: very high predictable risk. This category includes in particular clinical investigations on the following:
  - Class I (invasive or active), IIa, IIb or III MDs that are not marked "CE"
  - MDs of class III in research context

Each risk level corresponds to a different level of monitoring. For level A, monitoring mainly includes verification of consent (if consent was planned in the protocol). Serious adverse events (SAEs) should be communicated to the sponsor (who transmits them to the ANSM and CPP). A report must also be sent to the sponsor annually and at the end of the study. For level B, monitoring includes verification of the existence of the patients included, the signatures and consistency of the dates on consent, endpoints reported in files, the reporting and monitoring of SAEs, and the fulfillment of the eligibility criteria by comparing the data entered in the case report form to those of medical records and control of products' management.

Tripartite meeting

In November 2011, the tripartite meeting took place and involved:

- The main investigators (Jean-Pierre Attal and me)

- Representatives of the DRCD

- The main representatives of the URC interested in our project (the budget coordinator and our clinical study coordinator in particular)

At this meeting, the scientific and technical regulatory aspects were validated and some documents were signed. We decided that the trial was "***biomedical research" at A risk.***

Instruction stages with the URC

With our clinical study coordinator, we first established a Gantt schedule accounting for the times for approval by the different regulation bodies (Table 4 below) and for the documents to be submitted (described below) using the MS Project program.

Then we prepared the study materials: Case report form (CRF, Appendix 12), consent documents and other documents of the investigator workbook. We printed them or had them printed (CRFs in particular).

Regulatory body	Time for approval
DRCI	1-2 months
CPP	35 days
ANSM	60 days
CNIL	2-4 months
Ministry of research for collection declaration	3 months
ARS for collection declaration	3 months

Table 4 - Time for the response of regulatory bodies

We then looked at the implementation of the randomization. After determining that the randomization method most suitable for our trial was minimization incorporating 30% randomness, we determined how to implement this method. The statistician of the URC then told us about two options they use:

- the free Minim software running on MS-DOS and thus requiring a person of the unit to start the program for each randomization. This solution seemed inappropriate because work schedules of private practitioners often conflict with those of public sector employees (e.g., they work on Saturdays). In addition, the Minim software did not allow for incorporating randomness in the randomization.
- the Randoweb online software developed for AP-HP but which apparently only allowed for stratification.

On the internet, we found alternatives that were not free or were free for different types of minimization [119] but not allowing online minimization, and this seemed the most appropriate to facilitate recruitment.

Therefore, we developed our interface for online minimization. This interface allowed the investigator to connect with a login and password. The investigator would then include the patient by entering the first letters of the last name and first name and date of birth. In the same session or in a later one, the investigator could then randomize any patient already included after entering the necessary minimization characteristics. So that investigators (other than that us who had chosen the method) were not tempted to guess the treatment assigned to the next patient, we added factors not required for minimization. We also inserted a table where the investigator could access all inclusions, but the table mentioned only the treatment assigned to the last patient included to limit any indication compromising non-predictability of allocation.

However, because we also had to include patients and we had programmed the website, someone else needed to manage the website during the inclusion period and monitor inclusions. The IT engineer of the unit was supposed to do it. However, for reasons of time and confidence in the security of the interface, with agreement by the DRCD, we would not use our interface and we found that Randoweb could actually be modified to allow for minimization (the creator of Randoweb being an IT teacher of Paris VI University). A specific module was added. We tried to secure the data entered by the investigators as well as the software allowed, for example, by entering controls on patient birth dates (who should be between 18 and 70 years). Compared to the interface we had tailor-made, Randoweb had the following shortcomings:

- Inclusion and randomization modules were independent, and therefore patients who had not been included could be randomized. To limit this risk, we added a box to the randomization form where the investigator had to enter the inclusion number. However, that number could be wrong.
- Investigators could access all their inclusions at any time, which could compromise the non-predictability of allocations.

Very recently, a website for free online minimization was created [120].

In collaboration with the IT engineer and the statistician, the minimization algorithm and interface were tested before the inclusions started. A document explaining the process to investigators was created. The regulatory DRCD document on randomization implementation was completed and approved in July 2012.

Instruction stages with the DRCD

At the same time and with our DRCD manager, we prepared a list of the products that would be used in our study and their value to determine those for which we needed to establish a contract. Given the sums involved, we decided to establish contracts with the 5 major industrial contributors: Sirona Kerr, Ivoclar, Komet and 3M Espe.

Because these industrial partners would not be able to intervene at the time of analysis and publication of the trial results, we tried to offload them from tasks that are usually requested by the DRCD and performed them ourselves (specific labeling of all products, resupply of the different centers throughout the inclusions, registration of lot numbers and monitoring of all products) to facilitate and accelerate the acceptance of the contract (this step often takes a long time).

We also discussed the valorisation to industrial partners. To be able to intervene in the final publication, industrial partners must purchase the entire trial (the total budget +

valorisation costs). To access the report that we would submit to the DRCD and decide on this possible purchase, the fees charged to industry partners were very high. We asked for a decrease because these partners would have eventual access to the publication. An example of a contract (Appendix 13) and its Appendix (Appendix 14) are presented in the Appendix.

CLASSIFICATION OF MEDICAL DEVICES

For the Appendix, we needed to define the category of the medical devices used. Classification of medical devices is based on the following criteria [121] :

- The duration of implementation of the medical device

  Temporary: Normally intended for continuous use for less than 60 minutes.

  Short term: Normally intended to be used continuously 30 days or less.

  Long term: Normally intended for continuous use for more than 30 days.

Thus, in our trial comparing composite and ceramic inlays and onlays, temporary (powder for the optical impression, silicone impressions etc.) and long-term (adhesive, resin cement, composite or ceramic block) medical devices are used.

- The location of the medical device in the body

  Invasive device: device that partially or fully penetrates the body, through a body orifice or the body surface.

  Body orifice: Any natural opening in the body and the outer surface of the eyeball, or any permanent artificial opening, such as a stoma.

  Surgically invasive device: invasive device that penetrates the body through the body surface, by or as part of a surgical procedure.

  Devices other than those referred to above and which produce penetration other than through an existing body orifice shall be treated as surgically invasive devices.

  Implantable device: any device intended to be totally introduced into the human body or to replace an epithelial surface or the surface of the eye, through surgery, and remain in place after surgery. Any device intended to be partially introduced into the human body through surgical intervention and intended to remain in place after the procedure for a period of at least 30 days.

Thus, in our trial, the medical devices used are invasive but not surgically invasive.

The rule regarding the materials used in our trial is thus as follows:

All invasive devices with respect to body orifices, other than surgically invasive devices and which are not intended for connection to an active medical device or which are intended to be connected to an active Class I medical device are:

Class I if they are intended for temporary use,

Class IIa if they are intended for short-term use, except if they are used in the oral cavity to the pharynx, in an ear canal up to the ear drum or in a nasal cavity, in which case they are part of the class I,

Class IIb if they are intended for long-term use, except if they are used in the oral cavity to the pharynx, in an ear canal up to the ear drum or in a nasal cavity and are not likely to be absorbed by the mucous membrane, in which case they are included in class IIa.

Thus, in our trial, the medical devices used fall within class I for temporary medical devices and within class IIa for long-term devices.

Records for regulatory bodies and their acceptance

We also prepared the appropriate records for regulatory bodies (CPP and ANSM in particular).

COMPOSITION OF THE RECORD TO BE SUBMITTED TO THE COMMITTEE FOR THE PROTECTION OF PERSONS (CPP)

The record was submitted by email on March 20, 2012 and included the following:

a letter of submission

a form for opinion query (MDs)

the additional document (Appendix 15)

the IDRCB number: 2012-A00093-40

the protocol

the information and consent form (Appendix 16)

a document showing professionnal liability (Responsabilité civile professionnelle: RCP) or investigator's brochure

the insurance certificate

the DRCI opinion letter and letter of adequacy of resources

the draft case report form

operators curriculum vitae

The CPP gave a favorable opinion on the Cecoia trial on May 14, 2012.

COMPOSITION OF THE RECORD TO BE SUBMITTED TO THE NATIONAL AGENCY FOR THE SECURITY OF MEDICINES AND HEALTH PRODUCTS (ANSM)

The following documents were submitted to the National Agency for the Security of Medicines and Health Products (ANSM) by email on March 20, 2012:

- a letter of submission
- the IDRCB number: 2012-A00093-40
- the protocol
- a document showing professionnal liability or the investigator's brochure
- the insurance certificate
- the DRCI opinion letter
- the CPP opinion letter
- the form for authorization of a clinical trial
- the CE markings of the materials used in the trial

The ANSM authorized the research on May 22, 2012.

There was no submission to the CNIL or the CCTIRS because the project was part of the MR-001methodology of reference, that is, the URC and DRCD governing our project follow standards for the automated processing of personal data. This treatment must ensure the privacy, confidentiality and security of the data (staff training, staff and premises dedicated to computing, IT administrators and security of IT resources). Therefore, the submission of each project to the CNIL and CCTIRS is not necessary.

End of the instruction and authorization to start recruiting

At the end of January 2012, an insurance was subscribed for the trial. In August 2012, the DRCD authorized the recruitment to start. In September 2012, the trial was registered at ClinicalTrials.gov (Appendix 17) and recruitment began. In November 2012, the EUR 236 700 funding was released by the DRCD and assigned to our project.

Publication

The protocol was re-written following CONSOlidated guidelines for Reporting Trials (CONSORT) for non-pharmacological trials [122] and submitted in November 2012 to the journal *Trials*.

The article, as it was published, is presented below.

Fron Chabouis et al. Trials 2013, 14:278
http://www.trialsjournal.com/content/14/1/278

TRIALS

STUDY PROTOCOL Open Access

Efficacy of composite versus ceramic inlays and onlays: study protocol for the CECOIA randomized controlled trial

Hélène Fron Chabouis[1,2,3*], Caroline Prot[4], Cyrille Fonteneau[4], Karim Nasr[4,5,6], Olivier Chabreron[4,5,6], Stéphane Cazier[4], Christian Moussally[4], Alexandre Gaucher[4], Inès Khabthani Ben Jaballah[7], Renaud Boyer[7], Jean-François Leforestier[7], Aurore Caumont-Prim[7], Florence Chemla[1,2], Louis Maman[1,2], Cathy Nabet[5,6] and Jean-Pierre Attal[1,2]

Abstract

Background: Dental caries is a common disease and affects many adults worldwide. Inlay or onlay restoration is widely used to treat the resulting tooth substance loss. Two esthetic materials can be used to manufacture an inlay/onlay restoration of the tooth: ceramic or composite. Here, we present the protocol of a multicenter randomized controlled trial (RCT) comparing the clinical efficacy of both materials for tooth restoration. Other objectives are analysis of overall quality, wear, restoration survival and prognosis.

Methods: The CEramic and COmposite Inlays Assessment (CECOIA) trial is an open-label, parallel-group, multicenter RCT involving two hospitals and five private practices. In all, 400 patients will be included. Inclusion criteria are adults who need an inlay/onlay restoration for one tooth (that can be isolated with use of a dental dam and has at least one intact cusp), can tolerate restorative procedures and do not have severe bruxism, periodontal or carious disease or poor oral hygiene. The decayed tissue will be evicted, the cavity will be prepared for receiving an inlay/onlay and the patient will be randomized by use of a centralized web-based interface to receive: 1) a ceramic or 2) composite inlay or onlay. Treatment allocation will be balanced (1:1). The inlay/onlay will be adhesively luted. Follow-up will be for 2 years and may be extended; two independent examiners will perform the evaluations. The primary outcome measure will be the score obtained with use of the consensus instrument of the Fédération Dentaire Internationale (FDI) World Dental Federation. Secondary outcomes include this instrument's items, inlay/onlay wear, overall quality and survival of the inlay/onlay. Data will be analyzed by a statistician blinded to treatments and an adjusted ordinal logistic regression model will be used to compare the efficacy of both materials.

Discussion: For clinicians, the CECOIA trial results may help with evidence-based recommendations concerning the choice of materials for inlay/onlay restoration. For patients, the results may lead to improvement in long-term restoration. For researchers, the results may provide ideas for further research concerning inlay/onlay materials and prognosis.
This trial is funded by a grant from the French Ministry of Health.

Trial registration: ClinicalTrials.gov Identifier: NCT01724827

Keywords: Dental caries, Inlays, Composite resins, Ceramic, Survival analysis, CAD/CAM, Dental prosthesis, Dental restoration failure, Dental restoration wear

* Correspondence: helene.fron@parisdescartes.fr
[1]Faculté de Chirurgie Dentaire, Université Paris Descartes, Sorbonne Paris Cité, Montrouge 92120, France
[2]Service d'Odontologie, Assistance Publique – Hôpitaux de Paris (AP-HP), Hôpital Charles Foix, Ivry-sur-Seine 94200, France
Full list of author information is available at the end of the article

Background

The World Health Organization (WHO) estimates the prevalence of dental caries is over 90% among adults worldwide [1,2]. When the loss of tooth substance due to decay is minor, the dentist fills the tooth cavity. With substantial tooth substance loss, the dentist often treats the tooth with a crown, which presents the problem of further destroying the tooth. Large amalgam or build-up amalgam restorations are also used in such cases in many countries; however, amalgam is being abandoned for environmental reasons, especially in Europe [3]. An intermediate technique consists of manufacturing an inlay or onlay for the tooth and this type of restoration has become common because it is a minimally invasive solution (further information on inlays and onlays is available at http://cecoia.fr) [4]. Inlays and onlays can be made of metal alloy, ceramic or composite materials; however, patients tend to refuse metallic restorations for esthetic and financial reasons [5], and thus dentists generally have to choose between composite and ceramic materials.

The chemical composition differs between ceramic and composite inlays and onlays, and explains most of their clinical properties. Ceramic inlays and onlays (ceramics) are mainly composed of glass, with some crystals added to increase strength [6,7]. Composite inlays and onlays (composites) are made of a resinous matrix and fillers of different types [8]. Like glass, ceramics are thus brittle [9] and more prone to fracture than composites [10,11]. However, ceramics are harder than composites: they are thus more wear-resistant but can induce more wear than usual with the opposing tooth's surface [12]. Furthermore, adhesive cement interfaces are made of composite material, therefore the wear of the interface and restoration material should be closer for composites, with less marginal gaps [13,14]. Another disadvantage of composites is their resinous matrix. An incompletely polymerized matrix can result in monomers than are released into the mouth, which presents some toxicity, whereas ceramics are extremely biocompatible [15-19]. A disadvantage of ceramics is that manufacturing is time-consuming; composites are easier to polish and perhaps less costly.

Some factors may influence the clinical performance of ceramic and composite inlays and onlays differently. Ceramics are resistant to compressive forces but susceptible to shear stresses. Increased compressive forces can be expected with onlays, thus the inlay or onlay factor may influence the performance of the materials differently [10,11]. Bicuspids usually offer more favourable conditions for inlays and onlays than molars: cavities are usually smaller, the effect of masticatory forces and stresses at the adhesive interface are less intense, and access for dental treatment is easier [20]. Tooth type (bicuspid or molar) may thus influence the performance of composite and ceramic inlays and onlays [21]. Tooth vitality may also differently influence the clinical performance of both materials; some *in vitro* studies and simulations have suggested that composites could perform better than ceramics for non-vital teeth [22,23]. Finally, the operator (dentist) who performs the restoration is a key variable [20,24]; practitioners equipped with the computer-assisted design/computer-assisted manufacturing (CAD/CAM) system (CEREC, Sirona Dental Systems, Long Island City, NY, USA) used in this trial manufacture mostly ceramic inlays and onlays, and may require a slight learning curve to manufacture composite inlays or onlays.

A systematic search of the literature conducted for this report identified only two randomized clinical studies that have compared ceramic and composite inlays and onlays (see Research in context section) [25-27]. These studies were small in size (43 and 37 patients) and presented some risk of bias. The results from both trials suggested no clear evidence of a difference between ceramic and composite inlays or onlays. Since then, materials have improved, composites (especially as CAD/CAM blocks) have become much safer and consensus outcomes for evaluating dental restorations have been developed [28].

Research in context

Systematic search of the literature

Following the Cochrane methodology, we searched MEDLINE and Embase for reports of prospective randomized controlled studies comparing at least one composite and one ceramic material for inlay or onlay manufacturing, with a minimum follow-up of 6 months, and without any date or language restriction up to 11 October 2012.

Studies identified through the systematic search

- *In vitro*: 91 studies
- Only one ceramic or one composite (no control or luting agent/base material randomized): 20 studies (27 reports)
- Ceramic versus ceramic: three studies
- Composite versus composite: two studies
- Ceramic versus composite (non-randomized or retrospective study): five studies (eight reports)
- Ceramic versus composite (prospective randomized study): two studies (four reports)

Interpretation

Only two randomized studies were identified, which compared ceramic and composite materials for inlay or onlay manufacturing. In 2005, a study compared 80 VITA Mark II (ceramic; Vita Zahnfabrik, Bad Säckingen, Germany) and Paradigm (composite; 3M Espe, St Paul, MN, USA) CAD/CAM inlays in 43 adults after 3 years with use of

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the US Public Health Service (USPHS) modified criteria [29]. The composite inlays performed better for only two items: color match and restoration fracture [25]. In 2006, a study compared 58 CEREC, Vita Dur N (two ceramics; Vita Zahnfabrik), Brilliant DI (Coltene/Whaledent AG, Altstätten, Switzerland) and Estilux (two composites; Heraeus Kulzer GmbH, Hanau, Germany) inlays in 37 patients after 10 years with use of the California Dental Association criteria [30]: survival was similar for all inlays when repairs were not considered failures (75 to 80%) and was better for CEREC ceramic inlays than other inlays when repairs were considered failures (80% versus 51 to 67%) [26]. Data on the material to use for manufacturing inlays or onlays are thus controversial and a RCT is needed.

The main objective of the CEramic and COmposite Inlays Assessment (CECOIA) randomized controlled trial (RCT) is to compare the clinical efficacy of composite and ceramic inlays or onlays for treating moderate substance loss of posterior teeth in adults according to recent consensus outcomes. Secondary objectives include the overall quality, wear and survival of inlays and onlays made of both materials, and prognostic factors of restoration failure, including patient-related items.

Methods

This trial is a multicenter, randomized, open-label superiority trial with two balanced parallel arms. The trial received approval from the French ethics committee for the protection of persons (Comité de Protection des Personnes (CPP), Ile de France XI, trial number 12029) in May 2012.

Participants and setting

Eligibility criteria for patients

Patients are eligible to participate in the trial if they are adults aged 18 to 70 years, can tolerate restorative procedures and have a posterior moderate-sized dental caries or aged restoration necessitating an inlay or onlay. Exclusion criteria are allergy to one of the materials used, bruxism, severe or acute periodontal or carious disease (greater than or equal to four primary or secondary restorations due to caries in the preceding year) and poor oral hygiene; the tooth to be treated should not need endodontic treatment or retreatment, show mobility >1 mm or a periodontal socket >3 mm or support a removable partial denture.

Patients with a tooth showing a subgingival margin after cavity preparation, that cannot be isolated with use of a rubber dam, or that has cusps that all need to be covered by the restoration are not eligible.

Only one tooth per patient is eligible. If a patient needs more than one inlay/onlay restoration, the tooth with expected cervical limits that are the most coronal, is the eligible tooth. Other required inlays or onlays will be manufactured by the dentist with the usual material (leucite-reinforced glass-ceramic). In case of pulpal exposure, the operator will decide whether a direct pulp capping (with calcium hydroxide) or an endodontic treatment is necessary, randomize the patient after this treatment has been conducted and fill the corresponding fields in the adverse events section of the case report form (CRF).

Eligibility criteria for operators (dentists)

Operators will be eligible for inclusion if they have at least 3 years of clinical experience and at least 1 year of experience with chairside CAD/CAM, agree with the intervention protocol, and have no preference for either composite or ceramic to manufacture inlays and onlays.

Eligibility criteria for evaluators

Evaluators of restorations during follow-up will be two dentists different from the operators.

Setting

Patients will be included and treated in seven centers in France: the dental care departments of two hospitals (Hôpital Charles Foix, Ivry-sur-Seine and Hotel-Dieu Saint-Jacques, Toulouse) and five private practices (four in Paris and one in Lyon). Follow-up data will be collected in these seven centers. Any patient with the eligible criteria visiting one of the included centers will be asked to participate in the study. The consent form can be consulted at http://cecoia.fr: extra section.

Interventions

Patients will be allocated to receive a leucite-reinforced glass-ceramic or a composite CAD/CAM inlay or onlay.

Among the ceramics currently used, we chose a pressed glass-ceramic because fired feldspathic ceramics have shown higher fracture rates [31], and we chose leucite-reinforced glass-ceramic (IPS Empress CAD, Ivoclar Vivadent, Schaan, Liechtenstein) over lithium disilicate-reinforced glass-ceramic because the latter has been frequently evaluated clinically. Among available composites, we chose a recently developed material (Lava Ultimate, 3 M ESPE, St Paul, MN, USA), which we considered promising after laboratory testing.

Although the purpose was not to study CAD/CAM but to compare composite and ceramic as inlay or onlay materials, we decided to use CAD/CAM for the inlays or onlays in this trial to standardize the manufacturing (as compared with the necessary variability with a dental technician). This technology also simplifies the protocol and conduct of the trial, since some CAD/CAM systems allow for manufacturing inlays or onlays chairside during a single appointment.

For cavity preparation, the operator will choose the color for both evaluated materials (A1/A2/A3). With the patient under local anesthetic, if needed, the cavity will be prepared (for dental caries or former restoration eviction) using a burs sequence (Komet, Rock Hill, SC, USA) specifically designed for the CECOIA trial. Adjacent teeth will be protected (FenderWedge, Directa, Upplands Väsby, Sweden) [32,33]. The following thicknesses will be respected: 2 mm wide and 1.5 mm deep for isthmuses, and 1.2 mm wide for approximal boxes, the approximal overhang not exceeding the box width. Cusps will be covered if the width of the isthmus is greater than half of the intercusp buccolingual distance, the wall is ≤2 mm thick before preparation, the wall is ≤1 mm thick after preparation, the width of the isthmus is close to half the intercusp buccolingual distance and one or more cracks are observed or the preparation is mesio-occlusal-distal or with horizontal forces [34-36]. A base can be applied (dental dam; OptiBond XTR and Premise Flowable, Kerr, Orange, CA, USA).

Computer-assisted design/computer-assisted manufacturing (CAD/CAM)

After powder spraying (CEREC Optispray, Sirona Dental Systems), the operator will scan the preparation with use of a digital camera and design the restoration by use of CEREC software (Sirona Dental Systems). If eligibility criteria are still satisfied, the operator will then randomize the tooth to a treatment (randomization procedure described below), insert the corresponding block inside the milling machine and press the button for the restoration to be milled. The operator will then check the approximal contacts of the resulting restoration, correct them if need be, remove the machining lug and weigh the restoration.

Surface treatment and polishing of ceramic inlays or onlays

The operator can glaze (IPS Object Fix Putty, glazing paste and stains, Ivoclar Vivadent) or polish the inlay or onlay using the polishers provided in the sequence and diamond paste (OptraFine, Ivoclar Vivadent). The intaglio surface will then be treated with hydrofluoric acid (Porcelain Etchant gel, Bisico, Schaumburg, IL, USA) for 60 seconds, rinsed, dried, silanated (Monobond Plus, Ivoclar Vivadent) and left to dry for at least 3 minutes before sealing.

Surface treatment and polishing of composite inlays or onlays

The operator will polish the inlay or onlay using the polishers provided in the sequence, and may modify the color (Kolor Plus, Kerr) of pits and fissures. The intaglio surface will be sandblasted with 50 μm alumina, rinsed, dried, silanated (Monobond Plus) and left to dry for at least 3 minutes before sealing.

Inlay or onlay adhesive luting and finishing

A dental dam (DermaDam medium, Bisico) will be used. The tooth surface will be cleaned by air abrasion (RO NDOflex, KaVo, Biberach, Germany). Enamel will be etched with orthophosphoric acid (37.5%) for 15 seconds, rinsed thoroughly and dried gently [37]. Adhesive (Optibond XTR) will be applied by gently brushing the tooth surface for 15 seconds, followed by a 3-second air spray and light polymerization of the adhesive for 20 seconds. The inlay will be handled with use of a stick (Stik-N-Place, Directa); adhesive cement (NX3 yellow, Kerr) will be applied generously on the intaglio surface of the restoration. The inlay or onlay will be positioned and maintained. It may be light polymerized for 1 or 2 seconds. Excess cement will be carefully removed by use of dental floss and a curette. Glycerine gel will be applied on the limits of the restoration, followed by light polymerization of the cement for 40 seconds per face. The occlusion will then be adjusted, and the corrected surfaces and cement interface will be polished.

Outcomes

Primary outcome

The primary outcome, clinical efficacy of materials, will be measured by use of the Fédération Dentaire Internationale (FDI) World Dental Federation instrument for assessing dental restorations, described in 2007 [28] and updated in 2010 [38]. This instrument contains three dimensions (18 items): biological (six items), functional (seven items) and esthetic (five items). Each item is assessed by clinical examination on a 5-point Likert scale (1 corresponding to a perfect restoration and 5 corresponding to a restoration that needs to be replaced), and collected in the CRF. All items but one are assessed by the dentist; the remaining item is patient-reported satisfaction. The primary outcome is the worst score for all items (ranging from 1 to 5) at 2-year follow-up (the best material will be the one with the lowest score).

Operators and evaluators, who will assign scores, will be trained in the FDI criteria by means of the e-calib web-based software (http://zep01793.dent.med.uni-muenchen.de/moodle/) and group training sessions. They will use the evaluation kit specifically designed for evaluating the FDI criteria (EX-KIT 150/250, Deppeler, Rolle, Switzerland).

Secondary outcomes

Secondary outcomes will include each item of the FDI instrument, patient-relevant outcomes, quantified wear analysis (through silicone impressions) and overall quality

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of the restoration (as assessed by dentists). Survival may be evaluated if the follow-up is extended.

Follow-up evaluations

The restorations will be evaluated after 1 week by the operator, and after 1 and 2 years by two independent evaluators (Table 1). Follow-up is planned and funded for 2 years; it may be extended to 5 years (as recommended for indirect dental restorations by the FDI) if the grant can be extended.

Data collection

Investigators will use a CRF (available at http://cecoia.fr) to record all items required for outcomes analysis. The CRF comprises two adverse events forms (one concerning general health and one concerning inlay/onlay-related events). Patient data will be anonymous because patients will be identified by their inclusion number (the first letter of their first and last name and date of birth only will be registered in the CRF). A clinical research assistant (RB) will visit each center every 20 inclusions to monitor the collection of data (by checking that no CRF field is incomplete) and assess the quality (by comparing the data in the medical record, entered through the online inclusion and randomization software RandoWeb (Assistance Publique – Hôpitaux de Paris (AP-HP), Paris; http://randoweb.aphp.fr), written in the CRF). The data will be entered twice in the database by operators and checked by a data manager (more information about data management procedures is available at http://cecoia.fr: extra and protocole initial sections). Some elements in the CRF allow for checking for operators' adherence to the protocol.

Sample size

We estimated the required sample size for the primary outcome (score between 1 and 5, 5 corresponding to the worst score) for the 18 items for each patient. Since the resulting score is an ordinal variable, we used Zhao's formula, which is based on the expected distribution of responses in each of the five possible ratings [39]. To the best of our knowledge, no data on the FDI score are available. Consequently, we derived assumptions from previous studies [25,26,40-47] that involved the USPHS score [29], with dimensions close to that of the FDI score [28]. Thus, we derived assumptions regarding the expected distribution of ratings for the ceramic and composite groups for each of the three dimensions (biological, functional and esthetic). As a proxy for the FDI score, the worst score across the three dimensions, we estimated the three sample sizes required to guarantee a power of 80%, with a type I error rate of 1.7% (Bonferroni adjustment for three dimensions), to detect expected differences in distribution of ratings between the ceramic and composite groups for each dimension. We considered the largest required sample size, which was found for the biological dimension. Consequently, with an overall type I error risk of 5%, a sample size of 211 patients would guarantee 80% power to detect a difference between an expected 3% for scores 3, 4 or 5 in one group and an expected 7% in the other group. Finally, since several centers and several operators will participate, we expected that outcomes from a same center and a same operator will be more similar than those from different centers or different operators. We took this intracenter/operator correlation of data and applied an inflation factor [48,49], which resulted in an

Table 1 Schedule of enrollment, interventions and assessments

	Study period				
	Enrollment	**Allocation**	**Postallocation**		**Closeout**
Time point	- ≤ 1yr	0	1 wk	1 yr	2 yr
Enrollment:					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
Interventions:					
(composite or ceramic inlay/onlay)		X			
Assessments:					
Baseline variables					
(inlay/onlay, premolar/molar, vital/non vital, operator, sex, date of birth, restoration volume etc.)	X	X			
Outcome variables					
FDI criteria			X	X	X
Radiograph	X		X	X	X
Impression			X	X	X

estimated sample size of 358 patients. We will include 400 patients to account for patients lost to follow-up, although we will try to avoid missing data on outcome measures (in particular, by compensating each patient with 100 euros (€100) after 2 years) [50].

The enrolment capacity was estimated to be 75 patients per year for each hospital and 50 patients per year for each private practice. A 1-year period was planned for including these 400 patients.

Randomization sequence generation

From a literature review, we considered four major factors that could differentially influence the performance of ceramic and composite inlays and onlays (inlay/onlay, premolar/molar, vital/non-vital tooth and operator), and that we should aim for balanced distribution of these factors between the two groups. Consequently, treatment allocation will involve minimization with a 30% random element. Minimization was preferred over stratified randomization from the results of extensive simulations showing minimization with the lowest predictability and imbalance between treatment groups, considering the trial's sample size and these four factors (details about these simulations and the results are available at http://cecoia.fr) [51,52].

Allocation concealment

The operator will obtain each randomization allocation through a centralized secured web-based interface that runs the minimization algorithm (RandoWeb). The sequence is thus concealed until the intervention is assigned.

Implementation

The minimization algorithm was added to the RandoWeb software. It was programmed by an independent statistician. Investigators will enroll participants (inclusion numbers are obtained by use of RandoWeb).

Blinding/masking

Operators cannot be blinded to the randomization because the intervention differs between both arms (in particular, surface treatments of the upper and intaglio surfaces of the restoration). Moreover, a dentist can easily recognize each material, so neither operators nor evaluators can be blinded. Patients are not blinded, firstly because a few patients had been asked if they would prefer one material to the other and most did not have any preference; secondly because it would complicate the clinical session because the block is inscripted with the name of the material and the intervention differs between both arms; and thirdly because another dentist could tell them if their restoration is made of composite or ceramic.

Therefore, the trial will be open-label. Randomization was thus planned as late as possible to insure that the tooth cavity would be prepared in the same way for both groups and to limit bias due to the absence of blinding. Interventions were standardized as much as possible (in particular, similar adhesive luting procedure) to enhance similarity. The statistician will be blinded to the treatment arms during data analysis.

Statistical methods

The data will be analyzed by an independent statistician. The unit of analysis will be the patient (only one tooth treated per patient). The demographic and clinical characteristics of patients and treated teeth will be described for both treatment arms with the usual statistics: mean and SD or median and interquartile ranges for quantitative variables, number of subjects, and percentages for qualitative variables [53]. The analyses will be performed according to the intention-to-treat principle [54].

Primary outcome analysis

The main analysis will compare the final values of the FDI score (worst score over the three dimensions) between the ceramic and composite groups. The main analysis will be adjusted on the following pre-specified variables: inlay/onlay, premolar/molar, vital/non-vital tooth and operator [53,55]. An ordinal logistic regression model will be used. The operator variable will be modeled as a random effect. The main analysis will take into account missing outcome data by multiple imputation, with the assumption that data are missing at random. We will report the unadjusted analysis as well; that is, the contingency table showing the distribution of FDI scores in the ceramic and composite groups. The distribution of FDI scores will be compared by Fisher's exact test. All *P* values will be two-tailed, with significance level 0.05.

Secondary outcomes analysis

The same analyses will be used to compare both treatments by each of the three dimensions (with an α risk of 1.7% for each dimension). Secondary analyses will also involve FDI items, quantified analysis of wear (by silicone impressions) and analysis of the overall quality of the restoration (assessed by dentists).

Subgroup analyses

We will perform subgroup analyses [56] of the following variables: inlay/onlay, premolar/molar, vital/non-vital tooth, inlay/onlay volume, canine or group lateral guidance and occlusal tapping before luting of the inlay/onlay. If interaction tests are performed for six subgroups independent of each other and each at a significance level of 5% (two-sided), the risk of finding at least one false-

positive statistically significant interaction (that is, due to sampling fluctuations) is 26% (= 1 – (1 – 0.05)^6).

Discussion

For clinicians, the CECOIA trial will help provide evidence-based recommendations concerning the choice of material for inlay/onlay restorations. However, because the manufacturing technique explains part of the inlay/onlay's properties, the results concerning ceramic and composite inlay/onlay manufacturing will be applicable only for CAD/CAM inlays/onlays and not for traditionally manufactured inlays/onlays. In particular, CAD/CAM composite blocks contain few monomers, which could limit biological failures as compared with traditionally manufactured composites; ceramic blocks present better mechanical properties initially but milling may induce fissures. However, the materials still have a similar composition and this trial may give an idea of their clinical performance.

For patients who receive CAD/CAM inlays/onlays, this trial may lead to an improvement in the longevity of the restorations. For researchers, it may provide ideas for further research concerning the efficacy and prognosis of inlays and onlays.

Trial status

The trial was submitted for registration at ClinicalTrials.gov on 10 September 2012. Patient recruitment started on 14 September 2012. This protocol was submitted for publication on 20 November 2012. General information about the trial (such as the original protocol submitted to the ethics committee) can be obtained on the trial's website (http://cecoia.fr). We will share the data obtained.

Abbreviations

ANSM: Agence Nationale de Sécurité du Médicament et des Produits de Santé; AP-HP: Assistance Publique – Hôpitaux de Paris; CAD/CAM: Computer-assisted design/computer-assisted manufacturing; CECOIA: CEramic and COmposite Inlays Assessment; CONSORT: Consolidated Standards of Reporting Trials; CPP: Comité de Protection des Personnes; CRF: Case report form; DRCD: Département de la Recherche Clinique et du Développement; FDI: Fédération Dentaire Internationale; HEGP: Hôpital Européen Georges-Pompidou; ICH: International Conference on Harmonisation; PHRC: Programme Hospitalier de Recherche Clinique; RCT: Randomized controlled trial; USPHS: US Public Health Service; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; WHO: World Health Organization.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

HFC conceived the study and its design, participated in its coordination, and drafted the protocol in accordance with the International Conference on Harmonisation (ICH) E9 guidelines [57], the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement [58], the CONSORT statement extension for nonpharmacologic treatments [59], the CONSORT statement extension for abstracts [60] and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement [61]. IBJ, RB and ACP participated in the methods development and design of the study. JPA supervised the design and coordination of the study, and the drafting of the protocol. FC, LM and CN provided leadership for the hospitals to participate in the study. SC, CF, AG, CM, CP, KN and OC provided clinical advice. All authors read and approved the final manuscript.

Authors' information

HFC teaches dental material courses in Paris and specializes in clinical research; and is the trial's scientific coordinator. IBJ is the clinical trial coordinator, RB is the clinical research assistant, JFL is the informatics engineer and data manager (head of the Data Monitoring Committee, which is independent from the sponsor and competing interests), and ACP is the statistician. IBJ, RB, JFL and ACP work as methodologists at the clinical research unit, Hôpital Européen Georges-Pompidou (HEGP), Paris. SC, CF, AG, CM, CP, KN and OC are private dental practitioners specializing in direct CAD/CAM. KN and OC work part-time at Hotel-Dieu Saint-Jacques, Toulouse. CN specializes in epidemiology and clinical research; and leads the Toulouse team. LM and FC manage the department of dentistry at the Hôpital Charles Foix, Ivry-sur-Seine; the coordinating center. JPA teaches dental material courses in Paris and works as a private practitioner; and is the trial's main investigator. HFC, KN, OC, CP, CF, SC, CM and AG are the operators.

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Author details

[1]Faculté de Chirurgie Dentaire, Université Paris Descartes, Sorbonne Paris Cité, Montrouge 92120, France. [2]Service d'Odontologie, Assistance Publique – Hôpitaux de Paris (AP-HP), Hôpital Charles Foix, Ivry-sur-Seine 94200, France. [3]Ecole doctorale Galillée, Université Paris 13, Sorbonne Paris Cité, Villetaneuse 93430, France. [4]Private Dental Practice, Paris, France. [5]Faculté de Chirurgie Dentaire, Université Paul Sabatier, Toulouse 31062, France. [6]Pôle Odontologie, Hotel-Dieu Saint-Jacques, Toulouse 31059, France. [7]AP-HP, Hôpital Européen Georges-Pompidou (HEGP), Institut National de la Santé et de la Recherche Médicale (INSERM), UMR S872/20, Paris 75015, France.

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Supplementary information

Cecoia trial's website

To make the article easier to read and improve the visibility of the CECOIA trial, we also programmed a website entitled cecoia.fr, which is bilingual (English and French), updated regularly and includes information for researchers and patients (Appendix 18).

Comments on inclusion criteria

We decided not to allow proximal box elevation in the trial, because failures caused by this technique would be specific and significantly complicate the interpretation of the results concerning proximal FDI items. However, we believe that this technique is useful in many cases where the proximal margin is intra-sulcular or subgingival [123].

The use of a post was not indicated for endodontically treated teeth to better preserve hard tissues and because posts do not seem to increase the mechanical strength of endodontically treated teeth restored by an inlay or onlay [124, 125].

Summary of the work that was carried out: trial implementation and recruitment

Once the instruction phase was completed, we began the implementation phase, with the recruitment and follow-up of patients.

This stage began with the set-up meeting, which took place on 10 September 2012. Recruitment could then officially begin and the first patient was included on September 14, 2012. However, the opening of some centers was delayed for two reasons discussed below.

Opening centers in a multicenter trial

First, for any multicenter trial, it is necessary to send two documents to each French center:

- A letter of information about the trial to the Director and the pharmacist (for medical devices)

- A financial agreement

Inclusions can start in the center once the agreement is signed by the director of the center. Thus, the center of Toulouse could open in November 2012 only.

Modifying the protocol

Second, we were notified in August 2012 that one of the operators in Toulouse would not be able to include patients. Because the minimization was based on a given number of operators, we decided to include another private practitioner instead. This is considered a substantial modification of the protocol, and we needed to submit a letter specifying the amendment and the updated protocol to the CPP. The letter was submitted on October 5 and a favorable opinion was received on October 18.

Actions to promote the recruitment

Information, communication, and incentive measures were taken at different levels to best adapt to the circumstances and needs of each investigator.

In university hospitals: Charles Foix and Toulouse

COMMUNICATION

To facilitate inclusions, we created a small leaflet explaining the procedure to the medical staff of university hospitals (teachers, interns and externs) for any patient likely to match the inclusion criteria. We also organized briefing meetings every morning for a week in Charles Foix.

ORGANIZATION

We trained two last-year students, who helped us identify patients who may be included, to make the inlays and onlays and to make the one-week follow-up assessments. One of the two will be selected as an evaluator after she defends her dentistry thesis.

FINANCIAL ASPECTS

Note that, since the introduction of activity-based funding as a mode for financing French hospitals in 2004 (T2A) (see Figure 10 below), hospital department managers urge their medical staff to do clinical research. Indeed, clinical research is valued by MERRI funds (Missions of Education, Reference Research and Innovation), which include funding for

scientific publications (SIGAPS) and for clinical research (SIGREC). SIGREC comprises two scores: the "Trial" score and the "Inclusions" score.

For a multicenter phase III clinical trial, the Trial score is worth 10 points for the sponsor hospital, 1 point for other hospitals. One SIGREC point was worth 2523 euros in 2012, for a 25,000 euro fund for Charles Foix hospital and 2,500 euros for Toulouse hospital.

The Promoter Inclusions score counts the total number of inclusions made in the previous year for which the institution was a promoter. A point of this score was worth 523 euros in 2012; a penalty was applied for more than 200 inclusions, for 523x (200 + (200x0.8)) = 188,280 euros for our 400-inlusions trial (if all the inclusions were performed in hospitals) and thus 188,280 x 63 / 400 = about 29,600 euros for Charles Foix on 10 September 2013 (63 patients included).

The Investigators Inclusions score counts the number of inclusions made in the institution for trials sponsored by another health facility. A point was worth 496 euros in 2012, for 496x37 = about 18,000 euros for Toulouse to 10 September 2013 (37 patients included).

Thus, hospital department managers participate in encouraging trial recruitment.

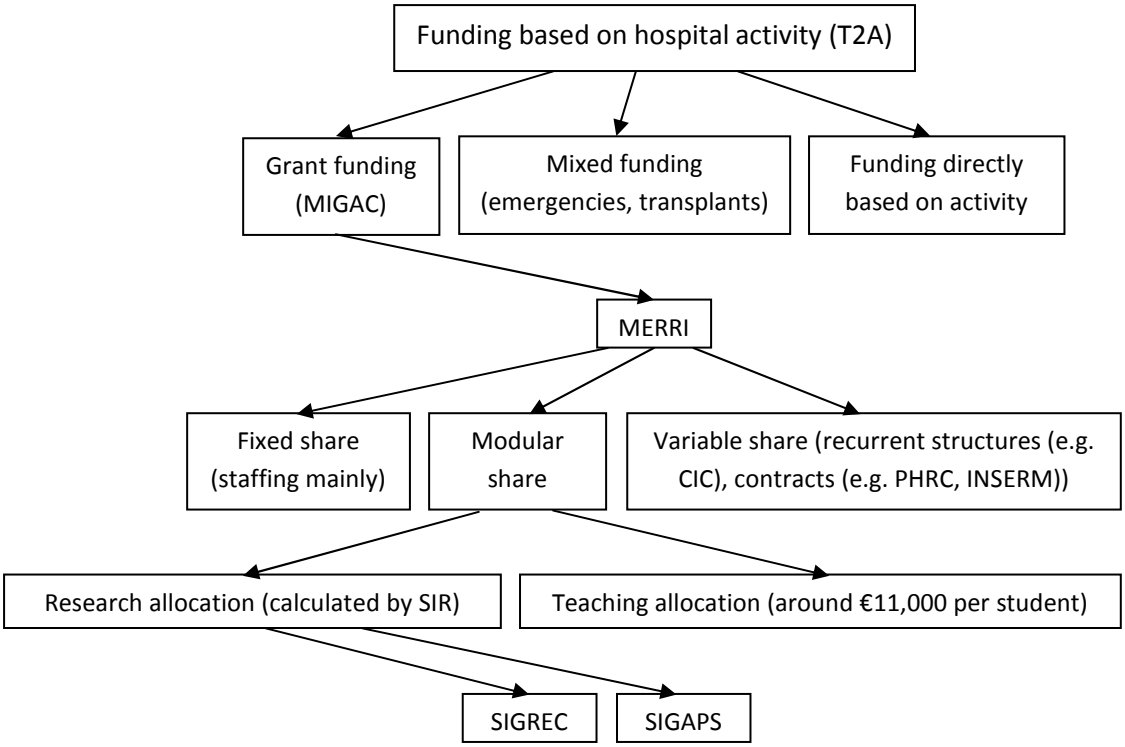


Figure 10. Funding of public hospitals in France (2010)
MIGAC: Misssions of general interest and assistance to contracting (Missions d'intérêt general et d'aide à la contractualisation), MERRI: Educationnal, reference and innovation missions (Missions d'enseignement, de référence et d'innovation), SIR : Research information system (Système d'information de la recherche), SIGREC: Research and clinical trials information and management system (Système d'information et de gestion de la recherche et des essais cliniques), SIGAPS : System for the query, management and analysis of scientific publications (Système d'interrogation, de gestion et d'analyse des publications scientifiques)

Private practice

Private practitioners invested in this project all have extremely busy schedules, and we did our best to limit the time they spent and the formalities to be completed.

For example, we had planned a compensation for the practitioner up to 100 euros per patient enrolled for the time spent in completing the documents, pouring plaster for study replicas etc. The DRCD usually distributes these funds annually and we arranged that practitioners would be paid every 20 inclusions, to encourage recruitment. To simplify their task, we prepared a standard invoice for each operator to be completed every 20 inclusions so that they would just have to send it by email to the DRCD.

In all centers

INFORMATION

A newsletter was sent regularly to the investigators to notify them of the evolution in number of inclusions and remind them of some aspects of the protocol according to the remarks made by the clinical research associate who does the monitoring etc.

After each inclusion and each randomization, all operators received an email.

COMMUNICATION

The main investigator received the inclusion curves and a table with the inclusions made by each center every month and contacted by telephone those operators who had made few inclusions in the previous month.

We held a second meeting in January 2013 to motivate investigators and share our experiences.

Inclusions rate

The following is the inclusions' curve as of September 10, 2013.

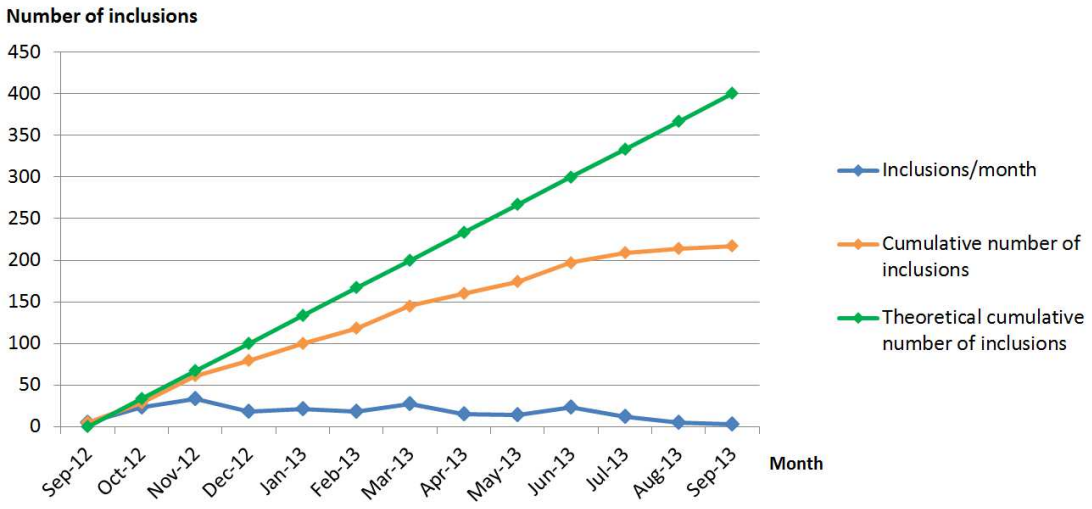


Figure 11. Inclusion rate up to September 2013

Even though we had submitted a questionnaire to the operators during trial design and we had downgraded the number of inclusions they announced and taken actions to encourage the inclusions, the inclusion rate was approximately two times lower than expected, as 219 patients had been included on September 10, 2013, instead of the 400 originally planned (13 September 2013).

Extension of the inclusion period

Because the inclusion period was supposed to end on September 13, 2013, we needed to extend the period of inclusion. This is a substantial change in the protocol and therefore we needed to re-ask the opinion of the CPP. Also, we needed to extend the insurance. Figure 12 shows the new inclusion curve obtained with a 2-year inclusion period.

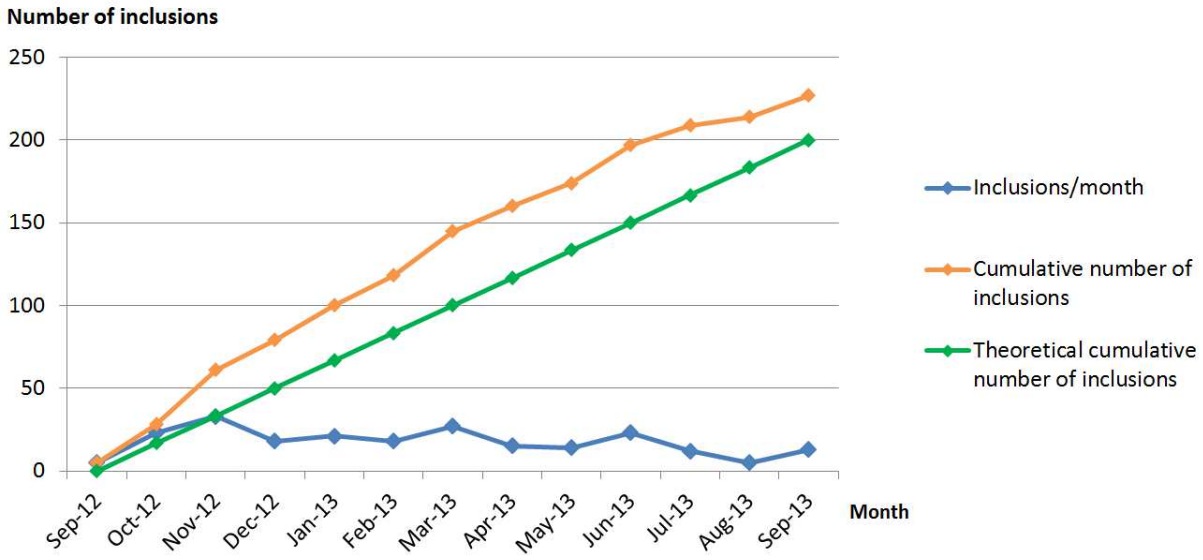


Figure 12. Inclusion curve with 2-year inclusion period (up to 28 September 2013)

Inclusions by center

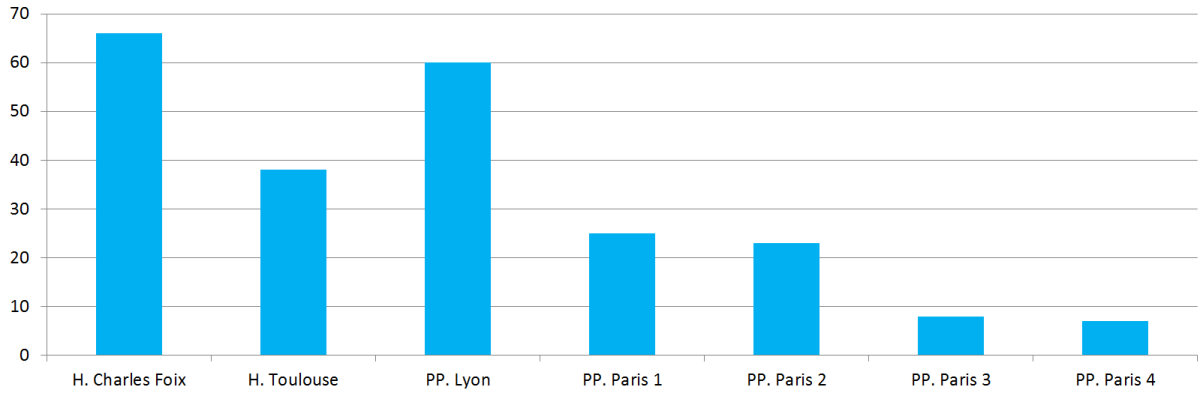
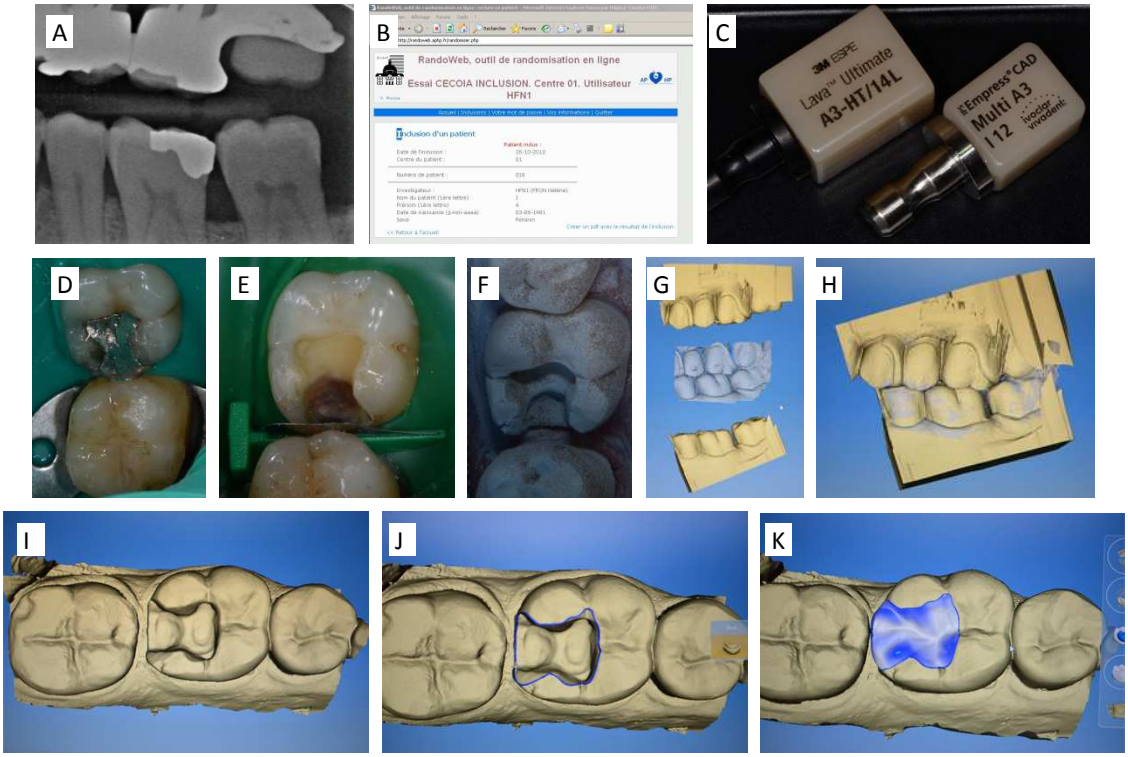


Figure 13. Trial recruitement by center (28 september 2013)
H: Hospital; PP: Private practice.

As Figure 13 shows, the number of inclusions varied by center. Only one patient refused to participate in the center of Charles Foix because of favorable conditions for the

patient (free inlay or onlay and compensation of 100 euros after the two follow-up visits). Two and one patients refused to participate at A. Gaucher's and C. Moussally's practices, respectively.

Figure 14 and Figure 15 show two examples of the clinical time-by-time protocol implemented for each patient included.



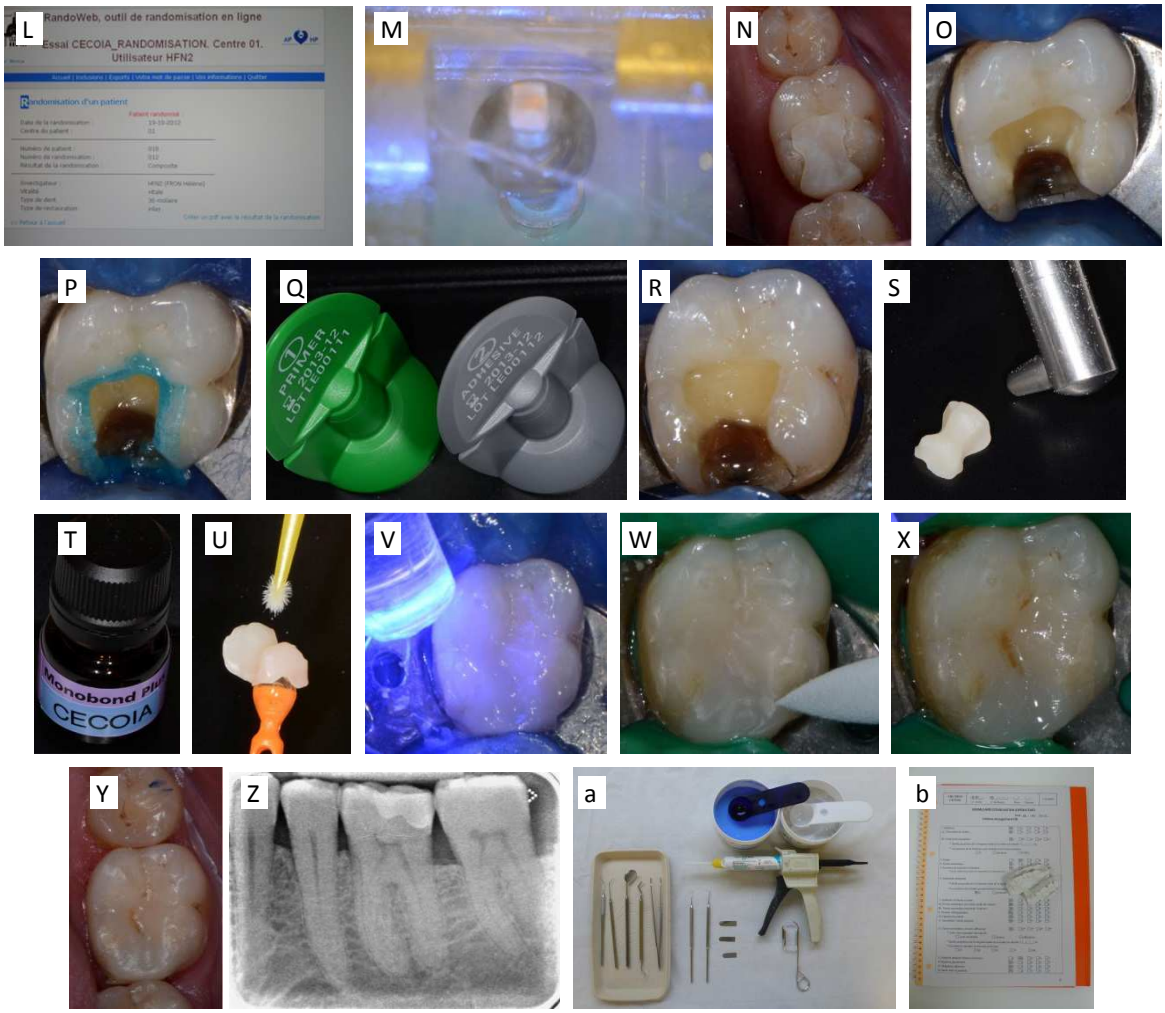


Figure 14. Realization of a composite inlay on vital tooth 36 (patient 018)
A. Inclusion bitwing radiograph. B. Patient online inclusion (on Randoweb). C. Choice of color for both a composite and ceramic block. D. Initial clinical situation: the tooth is restored by a defective aged amalgam. E. Situation after removal of amalgam. F. Powdered tooth for optical impression. G. 3 optical impressions made (maxillary, mandibular and buccal biting). H. Models in occlusion. I. Preparation. J. Outline of the preparation margins. K. Computer-aided design of the inlay. L. Randomization: a composite inlay will be realized. M. Machining of the inlay. N. Inlay try-in. O. A dental dam is placed. P. Etching of enamel. Q. The adhesive used (Optibond XTR, Kerr). R. The adhesive was placed. S. Sandblasting of the intaglio inlay surface (50 microns alumina). T. The silane used (Monobond Plus, Ivoclar Vivadent). U. Silane application on the intaglio inlay surface. V. Cementation, glycerin is placed on the cement margins and the cement is light-polymerized. W. Polishing of the margins. X. Application of colored light-curing flowable composites. Y. Final result. Z. Retro-alveolar radiograph at the one-week follow-up. a. Equipment used for the follow-up assessment. b. Completed case report form and plaster replicas.

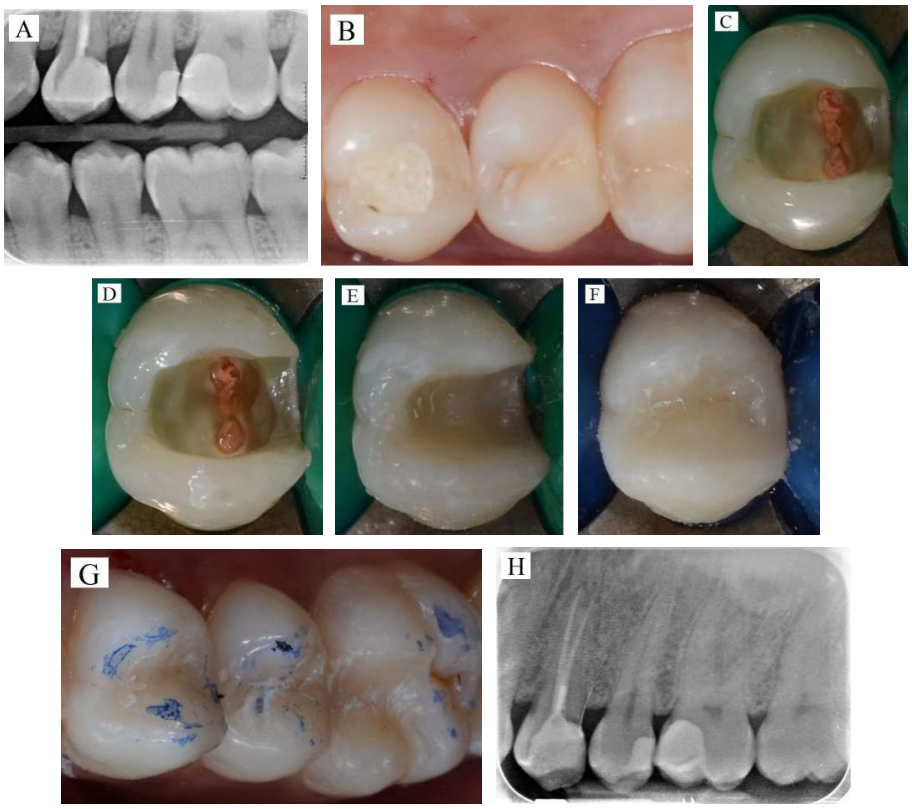


Figure 15. Realization of a ceramic inlay on non-vital tooth 24 (patient 006)
A. Inclusion bitwing radiograph. B. Initial clinical situation: the substance loss has been temporarily restored by glass ionomer after endodontic treatment. C. After removal of glass ionomer. D. After adhesive has been placed. E. After flowable composite base application. F. After the ceramic inlay has been adhesively cemented. G. Polishing and occlusion adjustment. H. Retro-alveolar radiograph at the one-week follow-up.

Baseline characteristics of included patients/teeth

Table 5 shows the demographic characteristics of included patients. Although these criteria are not taken into account at the time of randomization, the sex and age distributions are similar in both treatment groups.

	Composite	Ceramic	Total
Sex			
Male	45 (42.9%)	44 (40.7%)	89 (41.8%)
Age			
18-30	19 (18.1%)	24 (22.2%)	43 (20.2%)
31-50	46 (43.8%)	57 (52.8%)	103 (48.3%)
51-70	40 (38.1%)	27 (25%)	67 (31.5%)
Total	105 (49.3%)	108 (50.7%)	213 (100%)

Table 5. Baseline characteristics of included patients/teeth

Perspective

In the context of this work, we have completed the first step – the design – of a clinical trial comparing machinable composite and ceramics for the fabrication of inlays and onlays. The second stage, implementation, is well under way, but we need to finalize the recruitment of the 400 patients and insure the quality of patient follow-up for at least 2 years. Finally, in 2 years, we will be able to start analyzing the results, write the report required by the DRCD and the publication, with the analysis of the primary endpoint for composite versus ceramic inlays and onlays. We will also study the properties of the FDI instrument in the context of the CECOIA trial.

In the future, other clinical prognostic factors of inlays and onlays could be assessed. Proximal box elevation is a protocol increasingly common to treat deep cavities whose margins are below the cement–enamel junction, and comparing different protocols to optimize this procedure might be interesting [126]. In the CECOIA trial, we compared leucite-reinforced glass-ceramic (Empress CAD) and composite (Lava Ultimate) materials, but other machinable materials are appearing on the market (including Vita Enamic and the successor). We also mentioned earlier that the mechanical properties of ceramic inlays and onlays pressed by a dental technician could be higher than machined inlays and onlays and testing this hypothesis clinically could be of interest. Finally, erosive lesions are increasingly common in developed countries [127], and advanced stages often require a treatment with overlays; bonding the latter restorations to eroded hard tissues and maintaining them over time require clinical evaluations that could interest us, although these situations present a number of methodological and practical difficulties that would have to be overcome [128].

Résumé du chapitre en français

La première partie de ce chapitre concerne la conception de l'essai et en particulier un aspect méthodologique : la randomisation. Différentes méthodes permettent de prendre en compte les principaux facteurs pronostiques lors de la randomisation; les deux plus classiques sont la stratification et la minimisation. Le choix entre ces deux méthodes dépend de nombreuses caractéristiques de l'essai. Des statisticiens avaient suggéré que le choix de la méthode la plus adaptée pourrait se faire à l'aide de simulations, mais aucun programme n'était disponible. Nous avons ainsi décidé de réaliser un programme permettant de comparer la stratification et la minimisation en fonction des principales caractéristiques de l'essai (nombre de sujets nécessaire, nombre de centres…) en termes de l'équilibre d'effectif obtenu en fin d'essai entre les deux bras de traitement et de la prédictibilité de l'allocation pour les investigateurs recrutant les patients. Ce programme (Hermès) est accessible à tous gratuitement sur internet et le code a été explicité de sorte que des modifications puissent être apportées pour certains designs spécifiques.

La deuxième partie de ce chapitre traite de la mise en œuvre de l'essai CECOIA (CEramic and COmposite Inlays Assessment). Nous avons d'abord répondu à l'appel d'offre du Programme hospitalier de recherche clinique de 2011 et un financement de 237 000 euros a été accordé. Le projet a ensuite été instruit en partenariat avec le Département de la recherche clinique et du développement de l'Assistance publique – Hôpitaux de Paris et avec l'Unité de recherche clinique de l'Hôpital européen Georges Pompidou. Les autorisations nécessaires ont été obtenues auprès de l'Agence nationale du médicament et du Comité de protection des personnes; des contrats ont été établis avec les partenaires industriels fournissant le matériel ; les documents de l'essai ont été créés ou finalisés, en particulier le protocole et le cahier d'observation ; un site internet a été créé (cecoia.fr). L'essai a été enregistré dans le registre clinicaltrials.gov et le protocole a été publié dans la revue *Trials* : 400 patients nécessitant une restauration de type inlay-onlay doivent être inclus dans 2 centres hospitalo-universitaires et 5 cabinets dentaires, la randomisation prend en compte 4 facteurs pronostiques majeurs des inlays-onlays. Le recrutement a commencé en septembre 2012. En octobre 2013, 246 patients ont été recrutés et traités par un inlay-onlay en composite (Lava Ultimate) ou en céramique (Empress CAD), dont plus de 65 par nous-mêmes. Les restaurations sont évaluées à une semaine par les opérateurs et à 1 et 2 ans par deux évaluateurs à l'aide du critère de jugement principal de la Fédération Dentaire Internationale. Nous aurons les résultats en 2017.

Chapter 4
Composite versus ceramics for inlays and onlays: *in vitro* comparison of the adhesive properties of machinable materials

Background p.100

Summary of the work that was carried out p.104

Publication p.105

Supplementary information p.129

Perspective p.135

Résumé du chapitre en français p.140

Background

These pages are designed to better situate the publication that follows in the process of this thesis.

The clinical trial detailed in the previous section will, hopefully, provide valuable information on the comparative efficacy of composite and ceramic inlays and onlays and on clinical factors that may guide clinical decision to one or the other of the two materials.

However, the results will not be available until 2015-16, and in the meantime, it seems desirable to base clinical decisions on evidence from materials research rather than on empirical aspects.

In addition, the influence of some clinical factors could not be evaluated in the ongoing CECOIA trial, for example, the influence of the choice of adhesive cement on the relative effectiveness of the two interventions or the choice of the material of a same class that has a different microstructure (e.g., lithium-disilicate glass-ceramic rather than leucite reinforced glass-ceramic).

Finally, comparing data from the clinical trial and laboratory study might be interesting, and elements from *in vitro* research could perhaps help better understand the data observed clinically.

Among the important characteristics of materials mentioned in the introduction, this chapter describes the *in vitro* study of the adhesive properties of machinable materials. Actually, poor bond quality at the ceramic–cement or dentin–cement interface can significantly reduce the fracture initiation load-bearing capacity of inlays and onlays. Thus, a principal determinate in the long-term success of these restorations relies on the strength and durability of the interface between the resin cement and the bondable surface of the processed inlay-onlay intrados [129].

We selected several materials frequently used for machining inlays and onlays. These materials are described in Table 1 of the publication. We also studied the influence of the surface treatment and adhesive cement, which we will describe.

Surface treatment

Composite

Indirect composite inlays and onlays have a highly polymerized surface with few unreacted free-end radicals for bonding to the resin cement [81, 82].

Micromechanical component of adhesion

Several surface treatments have been advocated to promote adhesion between the resin cement and the indirect composite restoration: sandblasting with 50-µm alumina particles [71, 130] or reactive sandblasting with silica-coated alumina particles are the two recommended procedures [131]. Sandblasting is more common because alumina is cheaper and more common than silica-coated alumina in dental laboratories and offices; sandblasting is also the procedure recommended by the manufacturer of the composite evaluated (Lava ultimate, 3M Espe). The resulting surface topography can be seen in Figure 16.

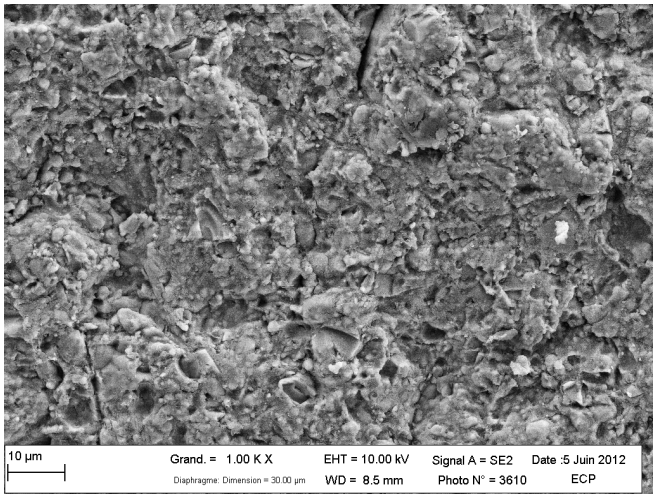


Figure 16. Scanning electron microscopy of the surface of a machinable composite (Lava Ultimate) treated by sandblasting.

Chemical component of adhesion and wettability

In addition to mechanical roughening, applying proprietary softening agents, wetting agents, or silane can enhance the bond strength between the restoration and the resin cement [71, 130].

As a bifunctional molecule, a silane is supposed to act as a coupling agent between the hydroxyl groups of the silica (of the inorganic fillers in composites) on the inlay-onlay surface and the methacrylic groups of the resin cement [132], thus resulting in a crosslinked siloxane polymolecular layer that forms an interpenetrating polymer network [133]; its role as a wetting agent has also been widely described [133]. The interest of silane in bonding indirect composites has been discussed [130, 134]; the manufacturer of the material studied recommends applying a silane if the cement requires one.

Note that the resin-infiltrated ceramic-based composite (Enamic, Vita) is not treated by sandblasting. Indeed, the recommendation of the manufacturer is to etch the surface with hydrofluoric acid. In the absence of literature on the subject, the latter surface treatment was selected (Figure 17). However, for characterization of the outer surface of the restoration, the manufacturer specifies that etching or soft sandblasting be performed.

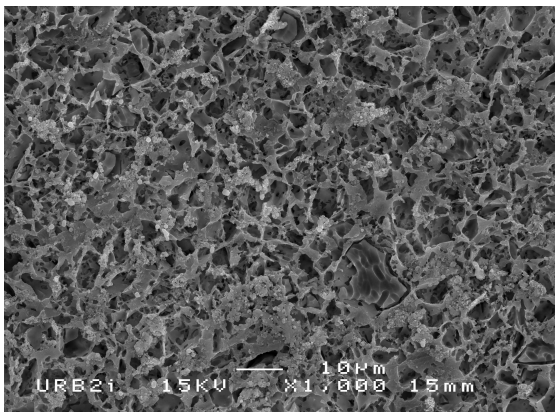


Figure 17. Surface of a machinable composite (Enamic, Vita) treated by hydrofluoric acid (HF)-etching (HF 10% 60 s).

Ceramics

The reference surface treatment for glass-based ceramics is etching with hydrofluoric (HF) acid [71, 135]. The resulting surface topography can be seen in Figure 18. The application of silane is generally recommended [71, 135].

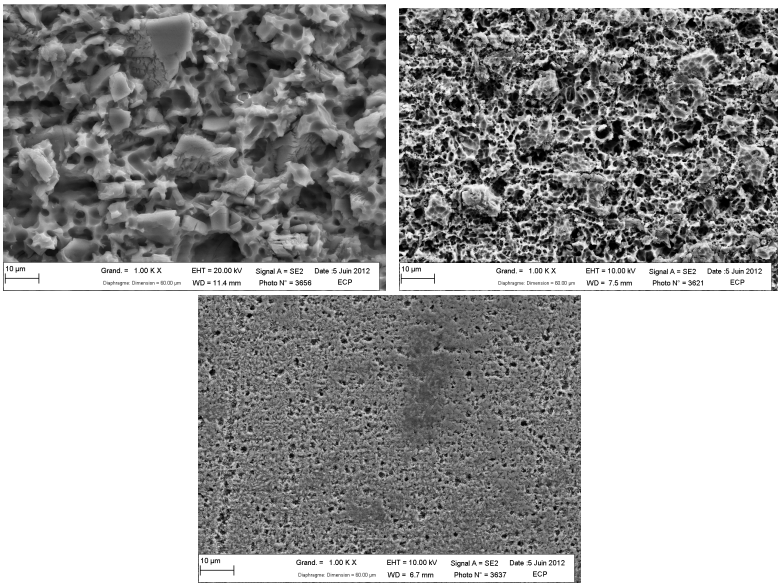


Figure 18. Surface of machinable ceramics treated by HF-etching.
From left to right: albite-reinforced glass-based ceramic (Vita Mark II),
leucite-reinforced glass-ceramic (Empress CAD) and
lithium disilicate-reinforced glass-ceramic (e.max CAD)

Resin cements

The choice of resin cement clearly plays a role in the quality and durability of the interface [71, 136, 137] as well as in the strength of the tooth restored with an inlay or onlay [138, 139]. We thus decided to evaluate this important factor in this work.

Different types of resin cements currently exist; resin cements can be classified according to their adhesive properties or mode of polymerization. We tested a representative from each of the three adhesive categories, as discussed in the article below.

Regarding the mode of polymerization, resin cements can be light-cured, dual-cured or chemically cured. We evaluated only dual-cured resin cements because chemically cured resin cements require a long setting time; light-cured resin cements allow for easier manipulation, but the thickness of the inlay or onlay and the tooth structure can lead to incomplete polymerization [140].

Summary of the work that was carried out

We realized 900 samples (5 machinable materials x 3 resin cements x 6 surface treatments x 10 samples per batch), which we tested in shear after 24 hr.

The 6 surface treatments were designed to assess the contribution of the micromechanical component (4000-grit polishing; 800-grit polishing; surface treatment of reference, i.e., sandblasting or etching) and chemical component (silane or not) in adhesion.

Publication

Influence of surface treatments on adhesion of cements to tooth-colored machinable materials

Hélène Fron Chabouis[1,2,3], Stéphane Le Goff[1], Mie-Leng Tang[1], Nicolas Lebon[1,3], Laurent Tapie[1,3], Jean-Pierre Attal[1,2]

1. Department of Biomaterials (URB2i, EA4462), Université Paris Descartes, Sorbonne Paris Cité, Montrouge, France

2. Dental Department, Charles-Foix Hospital, AP-HP, Ivry-sur-Seine, France

3. Université Paris 13, Sorbonne Paris Cité, Villetaneuse, France

Abstract

Objectives. The effect of different surface treatments on the adhesion of resin cements to tooth-colored machinable materials was evaluated.

Methods. Five materials (Mark II, MK; Empress CAD, EMP; e.max CAD, EM; Lava Ultimate, LU; Enamic, EN) were divided into 6 groups by surface treatment: polished to 4000 or 800 grit, sandblasted for LU / hydrofluoric acid (HF)-etched for other materials; with or without silane. A macro shear test was used to test adhesion of each material with 3 resin cements (NX3, Nx; Panavia F2, Pv; RelyX Unicem, Ru). Failure type was characterized. Polished specimens' roughness was evaluated with a contact profilometer. Data were analyzed by ANOVA and Tukey's test.

Results. Bond strength was significantly affected by surface treatment, cement and machinable material ($p<0.0001$). Bond strength was positively correlated with roughness for MK, EM, EN and LU.

Significance. Bond strength was mainly increased by sandblasting LU and HF-etching MK, EMP, EM and EN. Silanization may not be necessary for sandblasted LU or HF-etched MK and EMP but may be useful for EM and EN. Ru yielded the highest

bond strength, regardless of machinable material or surface treatment. These results need to be confirmed by other studies.

Keywords

Adhesion, cement, CAD/CAM, surface treatment, silane, sandblasting, etching, composite, ceramic, shear.

Introduction

Computer-assisted design/manufacturing (CAD/CAM) is becoming more common in dental laboratories or offices (chairside). Thus, single-unit dental restorations, particularly posterior crowns or inlays, are increasingly being made from blocks. Various tooth-colored materials exist for this type of restoration. Resin composite and glass ceramics are the 2 most common aesthetic alternatives. The longevity of these restorations depends on the quality of their adhesion to dental tissues [1, 2]. The adhesion depends on several factors, including the chosen resin cement and quality of the 2 interfaces: intaglio surface–cement and cement–dental tissues. The latter interface is better known, but information is lacking on the machinable material–cement interface.

Many resin cements are available. Resin cements can be divided into 3 subgroups based on the adhesive system used for treating the tooth surface before cement application: 1) etch-and-rinse adhesive system, 2) self-etching adhesive system and 3) no adhesive system is required for self-adhesive cements [3]. These cements have different affinities for machinable materials [4]. Reference surface treatments to establish the micromechanical component of the adhesion to the intaglio surface are hydrofluoric acid etching and sandblasting for glass ceramics [5] and composites [6], respectively. Silane application to add a chemical component for adhesion is controversial [7].

Different tooth-colored materials can be machined to produce posterior single-unit restorations. They include 3 ceramics (Mark II, MK; Empress CAD, EMP; e.max CAD, EM) and 2 resin composites recently marketed (Lava Ultimate LU; Enamic, EN) [8]. From a July 17, 2013 systematic search of the literature evaluating the bond strength of one of these materials to a resin cement, we identified 44 articles: 4 did not describe evaluation of bond strength to one of the machinable materials mentioned or to their traditional equivalent; most (n=17) described evaluation of bond strength to dentin [4, 9-24] and only 11 described evaluation of bond strength to CAD/CAM materials, all

machinable ceramics (1 EMP [4], 9 MK [14, 19, 20, 22, 23, 25-28] and 1 ProCad [29]). All other articles described materials obtained by conventional methods. No study has evaluated bond strength to EM, LU and EN. CAD/CAM-produced materials do not necessarily have the same properties as their traditional counterparts because their microstructure – or their chemical composition – differs.

Here, we evaluated the adhesive performance of contemporary, machinable, tooth-colored blocks. We monitored variables most often mentioned to modify adhesion: surface treatment impact on the shear bond strength of 3 resin cements to 3 glass ceramics and 2 resin composite machinable materials. Three null hypotheses were tested:

1 - The surface treatment does not affect adhesion of the resin cement to the machinable material.

2 - The resin cement does not influence adhesion to the machinable material.

3 - The machinable material does not affect adhesion of the resin cement.

Materials and methods

1. Specimens of CAD/CAM materials

We used 5 CAD/CAM materials: MK, EMP, EM, EN and LU. The manufacturers and compositions of the materials are in Table 1. For each material, we obtained 3-mm-thick slices by cutting 14-L blocks for Cerec using a diamond disc in a cutting machine (Discotom 5, Struers, Ballerup, Denmark) with a 2-mm/min feedrate. Slices were embedded in resin (3 cm diameter, 1 cm high) and ground-finished with 800- or 4000-grit silicon carbide metallographic abrasive paper (PSA backed Silicon carbide paper, Struers) under water-cooling in a polishing machine (Planopol-3, Struers).

Material	Product (composition[a])	Code	Batch no.	Manufac-turer
CAD/CAM material	Mark II fine particle feldspar (crystal phase <20 wt%) ceramic (SiO_2 56-64 wt%, Al_2O_3, Na_2O, K_2O, CaO, TiO_2, pigments)	MK	13021	Vita
	Empress CAD leucite-reinforced (35-45%vol) glass ceramic (SiO_2 60-65 wt%, BaO, Al_2O_3, CaO, CeO_2, Na_2O, K_2O, B_2O_3, TiO_2, pigments)	EMP	P73700	Ivoclar-Vivadent
	e.max CAD lithium-disilicate reinforced (70%vol) glass ceramic (SiO_2 >57 wt%, Li_2O, K_2O, P_2O_5, ZrO_2, ZnO, Al_2O_3, MgO, pigments)	EM	P69721	Ivoclar-Vivadent
	Enamic resin-infiltrated ceramic (Ceramic network 86 wt% : SiO_2, Al_2O_3, Na_2O, K_2O, B_2O_3, CaO, TiO_2 ; Infiltration resin : UDMA, TEGDMA)	EN	33320	Vita
	Lava Ultimate resin nano-ceramic composite (Matrix: highly crosslinked polymeric resin. Fillers 80 wt%: silica, zirconia, aggregated zirconia/silica clusters)	LU	N490537	3M ESPE
Cement	NX3 dual cured resin cement (TEGDMA, mineral fillers cont. resin composite)	Nx	4464987	Kerr
	Panavia F2 dual cured resin cement (Filler 2µm 71wt%: silanized Ba-B-Si-glass; BPEDMA, MDP, DMA, dibenzoylperoxide, N,N-diethanol-p-toluidine, silica sodium fluoride)	Pv	041120	Kuraray
	Rely X Unicem self-adhesive dual cured resin cement (Filler <9.5µm 72wt%: Glass particles, silane-treated silica & calcium hydroxide; methacrylate phosphoric acid ester, DMA, sodium p-toluenesulfinate, cont. resin composite)	Ru	495937	3M ESPE
Surface treatment	Hydrofluoric acid (9,5 % HF)	HF	1200001496	Bisico
	Porcelain Primer silane (ethanol, acetone, 3-methacryloxypropyl trimethoxysilane, >1%)	Si	1200001342	Bisico
Resin composite	Grandioso nano-hybrid resin composite (BisGMA, TEGDMA, 89% wgt inorganic fillers)	RC	1213455	Voco

Table 1. Materials used in this study
BisGMA: bisphenol-A-diglycidylmethacrylate; BPEDMA: bisphenol-A-polyethoxy dimethacrylate; DMA: aliphatic dimethacrylate; MDP: 10-methacryloxydecyl dihydrogen phosphate; TEGDMA: triethyleneglycol dimethacrylate; UDMA: urethane dimethacrylate; cont.: containing.
[a]Manufacturers' data.

2. Surface treatment of specimens

For each of the 5 CAD/CAM materials, specimens were randomly divided into 6 surface-treatment groups:

Group 1: Polished to 4000 grit (control group)

Group 2: Polished to 800 grit

Group 3: Polished to 4000-grit and silanized

Group 4: Polished to 800-grit and silanized

Group 5: Sandblasted for LU or hydrofluoric acid (HF) etched for MK, EMP, EN and EM.

Group 6: Sandblasted (LU) or HF etched (MK, EMP, EN, EM) and silanized.

Silanization involved use of a silane (Si) coupling agent that was applied on the surface with a microbrush for 60s, left to dry for 10 s and then gently air-dried with a hair-dryer 10 cm away from the surface (T° 50±5°C) for 30 s. MK, EMP and EN were HF-etched for 60 s. EM was HF-etched for 20 s. HF was rinsed thoroughly for 10 s. Then specimens were immersed in an ultrasonic water bath for 3 min. LU was sandblasted for 10 s at 2.0 bar pressure with 50 μm alumina.

3. Adhesive cementation of specimens

Resin composite (RC) cylinders (5 mm diameter and 5 mm high) were obtained with use of a Teflon mold, light polymerized, sandblasted with 50 μm alumina and silanized (with Si). One RC cylinder was adhesively luted to the treated machinable material surface (cleaned with alcohol by use of a microbrush) with 1 of 3 dual-polymerizing adhesive resins (NX3, Nx; Panavia F2, Pv; RelyX Unicem, Ru) under consistent pressure by the same operator. The polymerization light tip (Radii Plus, SDI) was placed 5 mm away from the adhesive interface and the resin cement was cured for 40 s from 2 opposite directions with a 1500 mW/cm^2 minimum output.

4. Shear testing of specimens

We obtained 10 specimens for each of the 6 surface treatments, 5 machinable materials and 3 adhesive resins combinations, for 900 specimens. The specimens were stored in a distilled water bath at 37°C for 24 h. A universal testing machine (Lrx, Lloyd) was used to apply the shear force at a crosshead speed of 0.5 mm/min. Shear bond strength (SBS) was recorded for each specimen.

5. Microscope examination

To assess the failure patterns, we examined the fractured interfaces of the specimens under a light microscope (SZM10, Olympus, Tokyo) at ×20 magnification. Debonded surfaces were assigned to patterns of cohesive failure (within the composite cylinder or within the machinable material), adhesive failure at the interface, or mixed adhesive/cohesive failure (within the composite cylinder or within the machinable material). Scanning electron microscopy (SEM; JSM-6400, JEOL Ltd, Tokyo) examination was conducted for the representative specimens of each failure pattern and to compare surface aspects of groups 1 and 5.

6. Roughness of surfaces

The roughness of polished surfaces (groups 1 and 2) was evaluated over a 1-mm^2 surface at a 2-µm pace with a contact profilometer (Talysurf, Taylor Hobson) and Winmmb software (Akilog, Besançon, France).

7. Statistical analysis

Data are presented as mean (SD) and were analyzed by ANOVA, with multiple comparisons by Tukey's test. Stata 12 (StataCorp., College Station, TX) was used for analysis. $P<0.05$ was considered statistically significant. Pearson correlation coefficient was used for correlation analysis.

Results

We could use 885 specimens for analysis; 15 specimens were lost because of manipulation or testing machine errors. Mean (SD) shear bond strength (MPa) of each machinable material/surface treatment/resin cement combination is presented in Table 2.

Surface treatment	Cement	CAD/CAM material				
		MK	EMP	EM	EN	LU
1. Control (4000 grit)	Nx	4.9 (1.8)	18.5 (4.4)	4.4 (1.3)	8.1 (2.7)	5.7 (1.5)
	Pv	5.5 (1.8)	5.5 (2.3)	3.7 (1.2)	8.8 (3.3)	0.0 (0.0)
	Ru	6.6 (5.2)	15.0 (7.4)	4.0 (0.9)	16.3 (8.5)	13.2 (6.3)
2. Polished (800 grit)	Nx	20.6 (8.8)	13.6 (4.5)	5.8 (1.3)	14.4 (4.8)	11.5 (4.7)
	Pv	14.5 (7.7)	9.4 (4.9)	4.6 (0.9)	15.8 (6.9)	5.9 (4.2)
	Ru	16.2 (5.5)	19.9 (9.2)	5.3 (2.3)	19.4 (6.7)	20.3 (6.7)
3. Silane (4000 grit)	Nx	7.8 (5.5)	6.5 (2.6)	18.7 (10.5)	24.6 (7.1)	7.8 (2.3)
	Pv	7.8 (3.7)	12.7 (7.9)	12.0 (4.0)	10.5 (4.1)	2.6 (5.2)
	Ru	9.6 (6.1)	15.1 (7.6)	26.4 (7.6)	22.1 (8.9)	16.3 (5.4)
4. Silane (800 grit)	Nx	24.0 (5.9)	24.4 (7.2)	9.4 (4.9)	25.7 (6.7)	17.6 (5.4)
	Pv	17.2 (4.7)	20.5 (4.4)	9.5 (3.4)	25.1 (5.4)	9.1 (3.6)
	Ru	30.4 (5.7)	26.5 (6.1)	24.5 (5.8)	27.3 (6.7)	28.8 (3.7)
5. Sandblasting/ HF etching	Nx	30.0 (4.8)	28.7 (6.3)	29.9 (6.8)	25.4 (7.6)	24.8 (6.9)
	Pv	36.2 (5.8)	36.5 (6.7)	24.3 (3.6)	33.3 (6.0)	24.3 (5.6)
	Ru	33.3 (4.6)	32.2 (6.7)	30.5 (4.6)	33.5 (5.5)	33.4 (5.2)
6. Sandblasting/ HF etching + silane	Nx	30.0 (4.7)	30.0 (3.6)	29.9 (4.6)	28.8 (6.3)	18.9 (5.4)
	Pv	29.3 (6.4)	31.1 (7.3)	31.2 (3.7)	34.4 (8.2)	19.9 (2.4)
	Ru	32.0 (7.8)	29.9 (9.4)	30.8 (3.8)	34.7 (4.6)	30.5 (6.6)

Table 2. Mean (SD) shear bond strength (MPa) of cements to tooth-colored machinable materials with different surface treatments.
HF: hydrofluoric acid

Mean (SD) MPa was 8.1 (6.5) for surface treatment group 1, 13.1[a] (7.9) for group 2, 13.5[a] (9.2) for group 3, 21.3 (8.7) for group 4, 30.3[b] (6.9) for group 5 and 29.5[b] (7.1) for group 6. Mean (SD) shear bond strength was 18.3[a] (10.5) for cement Nx, 16.8 [a] (12.1) for Pv and 22.8 (10.9) for Ru. Mean (SD) shear bond strength was 20.0[a,c] (12.0)

for MK, 20.7[a] (11.0) for EMP, 17.0[b,c] (11.4) for EM, 22.8[a] (10.5) for EN and 16.1[b] (10.7) for UL.

The surface treatment that yielded the highest SBS values was group 5 for UL, MK and EMP and group 6 for EM and EN (Table 6). The highest SBS values were obtained with the resin cement Ru whatever the machinable material. Highest SBS values were obtained with sandblasting/HF etching (surface treatment group 5) whatever the cement.

Surface treatment	CAD/CAM material				
	MK	EMP	EM	EN	LU
1. Control (4000 grit)	5.7 (3.4)^{AB}	13.0 (7.5)^{DEFG}	4.0 (1.1)^{A}	11.1 (6.5)^{BCDE}	6.3 (6.6)^{ABC}
2. Polished (800 grit)	17.1 (7.7)^{EFGH}	14.3 (7.7)^{DEFG}	5.2 (1.6)^{AB}	16.5 (6.3)^{EFGH}	12.6 (7.9)^{CDEF}
3. Silane (4000 grit)	8.4 (5.1)^{ABCD}	11.4 (7.2)^{BCDE}	19.3 (9.7)^{GHIJ}	19.7 (9.1)^{GHIJ}	8.9 (7.2)^{ABCD}
4. Silane (800 grit)	23.9 (7.6)^{IJKL}	23.8 (6.3)^{IJKL}	14.5 (8.6)^{DEFG}	26.0 (6.1)^{JKLM}	18.5 (9.3)^{FGHI}
5. Sandblasting/ HF etching	33.2 (5.6)^{N}	32.3 (7.1)^{MN}	28.2 (5.7)^{KLMN}	30.7 (7.3)^{MN}	27.5 (7.1)^{KLMN}
6. Sandblasting/ HF etching + silane	30.4 (6.3)^{LMN}	30.3 (7.0)^{LMN}	30.6 (4.0)^{MN}	32.6 (6.9)^{MN}	23.2 (7.3)^{HIJK}

Table 6. Mean (SD) shear bond strength (MPa) of CAD/CAM materials with different surface treatments and Tukey's analysis.
Mean values with letters in common are not significantly different according to Tukey's test ($p>0.05$).

Three-way testing (material, surface treatment and cement) revealed that the bond strength was most affected by the surface treatment ($F=398.9$, $P < 0.001$) and less affected by the cement ($F=92.4$, $P < 0.001$) and type of machinable material ($F=41.3$, $P < 0.001$), with significant interactions between these 3 factors ($P < 0.001$) (Table 3).

Source of variation	Sum of squares	df	Mean squares	F	P-value
CAD/CAM material	5249.2	4	1312.3	41.3	<0.0001
Surface treatment	63324.5	5	12664.9	398.9	<0.0001
Cement	5865.6	2	2932.8	92.4	<0.0001
CAD/CAM material x surface treatment	7432.0	20	371.6	11.7	<0.0001
CAD/CAM material x cement	2318.1	8	289.8	9.13	<0.0001
Surface treatment x cement	2148.4	10	214.8	6.8	<0.0001
CAD/CAM material x surface treatment x cement	4398.5	40	110.0	3.5	<0.0001
Total	116030.1	884			

Table 3. Three-way ANOVA of the shear bond strength by CAD/CAM material, surface treatment, adhesive cement and interaction terms

Failures were adhesive in 64.6%, 30.5%, 30.3%, 70.8% and 41.8% for LU, MK, EMP, EM and EN specimens, respectively (Table 4). Cohesive failures into the resin composite cylinder occurred rarely (n=7). Adhesive failure at the resin cement–resin composite cylinder interface never occurred. Few adhesive failures were dislodged (n=10, all in the LU group polished to 4000-grit and luted with Pv).

Surface treatment	Cement	CAD/CAM material				
		MK	EMP	EM	EN	LU
1. Control (4000 grit)	Nx	9/0/0	1/0/9	10/0/0	10/0/0	10/0/0
	Pv	9/0/0	10/0/0	10/0/0	10/0/0	10/0/0
	Ru	10/0/0	5/1/4	9/0/0	10/0/0	10/0/0
2. Polished (800 grit)	Nx	4/2/4	5/0/5	10/0/0	9/0/1	10/0/0
	Pv	0/10/0	8/1/1	10/0/0	8/1/1	10/0/0
	Ru	0/9/1	2/1/7	10/0/0	7/1/2	4/5/1
3. Silane (4000 grit)	Nx	9/0/1	10/0/0	9/1/0	4/3/3	10/0/0
	Pv	7/2/0	7/1/1	9/0/0	8/0/0	10/0/0
	Ru	10/0/0	4/1/5	8/2/0	4/2/4	10/0/0
4. Silane (800 grit)	Nx	0/2/8	1/3/6	10/0/0	3/4/3	7/2/0
	Pv	0/10/0	0/3/7	10/0/0	0/1/9	10/0/0
	Ru	0/4/6	0/3/7	6/4/0	1/2/6	1/7/2
5. Sandblasting/ HF etching	Nx	0/8/2	0/5/5	2/8/0	0/2/8	2/5/3
	Pv	0/7/3	0/2/8	1/9/0	0/5/5	3/6/1
	Ru	0/5/5	0/5/4	6/4/0	0/2/8	0/3/7
6. Sandblasting/ HF etching + silane	Nx	0/8/2	0/5/4	3/7/0	0/2/8	4/5/1
	Pv	0/2/8	0/3/7	0/10/0	0/1/9	2/7/0
	Ru	0/2/8	0/1/8	3/7/0	0/0/10	2/3/5

Table 4. Number of adhesive/mixed/cohesive failures after shear testing in each machinable material/resin cement/surface treatment batch

Cohesive failures into MK, EMP and EN produced material dust (which was removed before inserting the next specimen). SEM images of cohesive failures and fissure initiation in EMP and EN are in Figure 1.

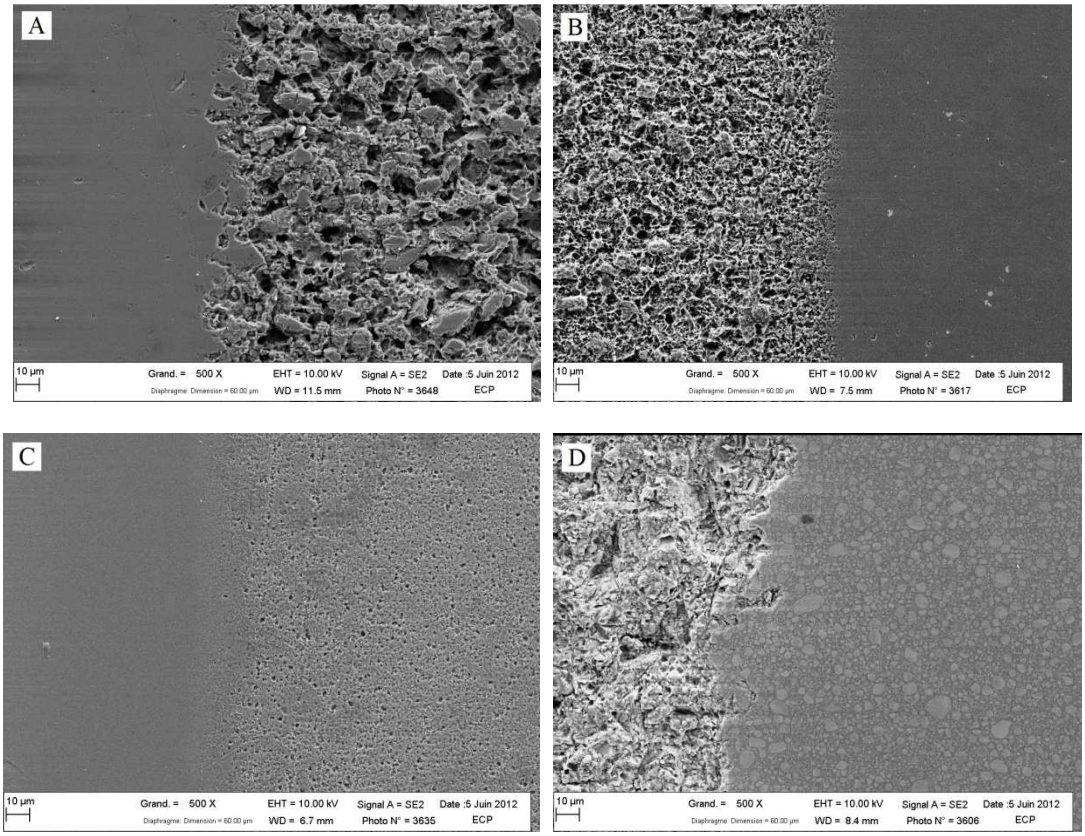


Fig. 1. SEM photomicrographs of cohesive failure and initial fissure stage in EMP and EN: (A) Cohesive failure in EMP with 800-grit treatment. (B) EMP fragment about to be pulled. (C) Fissure in EMP with adhesive failure. (D) Fissure in EMP at higher magnification. (E) Cohesive failure in EN with 800-grit treatment. (F) Fissure in EN with mixed failure. (G) Fissure in EN at higher magnification.

Mean shear bond strength of specimens without cohesive failure did not differ greatly from total values (Table 2, Table 5), except for the group 2–MK–Nx association (11.1 [4.1] MPa without cohesive failure vs. 20.6 [8.8] MPa for all 10 specimens).

Surface treatment	Cement	CAD/CAM material				
		MK	EMP	EM	EN	LU
1. Control (4000 grit)	Nx	4.9 (1.8)	18.4 (0)	4.3 (1.3)	8.1 (2.7)	5.7 (1.5)
	Pv	5.5 (1.8)	5.5 (2.3)	3.7 (1.2)	8.8 (3.3)	0 (0)
	Ru	6.6 (5.2)	12.4 (7.9)	4.0 (0.9)	16.3 (8.5)	13.2 (6.3)
2. Polished (800 grit)	Nx	11.1 (4.1)	12.3 (4.1)	5.8 (1.3)	13.9 (4.7)	11.5 (1.7)
	Pv	14.5 (7.7)	8.2 (3.4)	4.6 (0.9)	14.5 (6.1)	5.9 (4.1)
	Ru	15.7 (4.9)	11.1 (4.1)	5.3 (2.3)	17.4 (4.0)	18.9 (5.4)
3. Silane (4000 grit)	Nx	6.1 (1.8)	6.4 (2.6)	18.7 (10.5)	24.9 (7.3)	7.8 (2.3)
	Pv	6.7 (1.2)	10.3 (3.2)	12.0 (4.0)	10.5 (4.1)	2.6 (5.1)
	Ru	9.6 (6.1)	11.8 (5.8)	26.4 (7.6)	20.5 (10.4)	16.3 (5.4)
4. Silane (800 grit)	Nx	-	14.8 (0)	9.4 (4.9)	19.3 (6.1)	17.6 (5.4)
	Pv	17.2 (4.7)	22.5 (5.7)	9.5 (3.4)	28.1 (0)	9.1 (3.6)
	Ru	-	29.3 (0)	24.5 (5.8)	21.7 (6.0)	28.8 (4.0)
5. Sandblasting/ HF etching	Nx	-	-	29.9 (6.8)	35.4 (4.3)	22.1 (5.1)
	Pv	-	-	24.3 (3.6)	31.1 (7.1)	23.3 (4.5)
	Ru	-	-	30.5 (4.6)	37.4 (8.2)	26.68 (0)
6. Sandblasting/ HF etching + silane	Nx	-	-	29.9 (4.6)	30.4 (3.2)	17.8 (4.1)
	Pv	-	-	31.2 (3.7)	37.1 (0)	19.9 (2.4)
	Ru	-	-	30.8 (3.8)	-	25.2 (4.7)

Table 5. Mean (SD) shear bond strength (MPa) of cements to CAD/CAM materials with different surface treatments in specimens without cohesive failure.

Surface roughness parameters of the 5 machinable materials in surface treatment groups 1 and 2 are in Table 7. Roughness was greater in group 2 (800-grit) than group 1 (4000-grit) for all materials. Correlation of bond strength and roughness ranged from 0.4 to 0.69 for MK, EM, EN and LU. The correlation was negative (-0.11) for EMP.

Material	Surface treatment	Ra (µm)	Rq (µm)	Rt (µm)	Sd (%)	Correlation
MK	Control (4000 grit)	0.014	0.039	1.07	100.04	0.69
	Polished (800 grit)	0.077	0.181	69.56	100.14	
EMP	Control (4000 grit)	0.039	0.069	0.6	100.07	-0.11
	Polished (800 grit)	0.086	0.123	11.46	100.08	
EM	Control (4000 grit)	0.015	0.041	0.48	100.04	0.40
	Polished (800 grit)	0.128	0.172	1.46	100.21	
EN	Control (4000 grit)	0.008	0.045	1.19	100.02	0.40
	Polished (800 grit)	0.083	0.127	1.79	100.15	
LU	Control (4000 grit)	0.012	0.041	0.72	100.02	0.40
	Polished (800 grit)	0.165	0.301	71.44	100.36	

Table 7. Surface roughness parameters of the 5 polished machinable materials and correlation between surface roughness parameters and bond strength
Ra: Surface roughness arithmetic average; Rq: Surface roughness quadratic average;
Rt: Maximum height of the profile

SEM images of MK, EMP, EM and LU surfaces polished (group 1) and HF-etched (group 5) are in Figure 2.

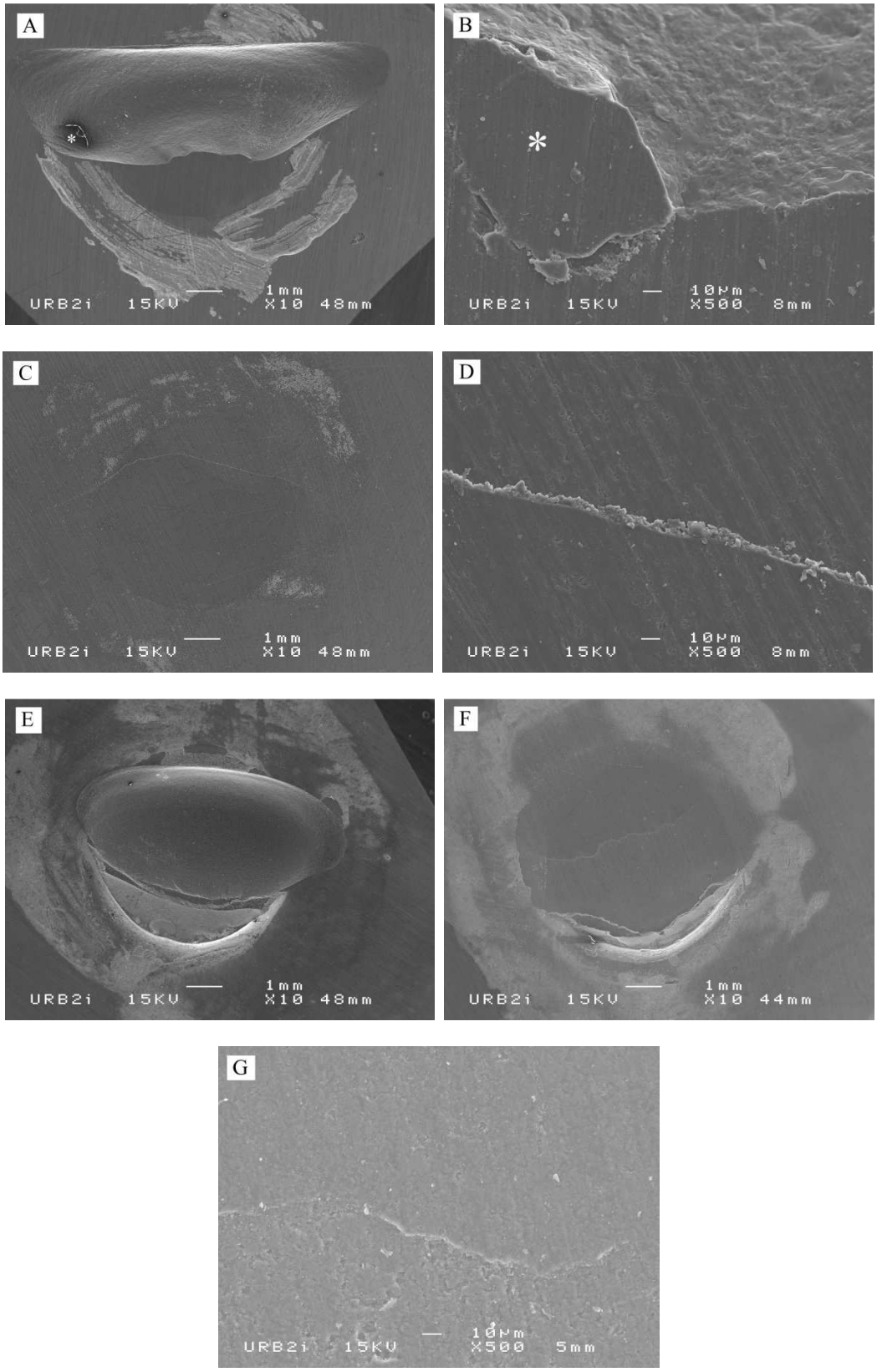


Fig. 2. SEM photomicrographs of machinable material surfaces HF-etched or sandblasted on one side vs polished on the other side: (A) MK, (B) EMP, (C) EM and (D) UL.

Discussion

This *in vitro* study was designed to investigate the effect of different surface treatments on the adhesion of 3 cements to five machinable materials for tooth restoration. Sandblasting/etching appears to be the key factor affecting bond strength to MK, EMP, EM, EN and LU materials (null hypothesis 1 is rejected). Bond strength exceeded 18 MPa with sandblasting/HF-etching for all 3 cements and all 5 machinable materials, so reliable adhesion to these materials can be expected. This finding seems to be commonly accepted for older MK, EMP and EM materials but has not been demonstrated for newer LU and EN materials. Bond strength was greater with Ru than with Nx and Pf cements in this study (null hypothesis 2 is rejected). The bond strength varied among materials (null hypothesis 3 is rejected).

This study confirmed the major influence of the surface treatment of the intaglio surface in 2 aspects. First, adhesion was greater for samples polished to 800 than 4000 grit. Although this was not significant for MK, a significant difference was observed for LU and EN; the difference was smaller for EMP and EM (Table 6). The major effect of the mechanical component can be explained by an increase in surface area that optimizes the chemical component of adhesion or by the influence of surface roughness, which allows for a micromechanical interlock. Some authors lean toward the first explanation [26, 30, 31], and others lean toward a greater influence of the second explanation. In this work, we found a positive correlation between bond strength and roughness of 0.40 to 0.69 for 4 materials. The correlation was slightly negative for EMP; properties of the polished EMP surface may be favorable to adhesion because bond strength values were > 13 MPa for Nx and Ru cements. Second, sandblasting or etching significantly increased bond strength. HF etching, by dissolving the glassy matrix and crystals differently, creates “Gruyere-cheese”–like cavities and undercuts in MK and EMP and smaller ones in EM (Figure 2). Airborne particle abrasion cleans and increases the surface area of polymeric materials [32]. We wanted to evaluate the correlation between increase in bond strength and surface roughness after etching or sandblasting, but the roughness created was in the micrometer range, and in undercuts for etching (Figure 2), so the profilometer used did not allow for correctly assessing the roughness. Although 2D technologies have been used in several studies [33-36], 3D high-resolution technologies (e.g., 3D-laser scanning microscopy [30] or focused ion beam) would allow for evaluating this association of roughness and adhesion. Studying this association and defining the ideal roughness profile for bonding each material would allow for adapting the machining strategies. It would also require some knowledge about the roughness parameters of intaglio surfaces obtained with contemporary machining systems used in dentistry and their burs.

Overall, we revealed a significant effect of silanization on samples polished to 4000 grit. This difference was significant for EM and EN but not MK, EMP and LU materials. The silane is meant to increase hydrophobicity of the surface and therefore allow for better wettability by the cement, which is generally hydrophobic. Covalent bonds with hydroxy groups of the surface and methacrylic groups of the cement can also be expected. EM and EN surfaces could be less hydrophobic or more prone to forming siloxane bonds; contact angle measurements could help determine the mechanism.

However, we could not demonstrate a significant effect of silanization after sandblasting or etching. Furthermore, bond strength values were slightly higher after silanization for EM and EN materials although not significantly and slightly lower for MK, EMP and LU materials (Table 6). The surface behavior of EM and EN may differ from that of MK, EMP and LU. According to manufacturer's instructions, surface treatments for cementing these machined restorations are as follows: HF etching, silanization and optional application of a thin layer of bonding material (for luting composites of higher viscosity) for MK; HF etching and silanization for EMP, EM and EN; and 2-bar sandblasting with ≤ 50 µm alumina particles for LU. Thus, our results are in line with manufacturer recommendations for EM, EN and LU, but silanization of MK and EMP may not be required. For MK, another study found significant improvement with silanization in adhesion of polished specimens but no significant improvement of HF-etched specimens with the Vickers indenter methodology [37]. For LU, a study of a traditional indirect composite showed that sandblasting was mandatory and silanization was optional [6].

The silane solution we used was 1 bottle and contained ethanol and acetone as solvents; solvents can vary between commercial formulas. Determining whether the effect of silane on MK and EMP depends on solvents or conditioning in 1 or 2 bottles could be of interest. However, our results are consistent with those of previous studies [29, 38, 39]; the >1% concentration of 3-methacryloxypropyltrimethoxysilane is typical of dental silanes, and silane condensation was promoted by heat as recommended by many authors [31, 40].

SBS values differed between cements. Therefore, bonding mechanisms other than surface texture and silane application occurred. The superior adhesion of Ru could be explained in several ways. First, its mechanical properties may be greater; indeed, Ru allows for extensive cross-linking of cement monomers, thus resulting in high molecular-weight polymers [3]. Second, its viscosity may be lower or its fillers smaller, allowing for microcavity infiltration; in fact, because its fillers are larger than those of Pv (see Table 1), only the assumption of lower viscosity remains possible. While preparing specimens, Pv seemed more viscous than Nx and Ru; Nx low viscosity could also explain the good adhesion of Nx, which does not contain reactive groups, to EMP

polished surfaces. Third, the wettability of Ru could be high, for example, because of greater hydrophobicity, but it is supposed to be hydrophilic before it forms a hydrophobic matrix [3]. Finally, it could develop chemical interactions with the machinable materials studied. Indeed, Ru can allow for the formation of strong hydrogen bonds with hydroxyl groups because of its multifunctional methacrylate acid groups [3], but the improvement in bond strength due to silanization in polished specimens questions this explanation.

The phosphate ester group in methacryloxydecyl-dihydrogen-phosphate (MDP)-based Pv has been reported to interact with porcelain surfaces and facilitate adhesion. However, in this study, the bond strength values with Pv were no better than those with Nx. Actually, Pv is popular especially for infiltrated and polycrystalline ceramics [41, 42]. Ru is particularly efficient for the materials used in this study [4, 12]. Another study showed short-term shear adhesion values more favorable for Ru than Pv; after thermocycling, bond strength was similar for both cements with IPS Empress but remained more favorable for Ru with Empress 2 [43]. The only dislodged adhesive failures occurred for the Pv–LU combination; another study found that bond strength values with an indirect composite were lower for Pv than 2 other cements [11].

This study showed that bond strength differed depending on the selected machinable material. In samples polished to 4000-grit, SBS values were greater for EMP and EN than LU, MK and EM. Roughness could be responsible in part for this result because EMP had the highest Ra value (0.039 µm) and EN the highest Rt value (1.31 µm). However, roughness is not sufficient to explain the results obtained for the samples polished to 800 grit. Other surface variables may be involved, such as pollution of the surface, surface energy, microstructure and crystal/matrix proportion. One could expect the bond strength of a machined composite to be slightly lower than that of an indirect composite restoration obtained in the traditional way because of higher conversion rates. LU bond strength was indeed the lowest in this study. Note that EN has no traditional equivalent. According to manufacturer's instructions, Ru should not be used to cement EN inlays and onlays. However, we found that SBS values for EN were higher for Ru than Pv and Nx.

Different adhesion tests have been described, the most classic being microtensile and shear bond strength testing. Considering the clinical significance of experiments, shear testing takes into account all component forces involved in the mouth (e.g., tension, compression). The disadvantage of this test is that it can exacerbate the importance of the mechanical component of adhesion. Therefore, the major effect of surface treatment we demonstrated may be explained largely by the test chosen. However, the microtensile test favors the chemical component, and one study found higher microtensile bond strength after HF etching than after HF etching and

silanization for the machinable ProCad glass ceramic [29]; this finding seems to agree with our results for MK and EMP.

Finally, it would be best to use a fracture mechanic approach [44, 45]; apparent interfacial fracture toughness has been used [46], but microtensile samples must be prepared so that the cement interface can be weakened when sawing; the notchless triangular prism (NTP) method [47] is being used to test cement adhesion to machinable materials so examining SBS and NTP results will be of interest. For a leucite-reinforced ceramic polished to 1 µm or HF-etched, Moharamzadeh et al. found 317 and 364 J/m^2 toughness, respectively, after 24-hr aging by the chevron-notch short-rod method; this result is in line with our findings for EMP cemented with Nx (18.5 vs 28.7 MPa) [55].

Testing a machinable material–cement–machinable material rather than a machinable material–cement–resin composite assembly might have limited the number of variables of influence. This has been done in some studies evaluating materials obtained in the traditional way [29, 38, 39, 48]. However, obtaining such cylinders from machinable blocks is difficult but may be pursued to confirm our results. However, we found almost no failure in the composite cylinder, and in contrast to other studies involving cylinders made of cement [26, 28, 49, 50], the same composite material was used to apply the shear stress in all samples.

We did not perform luting procedures under a constant load, and cement thickness may have varied among samples. The disadvantage of this technique consists in increased variability. However, the advantage is that we kept close to clinical bonding conditions, in which cement thickness is variable and the application is not under constant pressure.

Many cohesive failures occurred in the materials, especially MK, EMP and EN materials. These testing results may be interpreted as mechanical strength of the materials rather than bond strength between the machinable material and luting agent. Scherrer et al. proposed to discard all broken specimens with cohesive failure [45]. However, bond strength values of specimens without cohesive failure (Table 5) were almost the same as overall values (Table 2). The main difference concerned the group 2–MK–Nx association: the value without cohesive failure seemed to be more in line with other values. Furthermore, the clinical durability of MK and EMP is well documented, so cohesive failures may indicate that adhesion of the cement to these materials is sufficient, and retrieving results of samples with cohesive failures may select samples that were less well bonded.

We did not implement artificial aging. However, several studies have shown that artificial aging does not necessarily alter bond strength values [4, 28, 51]. Nevertheless, other studies have found a significant difference [38, 44, 52, 53]. Thermocycling, the most commonly used technique, does not always result in lower adhesion values [44]

and could induce a post-polymerization of polymeric materials that would differ from the phenomena that occur in the mouth [43]. Testing sample fatigue would be interesting [52]; however, one study failed to show a significant effect of fatigue on shear bond strength to leucite-reinforced glass ceramic [54].

Our *in vitro* results must be confirmed by clinical studies. The current study was a preliminary investigation of possible results and variables that we will not be able to study in our randomized controlled trial comparing LU and EMP inlays and onlays adhesively cemented to dental tissues with an etch-and-rinse adhesive (Optibond XTR) and a dual-polymerizing resin cement (Nx).

Conclusion

In our study of the effect of different surface treatments on the adhesion of resin cements to tooth-colored machinable materials :

1. Shear bond strength was most affected by sandblasting of LU and HF etching of MK, EMP, EM and EM materials.

2. Silanization did not increase the bond strength of sandblasted LU or HF-etched MK and EMP specimens. The bond strength of HF-etched EM and EN was increased with silanization but not significantly.

3. The cement also influenced bond strength values. Overall, bond strength was greater with Ru than Pv and Nx cement.

4. Bond strength differed between materials; we found cohesive failures with MK and EMP and to a lesser extent EN.

5. Shear bond strength was positively correlated with roughness parameters for 4 of the machinable materials evaluated.

These conclusions need to be confirmed by durability and clinical studies.

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Supplementary information

For this article, we performed a systematic search of the literature. The elements necessary for the implementation of this review, the results of which are briefly presented in the introduction section of the publication, are in Appendix 19.

In addition, we performed mechanical tests, a scanning electron microscopy study and a study of roughness, of which we will present the main results.

Mechanical testing of evaluated machinable materials

We evaluated some basic mechanical properties of the machinable materials evaluated in the preceding publication.

Materials and methods

For each machinable material, 2-mm-thick slices were obtained by cutting 14-L blocks for Cerec using a diamond disc in a precision cutting machine (Isomet, Buehler, Lake Bluff, IL, USA) at 275 rpm. The slices were ground-finished to 4000-grit silicon carbide metallographic abrasive paper (PSA backed Silicon carbide paper, Struers, Ballerup, Denmark) under water-cooling in a polishing machine (Planopol-3, Struers, Ballerup, Denmark). One slice of each material was gold-sputtered in a sputtering device. Vickers hardness was measured (MH-3, Metkon, Bursa, Turkey). Other slices were cut by use of the precision cutting machine, to obtain 10 bar-shaped specimens of each material (2 mm x 4 mm x 18 mm). Flexural strength of the materials was measured and adapted to accommodate bar sizes that could be sectioned from commercially available mill blocks. The three-point bending test was performed on the specimens using the universal testing machine at a cross-head speed of 1 mm/min. The flexural strength (FS) in MPa was calculated as:

$$FS = \frac{3pL}{2bd^2}$$

where *p* is the load at fracture (N), *L* is the span length (16 mm), and *b* and *d* are the width and thickness, respectively, of the specimens in mm.

Results

The results are presented in Table 6.

	MK	EMP	EM	EN	LU
Vickers hardness (HV1/20)	620.6 (34.8)	514.5 (34.9)	615.7 (14.6)	207.8 (15.8)	105.9 (3.3)
Flexural strength (MPa)	102.3 (7.1)	123.2 (15.0)	330.3 (46.3)	125.1 (12.3)	219.9 (7.1)

Table 6. Mean Vickers hardness and flexural strength (SD) of machinable materials

Discussion

Our results are relatively similar to those advanced by industry (presented in Chapter 1). All flexural strength values are a little lower than those from the manufacturers, except for LU. Because the materials used throughout this work are from the same batch, we wanted to check that they had performances similar to those reported by their respective manufacturers.

Scanning electron microscopy imaging of evaluated machinable materials

Materials and methods

Specimens that were 800-grit and 4000-grit polished were gold-sputtered in a sputtering device and analyzed by scanning electron microscopy (SEM) (JSM 6400, Jeol, Tokyo, Japan) at 15 kV to observe topographical changes of surfaces.

Results

The results are presented in Figure 19.

Discussion

This study allowed for better understanding, by observing surface images, the adherence observed for the different materials polished. For samples polished to 4000-grit, MK and EM seem to be the least rough, and their adherence is the lowest. For samples polished to 800-grit, the surface of EM seems less rough and its adherence is the lowest; surfaces of MK, EN and EMP appear rougher and their adherence values are the highest. EN roughness seems to be explained by its two-phase structure, whereas the surfaces of MK and EMP appear to have surface defects, mainly of tear-type (which machining grooves seem to confirm).

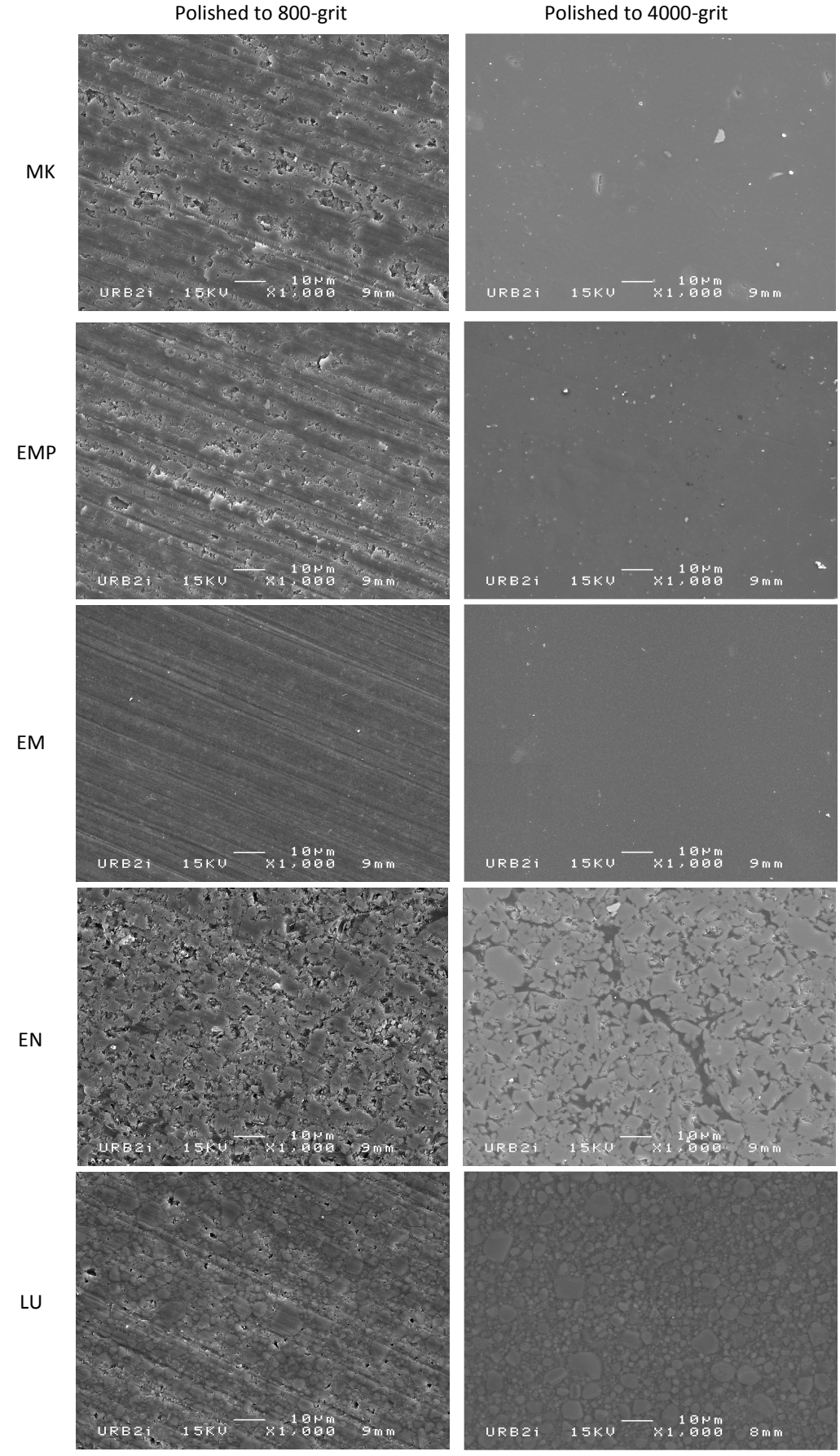

Figure 19. Surfaces polished to 800-grit (left) and 4000-grit (right)
of machinable materials (from top to bottom: MK, EMP, EM, EN and LU).

Roughness evaluation of machinable materials evaluated

We wanted to study the correlation between surface roughness and adherence, that is, quantify the contribution of the mechanical component in adhesion of machinable materials.

SEM images showed that the anfractuosities created by the action of etching ceramics – with their cavernous geometry – would not be available to traditional roughness assessment techniques. However, to become familiar with these techniques and roughness parameters, we applied three techniques:

1. Mechanical profilometry with a mechanical scanning microscope (Talysurf, Taylor Hobson) applied only on polished surfaces because the tip comes into contact with the material in this technique and cavernous hollows might therefore damage the tip (the tip used was a Vickers diamond).

   Area assessed: 1 mm^2. Pitch: 2 µm.

   The results are presented in the previous publication.

2. Profilometry with an atomic force microscope (AFM, Nano-R2, Pacific Nanotechnology) used in non-contact mode but still a risk of damaging the tip because of the crevices created by the etching of ceramics.

   Area assessed: 400 μm^2. Pitch: 19.5 nm.

- Optical profilometry by focal variation (Alicona): This technique is non-contact, and we applied it to surfaces polished and treated with the reference treatment (Figure 20 and Figure 21).

  Area assessed: 0.2 mm^2. Vertical resolution: up to 10 nm.

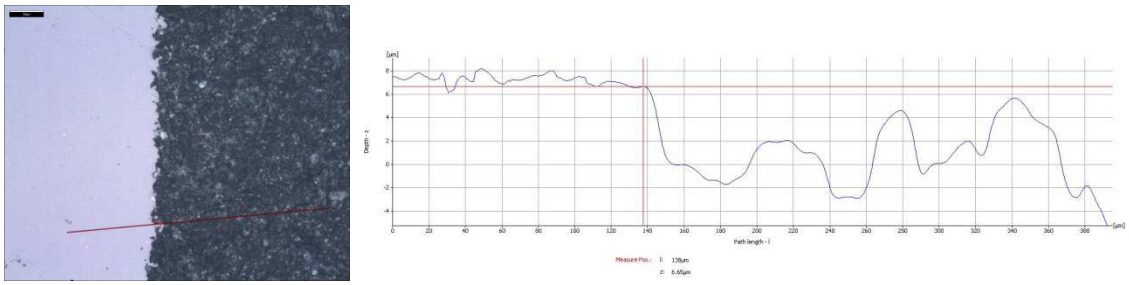

Figure 20. Acquisition of roughness parameters through focal variation (Alicona).
Composite sample (Lava Ultimate) polished on its left and sandblasted on its right
Left: 2D image acquired under the microscope with cutting axis in red.
Right: roughness profile (from which roughness parameters are calculated)

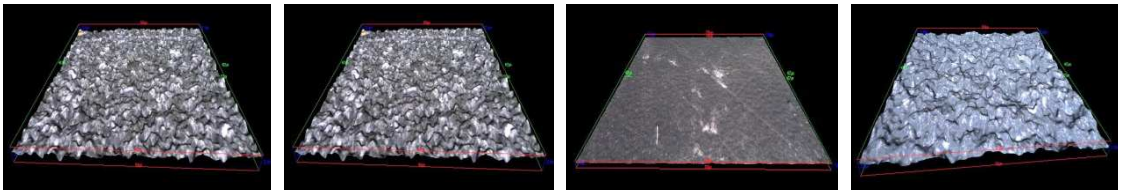

Figure 21. 3D representation of the different machinable materials treated with their reference surface treatment obtained by focal variation
From left to right: MK, EMP, EM and LU.

Roughness parameters obtained by these two techniques are in Table 7. The least rough surface would be for EM and the roughest would be for MK. Regarding EMP and LU, the results differ depending on the technique. Although MK may have among the highest adherence values (at least using the traditional resin cement Nx), EM did not have the lowest adherence values because its values were very close to those of MK. This finding is probably due to partial assessment of the crevices and cracks created by reference surface treatments because of insufficient resolution (for focal variation perhaps) or undercuts that are not accessible.

Technique	Parameter	MK	EMP	EM	LU
Focal variation (µm)	Ra	1.56	0.42	0.0653	1.34
AFM (µm)	Sa	0.67±0.05	0.62±0.08	0.09±0.003	0.45±0.04

Table 7. Summary of average roughness parameters (Ra and Sa) of the machinable materials with their reference surface treatment obtained by focal variation or AFM, respectively.

Perspective

Because traditional rugosity evaluation techniques do not allow for properly assessing the rugosity of HF-etched glass ceramics, we will investigate other techniques that may help to explore this rugosity parameter more comprehensively.

We have tested samples for adhesion in shear after 24-hr water storage, but our results could be affected by the aging of samples.

We conclude this chapter with the correlations that we could observe between our *in vitro* results and the clinical results of the CECOIA trial we are conducting.

Adhesion and surface roughness

Traditional methods do not allow for accurate assessment of the roughness of the samples treated with the reference surface treatment, mainly because these techniques do not explore undercuts. For samples polished to different grits, some studies have used a confocal microscope. However, this technology would probably also not allow for complete exploration of the caves created by etching ceramics, which are close to or smaller than 1 µm (Figure 22).

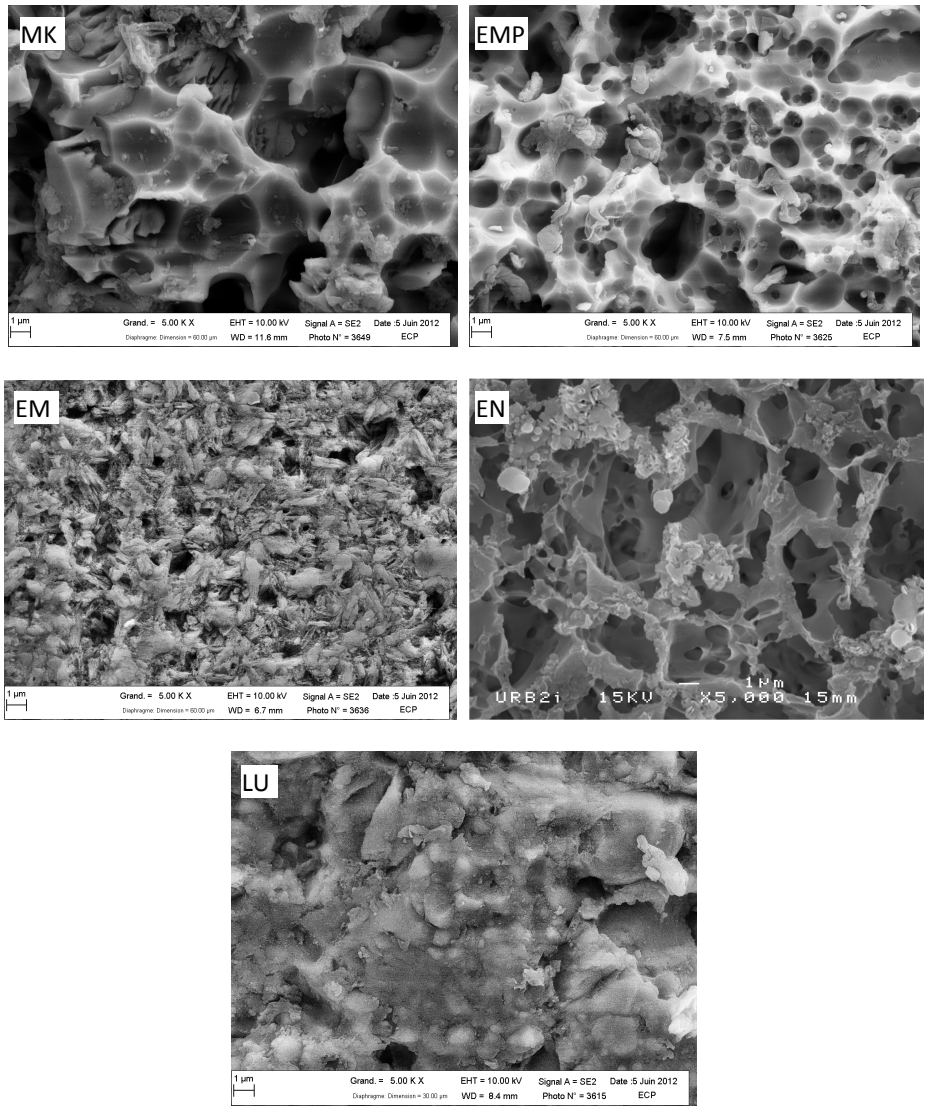

Figure 22. SEM imaging of the surface roughness of the different machinable materials treated with their reference surface treatment (Mark II [MK], Empress CAD [EMP], e.max CAD [EM], Enamic [EN] and Lava Ultimate [LU])

A 3D technique seems be required because undercut shapes should be imaged. Figure 23 shows the various 3D analysis techniques as well as their resolution.

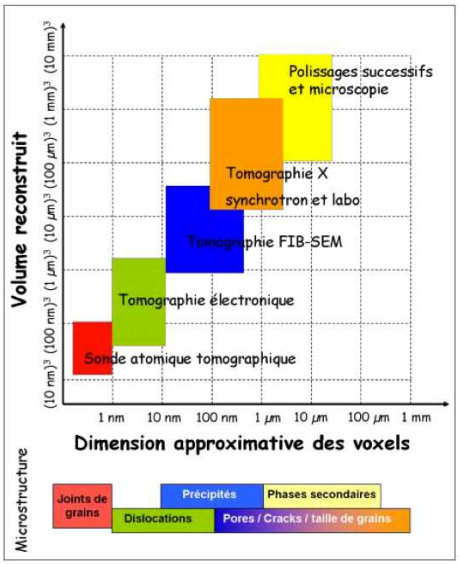

Figure 23. Resolution and sample volume analyzed with various 3D analysis techniques. According to Vivet [54]

Because it takes at least 3 voxels in each of the three directions to view an object, a voxel should be < 300 nm in our case. Non-destructive X-ray micro-computed tomography would not image 1-µm crevices because the voxel size is at least 0.75 µm (with standard micro-CTs). Therefore, images must be obtained by dual-beam Focused Ion Beam (FIB)/SEM. This technology has the disadvantage of being destructive but the advantage of being 3D and having a suitable resolution (each voxel is typically a few nanometers) for the roughness of our surfaces. Acquisitions of samples similar to those used for the shear tests would provide different information, including extent of the surface modifications induced by surface treatments; structure of the material at the heart of the block (without the modifications due to sawing of the block); structure, geometry and surface roughness of the surface-treated machinable material; and resin cement penetration into the cracks.

Adherence and aging

In conclusion of the article, we mentioned that it would be interesting to compare the results obtained after 24 hr to that obtained after aging. To this end, we made an additional 200 samples that are currently in the oven, comprising 40 samples of each of the 5 machinable materials studied (MK, EMP, EM, EN and UL), cemented with resin cement Nx, and treated with the following surface tretments:

- polished to 4000 grit

- polished to 4000 grit and silanized
- HF-etched (MK, EMP, EM and EN) or sandblasted (UL)
- HF-etched (MK, EMP, EM and EN) or sandblasted (UL) and silanized.

We will apply 6-month water storage before testing these specimens, to comply with current reommendations [141]. We will thus better understand the aging process of the machinable material–resin cement interface involved in aging of inlays and onlays. We will especially get a better idea of the value of silane application, because some authors have reported that the addition of silane may lessen over time. This could be due to the hydrolysis of siloxane (-Si-O-Si-) bonds [142] and/or to susceptibility to stress corrosion and water uptake of the interface between the resin cement and the silane coupling agent [143].

In vitro adherence results and clinical CECOIA trial results

Regarding the CECOIA clinical trial, the machinable materials used are LU and EMP, treated by sandblasting/etching and silanization, respectively, and the resin cement used is Nx (corresponding to batch numbers 88 and 34 of our *in vitro* study). The bond strength values for both groups after 24-hr water-storage are 18.9 (5.4) for LU and 30.0 (3.6) for EMP. Although **bond strength was lower for LU than EMP**, Tukey's analysis performed on all 90 batches did not reveal a significant difference between these two batches at alpha risk 5%.

One can expect the bond strength to be related to the following FDI items:

- Item 5 (Fracture of material and retention), especially in terms of retention. However, because shear bond strength values are relatively high for both materials, the retention rate should be close to 100% and this item will probably mostly reflect material fractures. Actually, fractures appear to be one of the most common types of failures, especially for ceramic inlays and onlays (see systematic review p.36).

- Item 13 (Tooth integrity - enamel cracks, tooth fractures). We have seen that adhesion strengthens the tooth-restoration assembly. Therefore, composites (LU) could also be less favorable than ceramics (EMP). However, because bond strength values are not significantly different, this item should be considered in relation to other factors involved in the occurrence of tooth fractures such as as the volume of residual dental tissues, pre-existing cracks, the thermal expansion coefficient of the material, the contact intensity with the antagonist, the existence of parafunctional habits or stress intensity due to polymerization shrinkage [139]. However, the resin cement used is the

same for both materials and should not differentially influence their clinical success. The other factors are identified in follow-up sessions or may be deduced from the registered data.

These assumptions are valid for the initial clinical assessment (one week) but not for the clinical assessment after 2 years. To get an idea of the latter, the study of aged samples seems necessary.

Finally, the FDI item 11 concerns postoperative sensitivity and tooth vitality and we know that the quality of adhesion greatly affects the pulp response [141]. Composites (LU) could, thus, be less favorable than ceramics. However, we will see in the conclusion that the pulp response may be mainly affected by the resin-cement biocompatibility.

Résumé du chapitre en français

Dans le premier chapitre, nous avions vu que les propriétés adhésives des différents matériaux usinables permettant de réaliser des inlays-onlays avaient été peu étudiées. C'est pourquoi ce chapitre compare l'adhérence en cisaillement des principaux matériaux disponibles. Notre objectif a été d'étudier l'influence de trois paramètres sur l'adhérence : le traitement de surface appliqué sur l'intrados prothétique, la colle utilisée et le matériau usinable choisi (composite ou céramique). 6 traitements de surface ont été appliqués (polissage au grain 4000, polissage au grain 800, sablage/mordançage à l'acide fluorhydrique ; suivi ou non de l'application de silane) afin d'évaluer l'importance relative de la composante micromécanique et de la composante chimique dans l'adhérence finale. La rugosité des surfaces polies a été évaluée à l'aide d'un profilomètre afin d'étudier la corrélation entre rugosité de surface et adhérence. 3 colles duales ont été appliquées (NX3 : colle traditionnelle appliquée après un adhésif de type mordançage-rinçage ; Multilink Automix : colle traditionnelle appliquée après un adhésif automordançant ; Rely X Unicem : colle auto-adhésive). 5 matériaux usinables ont été évalués : Mark II, Empress CAD, e.max CAD, Enamic, Lava Ultimate. Au total, 900 échantillons ont été réalisés et testés après stockage dans l'eau pendant 24h à 37°C.

L'adhérence était essentiellement influencée par le traitement de surface (le sablage pour le composite et le mordançage à l'acide fluorhydrique pour les céramiques et l'Enamic augmentent significativement l'adhérence). L'application de silane, qui est recommandée par certains auteurs, n'augmentait pas significativement l'adhérence des échantillons traités par sablage ou mordançage (e.max et Enamic) voire la diminuait (Mark II, Empress CAD et Lava Ultimate). La colle influençait aussi l'adhérence et le Rely X Unicem permettait une meilleure adhérence. Les ruptures cohésives étaient fréquentes pour la Mark II, l'Empress CAD et l'Enamic mordancés, du fait de leur plus faible ténacité. Une corrélation positive entre rugosité et adhérence a été observée pour 4 des 5 matériaux évalués.

Outre ce travail, les propriétés mécaniques (résistance en flexion, dureté Vickers) et la rugosité de ces matériaux ont été évaluées. Les perspectives comprennent une évaluation plus précise de la rugosité des surfaces traitées, l'évaluation de l'adhérence après stockage dans l'eau pendant au moins 6 mois et l'étude de la corrélation entre les résultats observés *in vitro* et ceux qui seront obtenus dans le cadre de l'essai clinique.

Conclusion

In the **first chapter**, we showed that no tooth-colored machinable material fully meets the specifications for fabricating inlays and onlays. A compromise is necessary, and comparison of the different materials, including clinically, is required. This situation motivated this work.

The **second chapter** describes a systematic review of randomized clinical trials comparing composite and ceramic inlays and onlays. Only two studies were selected; both had a high risk of bias. The quantitative synthesis of results for failures from these two studies showed an overall 3-year risk ratio for failure of 2 [95% confidence interval 0.38-10.55] ($p>0.05$), favoring ceramic inlays. However, this trend could be reversed in the long term. In addition, no study has compared composite and ceramic onlays and no study has compared these two materials for non-vital teeth. Thus, further clinical studies are needed.

In the **third chapter**, we first introduced the methodological tools for the design of such studies; we created a special tool for any investigator to choose the randomization method most suitable for the intended clinical trial. The trial considered will include 400 patients with vital or non-vital teeth to be treated by an inlay or onlay in order to obtain 358 patients randomized. We then obtained a budget of €237,000 and implemented the trial to limit bias as much as possible. More than 230 patients have been included so far in the 7 centers, including more than 60 in our center. We will have to wait until the inclusions and 2 years of follow-up are completed to analyze the comparative clinical effectiveness results of composite and ceramic inlays and onlays; we also hope to obtain funds to extend the follow-up duration. We also discuss different clinical studies we would be interested in conducting.

In the **fourth chapter**, while waiting for the results of the clinical trial and to better understand them, we decided to compare the adhesion of different machinable composites and ceramics to produce inlays and onlays. We took this opportunity to study the influence of other factors that we could not assess in the clinical trial such as resin cement and surface treatment choice. We found that shear bond strength was most affected by sandblasting or hydrofluoric acid (HF) etching of the machinable material**,** that silanization did not necessarily increase the bond strength of sandblasted or HF-etched machinable material surfaces, that the cement also influenced bond strength values, that bond strength differed between materials and that shear bond strength was positively correlated with roughness parameters for most machinable materials evaluated.

In tandem with our clinical trial projects, other aspects could be studied *in vitro*, which would help better understand the clinical efficacy of the two materials and the results to be obtained in the trial. The differential **machinability** of materials is an

important aspect that has been little studied. We will see **in the first part of this conclusion** which aspects of machinability we would study and why. Studying how and why machinable materials age is also fundamental to understanding the failures occurring in clinical trials and to develop new and better materials. We will discuss various aspects of **aging** that we would like to study in a **second part of this conclusion**.

Machinability

As observed in the introduction, CAD/CAM production of dental restorations is the way of the future. However, machining causes changes in the structure and surface of the material, the extent and consequences of which have been little studied. Different research paths seem particularly interesting in terms of clinical practice. Such paths include better understanding the structure and surface changes resulting from machining the different materials depending on machining parameters, attempting to optimize the polishing of the upper inlay or onlay surface after machining, trying to define which intaglio surface roughness is desirable to reduce the risk of fracture of the restoration and, finally, comparing the respect of thin layers of restorations depending on material and machining parameters.

Machinability and surface defects

Milling could be responsible for the creation of surface defects or microcracks (see Figure 24 below). Defects are sites of initiation of cracks that secondarily develop into fractures [144]. One of the extensions of our work may thus involve study of phenomena occurring at the surface during machining and the quantification and classification of defects depending on the material and machining parameters (wear of burs, among others).

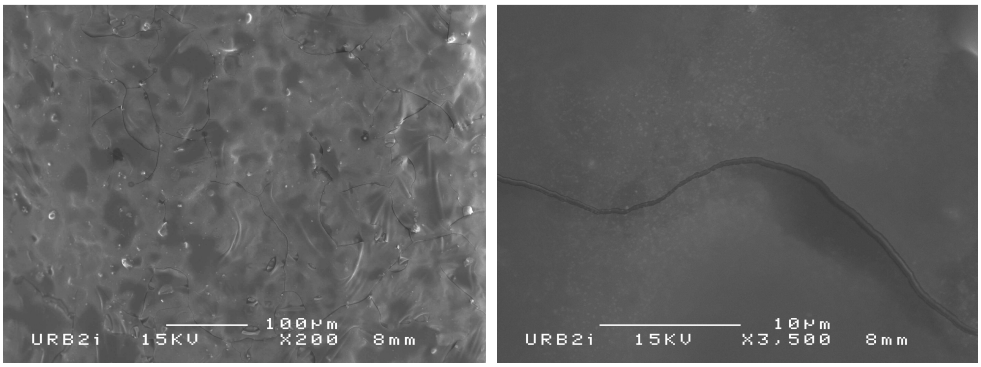

Figure 24. Marginal ridge of a ceramic inlay made of lithium-disilicate reinforced glass-ceramic (e.max CAD) machined with a milling unit (MCXL CEREC, Sirona)

Condition of the upper surface, glazing/ characterization and polishing

The condition of the upper surface is important, both in tribological (a rough upper surface wears out more and wears the antagonist more) and mechanical terms (micro-surface defects are initiation sites for fractures). Studying the effectiveness of maneuvers of polishing and glazing for ceramics or characterizing for composites to eliminate defects and machining grooves (Figure 25 and Figure 26), depending on the material and relevant machining parameters, would be of interest.

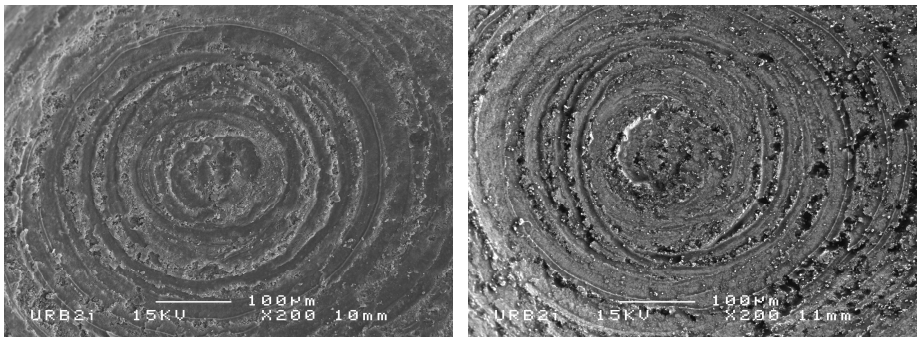

Figure 25. Marginal fossa of a composite inlay (Lava Ultimate)
Left: raw machining. Right: polished (with cups)

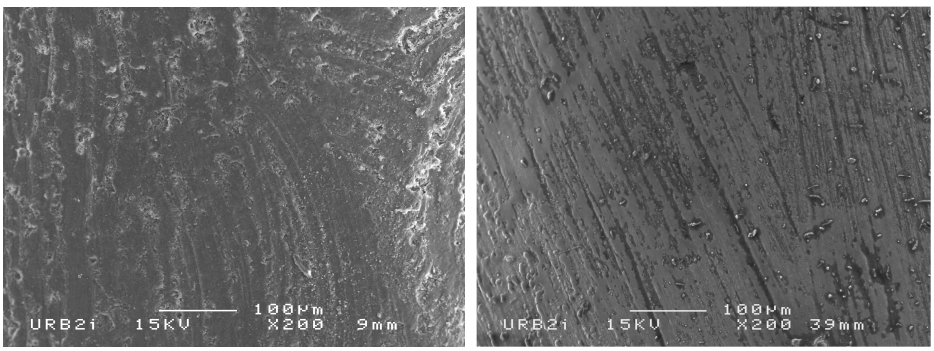

Figure 26. Marginal ridge of a composite inlay (Lava Ultimate)
Left: raw machining. Right: polished (with cups)

Surface condition/roughness and fracture mechanics

As Anusavice recommended [52] and Lohbauer did [144], we could try to estimate the fatigue lifetime of machinable materials depending on their surface roughness. We should adapt the methodology these authors used: confocal laser scanning microscope for surface roughness evaluation would not allow for correct

evaluation of the roughness of etched ceramics, and the four-point bending test they used to evaluate flexural strength and slow crack-growth parameters cannot be implemented with CAD/CAM blocks of length < 20 mm. This procedure would allow, as in the work of Lohbauer, to compare the results expected by these calculations to those observed in the CECOIA trial.

Machinability and respecting thin layers

Minimal invasive dentistry often requires making partial restorations of fine thickness, and our restorations usually have thin layers at the margins. Hence, comparing the respect of thin thicknesses depending on the material and machining parameters could also be an interesting line of research. Composites seem more favorable than ceramics in this aspect (Figure 27 below, Appendix 20 and Appendix 21), which could lead to better marginal adaptation of composite inlays and onlays, in light also of the material wear being closer to that of the resin cement [74, 145].

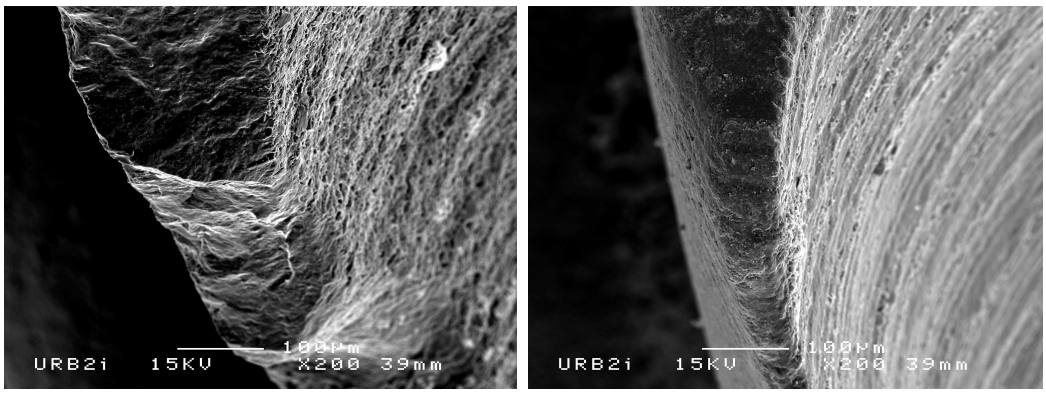

Figure 27. Respect of thin layers during milling: proximal edge of a ceramic inlay (Left: Empress CAD) and the same inlay made of composite (Right: Lava Ultimate)

Aging

Aging of inlays and onlays can be mechanical, tribological or chemical, among other types.

Mechanical aging

Fatigue

To study mechanical aging, performing fatigue tests would be of interest [52]. Indeed, the forces applied in conventional mechanical tests are much higher than normal functional forces (about 10 to 40 N during chewing and swallowing, the maximum bite force being around 230 N) [146]. Fatigue tests were performed on extracted endodontically treated molars restored by machined composite (Paradigm MZ100, 3M Espe) or ceramic (Mark II, Vita) overlays. The survival rate after 185,000 fatigue cycles (force 200–1400 N) was 0% for ceramic overlays and 73% for composite overlays [147]. This result can be explained by the brittle behavior of ceramics [20, 96] and the lower elastic modulus of composites.

This study is interesting but concerns a particular clinical situation. The behavior should be verified to be similar for inlay restorations and different machinable materials compared. The structure of Enamic (Vita) in particular is very different from that of the materials used so far. The cement also seems to play an important role [148].

Computer simulations to study the mechanical strength and aging of adhesively cemented machinable materials

We saw that bonding enhances the mechanical strength of the inlay or onlay [36, 38-40]; for glass ceramics in particular, fracture failure is typically initiated from the internal surface and resin cements may strengthen these materials by crack-bridging [40, 149]. Thus, conventional mechanical tests in which the materials are tested

independently of the cement and dental tissues fail to reveal how they will behave once cemented. A 3D-modelling and finite element analysis of the different partners of the assembly, taking into account their structure, followed by simulated fatigue of the assembly [150-152], could help better understand mechanical aging phenomena [52] occurring by the different partners and compare the biomechanical behavior of machined composite and ceramic inlays and onlays. This work was started by Magne (2D modeling of two inlay and onlay configurations on vital maxillary molars [153]), and our work would consist of perfecting the models and studying the impact of prognostic factors (pulp vitality, premolar or molar, inlay or onlay etc.) on the choice of the most suitable machinable material.

Models could be controlled and calibrated using the fatigue tests and calculations of fatigue lifetime of machinable materials mentioned above, then using the results of the CECOIA clinical trial. We may also attempt to determine the optimal thickness of resin cement for each material, because we have seen that the cement is needed on biomechanical and adhesive grounds, but a minimum thickness is desirable in terms of biocompatibility (see Chemical aging and biocompatibility below), microleakage [54] and marginal aging and adaptation [154].

Tribologic aging

The aging of surfaces is also an interesting aspect that could influence the choice of machinable material for an inlay or onlay. Several studies of materials obtained in the traditional way showed that aging of the upper surface was greater for composite than ceramic inlays and onlays [155], but the wear of the opposing enamel surface in contact with the inlay or onlay was higher for ceramics [156].

Regarding machinable materials, Mörmann recently compared the wear of 10 machinable materials and enamel [105]. We reported the results obtained in Chapter 1 (p. 27). These results should be enough to understand the results observed in the Cecoia trial: composite (Lava Ultimate) seems to wear slightly more than ceramic (Empress CAD), whereas ceramic should lead to increased wear of the enamel antagonist. We will determine whether our **clinical results** confirm Mörman's ***in vitro* results**.

The wear of restorations in the trial can be measured by **traditional methods** using replicas (e.g., the method developed by the Oral Health and Science University [OHUS] [69]) and we will also consider trying to obtain it from **optical impressions** and the resulting point clouds to compare measurement methods.

Chemical aging and biocompatibility

Finally, chemical degradation over time could be a decisive argument in favor of ceramic inlays and onlays. Actually, because ceramics are oxides, they are fundamentally inert. This nonreactive quality provides synthetic ceramics with excellent biocompatibility [90]. In contrast, composites contain a resinous matrix, the conversion of which does not reach 100% even if the rate can exceed 80% for indirect composites (direct composites can approach 50%) [81].

Although all marketed materials have passed the tests defined by ISO standards [157, 158], most studies conclude a certain toxicity of released monomers and oligomers [159]. Bisphenol A, which could be released by composites with Bis-GMA in their matrix, is currently under the spotlight, but other monomers and components could be released and show toxicity [160-162].

However, no study has compared the biocompatibility of the different machinable materials. Few studies have determined the relative areas of adhesive, cement and machinable material exposed in the mouth for an inlay or onlay. Thus, we would like to begin by determining these surfaces for a composite or a ceramic inlay or onlay, using the replicas made for the Cecoia trial.

Then we would like to quantify the conversion rate of machinable materials containing resin and the relative monomer release of these machinable materials and some cements and adhesives [163]. Indeed, unbound, free monomers seem to be greatly responsible for the cytotoxicity of resin composites on pulp and gingival cells and may be implicated in the allergic potential of these materials [159]. We have already begun this work: Figure 28 shows the compared release of two machinable composites and Figure 29 shows their release compared to that of a same exposed surface of two resin cements.

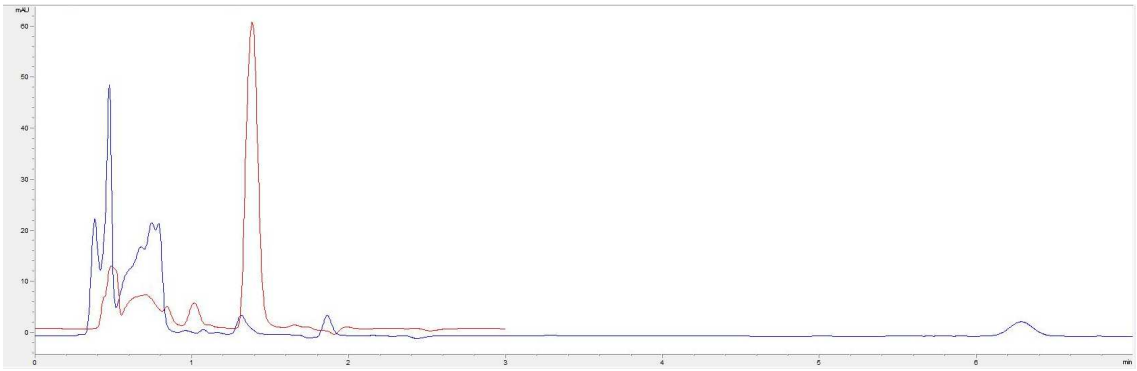

Figure 28. Chromatogram of two machinable composites (Lava Ultimate and Enamic) obtained by High-performance liquid chromatography (HPLC) after 15 days. Retention times with the parameters used are about 0.6 min for HEMA, 0.95 min for TEGDMA, 1.35 min for UDMA and 1.7 min for bis GMA. The earliest peaks correspond to solutions of the stationary and mobile phases or impurities. Manufacturers mention the following monomers in the composition of their products: UDMA, bis-GMA, TEGDMA and a complex in Lava Ultimate; UDMA and TEGDMA in Enamic.

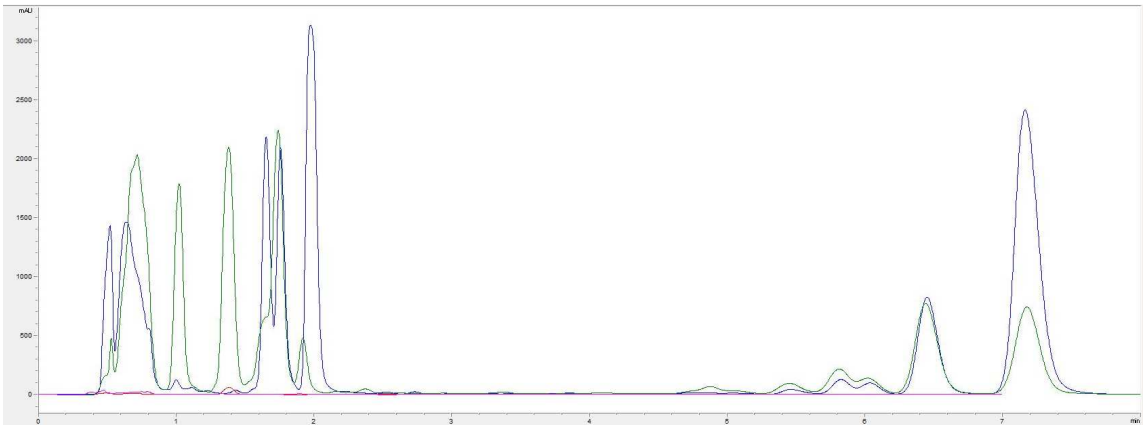

Figure 29. Chromatogram of two machinable composites (Lava Ultimate Enamic) and two resin cements (Nexus 3, Kerr ; Panavia F2, Kuraray) obtained by HPLC after 15 days. The release of the machinable composite is almost not detectable at this scale, whereas the release of cements is very detectable. Manufacturers mention the following monomers in the composition of their products: HEMA in Nexus 3; the description is vague for Panavia.

The toxicity of amalgams [11] and resin composites [159] used for the direct technique seems increasingly obvious, and indirect partial restorations are a solution to reduce this toxicity while meeting the principles of tissue preservation. Such restorations allow for esthetic restorations and limiting the release and potential toxicity almost to the single cement margin.

Moreover, new materials being developed and marketed could better meet the specifications of machinable restoration materials and help with more efficient and sustainable restorations; examples are zirconia-reinforced lithium silicate ceramics (Suprinity, Vita and Celtra, Dentsply/Degudent) [100] or the next generation of polymer-infiltrated ceramic-network composites developed by Dr. Sadoun.

Further progress could still be made in terms of the structure or composition of machinable materials. In terms of structure, multi-layer blocks could better adapt to the dental structure composed of two hard tissues with different properties [53, 164]. In terms of composition, blocks or adhesive systems could benefit from incorporation of bio-active [165] or anti-oxidant [159] elements or functional nanoparticles [51, 166]. Finally, the necessary evolution toward additive CAD/CAM techniques will necessarily be accompanied by an evolution of materials and their properties [41]. A world of possibilities to treat our patients is thus opened at the intersection of adhesive partial restorations, science materials and dental CAD/CAM.

We finish this report of the study of materials by emphasizing that choosing an effective material is necessary but not sufficient for the success and longevity of our inlays and onlays. Restoration longevity depends on many other factors such as the operator, the teaching hospital or private practice framework and time constraints faced by practitioners, patient clinical factors (e.g., occlusion, inlay or onlay, vital or non-vital tooth, caries risk and compliance) or restoration maintenance and health policies (inlays and onlays are poorly covered by health insurance and maintenance of restorations cannot be codified with the French social security). The clinical setting, which probably is of paramount importance, has not had the important place it deserves in this thesis, but the analysis of the results of the CECOIA trial should allow us to obtain a better idea of the relative importance of some of these factors in the success of inlays and onlays. Other studies, *in vitro* and clinical, will be needed to confirm our results and explore aspects that we could not study in this work. Step by step, we can improve the quality and longevity of our restorations and contribute to the improvement of the oral and general health of our patients.

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Appendix

Appendix 1. Detailed search strategies applied to MEDLINE, Embase and Central for the systematic review

Search equations for each database included the Cochrane filter for randomized controlled trials, slightly modified by including the term « clinical study ».

1. Medline search strategy:

(composit* OR paradigm[Title/Abstract] OR Isosit[Title/Abstract] OR Coltene Brilliant[Title/Abstract] OR Visio-Gem[Title/Abstract] OR Concept[Title/Abstract] OR Artglass[Title/Abstract] OR belleGlass[Title/Abstract] OR Targis[Title/Abstract] OR Colombus[Title/Abstract] OR Sinfony[Title/Abstract] OR Sculpture[Title/Abstract] OR Cristobal[Title/Abstract] OR Herculite[Title/Abstract] OR Targis[Title/Abstract] OR Vectris[Title/Abstract] OR Tescera[Title/Abstract] OR Gradia[Title/Abstract]) AND (*ceramic* OR Empress OR emax OR e.max OR Mk II OR MkII OR Mark [Title/Abstract]) AND (inlay* OR onlay* OR partial coverage restoration*[Title/Abstract]) NOT (fixed partial denture* OR FPD* OR bridge* OR implant*[Title/Abstract])

combined with the Cochrane Search filter for randomized controlled trials for MEDLINE (slightly modified: « clinical study » added):

"randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "drug therapy"[MeSH Subheading] OR "randomly"[Title/Abstract] OR "trial"[Title/Abstract] OR "clinical study"[Title/Abstract] OR "groups"[Title/Abstract]) NOT "animals"[MeSH Major Topic]

2. Embase search strategy:

(composit*:ab OR paradigm:ab OR (Coltene NEAR/1 Brilliant):ab OR Visio-Gem:ab OR Concept:ab OR Artglass:ab OR belleGlass:ab OR Targis:ab OR Colombus:ab OR Sinfony:ab OR Sculpture:ab OR Cristobal:ab OR Herculite:ab OR

Targis:ab OR Vectris:ab OR Tescera:ab OR Gradia:ab) AND (ceramic*:ab OR empress:ab OR emax:ab OR mkii:ab OR mark*:ab) AND (inlay*:ab OR onlay*:ab) NOT ((partial NEAR/1 denture*):ab OR fpd*:ab OR bridge*:ab OR implant*:ab)

combined with the Cochrane Search filter for randomized controlled trials for EMBASE (slightly modified: « clinical study » added):

random*:ab OR factorial*:ab OR crossover*:ab OR (cross NEAR/1 over*):ab OR 'cross-over':ab OR placebo*:ab OR (doubl* NEAR/1 blind*):ab OR (singl* NEAR/1 blind*):ab OR assign*:ab OR allocat*:ab OR volunteer*:ab OR 'crossover procedure' OR 'double-blind procedure' OR 'randomized controlled trial' OR 'single blind procedure' OR (clinical NEAR/1 study):ab NOT animal NOT nonhuman NOT 'animal experiment'

3. Central Search Strategy:

#1 COMPOSITE RESINS single term (MeSH)

#2 Paradigm or (Coltene near Brilliant) or (Visio near Gem) or Concept or Artglass or belleGlass or Targis or Colombus or Sinfony or Sculpture or Cristobal or Herculite or Targis or Vectris or Tescera or Gradia

#3 (#1 or #2)

#4 CERAMICS single term (MeSH)

#5 Empress or Emax or Mkii OR Mark

#6 (#4 or #5)

#7 INLAYS single term (MeSH)

#8 inlay* or onlay*

#9 (#7 or #8)

#10 (partial near denture*) or FPD or bridge* or implant*

#11 (#3 AND #6 AND #9 NOT #10)

Appendix 2. Data extraction form for the systematic review

IO materials review: data extraction form

STUDY AND REVIEWERS

Reviewer ID: ☐ **Study ID N:** ☐

Authors: ☐ Year of publication: ☐

Verification / selection of study eligibility

		YES	NO	UNCLEAR	Comments
Clinical study		☐	☐	☐	
Design	**Randomized**	☐	☐	☐	
Comparison	**At least 1 ceramic and 1 composite**	☐	☐	☐	
Intervention	**Inlay / onlay**	☐	☐	☐	
Study eligible		☐	☐	☐	

Risk of bias

Bias	Judgement	Support of judgement
Generation of sequence allocation	Unclear risk	
Allocation concealment	Unclear risk	
Blinding of participants	Unclear risk	
Blinding of outcome assessors	Unclear risk	
Complete outcome data (both intention to treat and missing data)	Unclear risk	
Selective reporting of outcomes	Unclear risk	
Others bias	Unclear risk	

Notes:

2

Clinical data

Item	Data extracted
Number of patients treated	
Number of teeth treated	
Follow up duration	
Inlay-onlay materials	
Techniques used	☐ Direct inlay-onlay ☐ Indirect inlay-onlay manufactured by technician ☐ Indirect inlay-onlay CAD/CAM manufactured
Restoration types	☐ Inlays only ☐ Onlays only ☐ Inlays and onlays

3

Appendix 3. Protocol of the systematic review registered in Prospero

THE UNIVERSITY of York
Centre for Reviews and Dissemination

NHS National Institute for Health Research

PROSPERO International prospective register of systematic reviews

Clinical efficacy of composite vs ceramic for inlays and onlays manufacturing: a systematic review

Helene Fron Chabouis, Jean-Pierre Attal, Violaine Smail Faugeron

Citation
Helene Fron Chabouis, Jean-Pierre Attal, Violaine Smail Faugeron. Clinical efficacy of composite vs ceramic for inlays and onlays manufacturing: a systematic review. PROSPERO 2013:CRD42013003441 Available from http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013003441

Review question(s)
Is the clinical efficacy of composite or ceramic better for inlays and onlays manufacturing?

Searches
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) will be searched without any date or language restriction

Types of study to be included
Inclusion criteria: Prospective randomized clinical studies or trials comparing at least two esthetic materials for inlay/onlay manufacturing (at least one ceramic and at least one composite).
Exclusion criteria: in vitro study, review, retrospective study, non randomized study, only one inlay-onlay material evaluated, more than one ceramic but no composite evaluated, more than one composite but no ceramic evaluated.

Condition or domain being studied
Dental caries is a common disease. Inlay or onlay restoration is widely used to treat the resulting tooth substance loss.

Participants/ population
Adults (18-90 years' old).

Intervention(s), exposure(s)
Composite inlays or onlays.

Comparator(s)/ control
Ceramic inlays or onlays.

Context
All dental clinical settings are accepted.

Outcome(s)
Primary outcomes
Clinical performance of the dental restorations (USPHS criteria, CDA criteria, FDI criteria...)
Inclusion criteria: minimum follow-up period of 6 months.
Exclusion criteria: Follow-up < 6 months.
Secondary outcomes
None.

Data extraction, (selection and coding)
Titles and then abstracts of studies retrieved using the search strategy will be screened independently by two review authors (HFC and VSF) to identify studies that potentially meet the inclusion criteria outlined above. The reasons for exclusion will be reported in a table.
The full text of the potentially eligible studies will be retrieved and independently assessed for eligibility by the same authors. Again, the reasons for exclusion will be reported in a table so that the reports selection will be completely transparent.
A standardised, pre-piloted form will be used to extract data from the included studies for assessment of study quality and evidence synthesis. Extracted information will include: risk of bias (according to the Cochrane risk of bias tool), methods used (rubber dam isolation, base or liner application, adhesive and cement used), participants treated (number of patients treated, number of inlays or onlays manufactured, number of operators), intervention

characteristics (materials used and manufacturing technique(s)), outcomes (USPHS, CDA, FDI, failures)

Risk of bias (quality) assessment
The risk of bias of each clinical study will be assessed using the Cochrane risk of bias tool.

Strategy for data synthesis
The data to be used will be aggregate (those reported in the reports). A quantitative synthesis is planned if similar outcomes are reported in different reports, with a similar follow-up duration, otherwise, a narrative synthesis is planned.

Analysis of subgroups or subsets
None planned.

Dissemination plans
A paper will be submitted to a leading journal in this field.
Furthermore, should the review include a few clinical trials with a low risk of bias, a recommendation will be prepared according to the GRADE process.

Contact details for further information
Helene Fron Chabouis
1 rue Maurice Arnoux
92120 Montrouge
helene.fron@parisdescartes.fr

Organisational affiliation of the review
Universite Paris Descartes, URB2i / EA4462
http://recherche.parisdescartes.fr/ea4462

Review team
Dr Helene Fron Chabouis, Université Paris Descartes (URB2i, EA4462), 92120 Montrouge ; Hôpital Charles Foix (Service d'odontologie), 94200 Ivry sur Seine
Dr Jean-Pierre Attal, Université Paris Descartes (URB2i, EA4462), 92120 Montrouge ; Hôpital Charles Foix (Service d'odontologie), 94200 Ivry sur Seine
Dr Violaine Smail Faugeron, Université Paris Descartes (URB2i, EA4462), 92120 Montrouge ; Hôpital Bretonneau (Service d'odontologie), 75018 Paris

Details of any existing review of the same topic by the same authors
None.

Anticipated or actual start date
20 November 2012

Anticipated completion date
31 January 2013

Funding sources/sponsors
Université Paris Descartes, Faculté de chirurgie dentaire, EA 4462 / URB2i (Montrouge) ; Université Paris 13, Ecole doctorale Galilée (Villetaneuse) ; Hôpital Charles Foix, Service d'odontologie (Ivry sur Seine) ; PRES Sorbonne Paris Cité

Conflicts of interest
None known

Language
English

Country
France

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Composite Resins; Dental Bonding; Dental Porcelain; Dental Restoration, Permanent; Dentin-Bonding Agents; Humans; Inlays; Resin Cements

Any other information
The drafting of this review has been undertaken as part of a PhD thesis and as part of the planning for a randomised trial to compare composite and ceramic for inlays and onlays manufacturing (the CECOIA trial: http://cecoia.fr).

Date of registration in PROSPERO
02 January 2013

Date of publication of this revision
28 March 2013

Details of final report/publication(s)

Stage of review at time of this submission	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes
Prospective meta-analysis	No	No

Appendix 4. Records identified through the systematic search

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Appendix 5. Record selection and reasons for exclusion on the basis of the title and abstract

Record n°	Selection on title		Selection on abstract		Comments concerning clinical studies					
	I/E	*Reason for exclusion*	*I/E*	*Reason for exclusion*	*N patients*	*N teeth*	*Follow up*	*Material*	*Technique*	*Restoration*
1	I		E	In vitro						
2	E	In vitro								
3	I		E	In vitro						
4	I		E	In vitro						
5	I		E	In vitro						
6	E	In vitro								
7	I		E	In vitro						
8	E	In vitro								
9	I		E	In vitro/no follow up	-	53	0	Ce8	CC	I
10	E	In vitro								
11	E	In vitro								
12	E	In vitro								
13	E	In vitro								
14	E	In vitro								
15	E	In vitro								
16	E	In vitro								
17	E	In vitro								

18	E	Not IO								
19	E	In vitro								
20	E	In vitro								
21	E	In vitro								
22	E	In vitro								
23	E	In vitro								
24	I		E	In vitro						
25	I		E	Comparison: IO materials (but no ceramic)	?	?	3 y.	Co6 Co7	T	?
26	E	Not IO								
27	I		E	In vitro						
28	I		I	Comparison: IO materials	43	80	3 y.	Ce4 Co5	CC	I
29	E	Not IO								
30	I		E	In vitro						
31	I		E	Comparison: luting agent	34	96	6 y.	Ce1	T	IO
32	I		E	Comparison: luting agent	39	98	51 m.	Ce2	T	I
33	I		E	In vitro						
34	I		E	Comparison: luting agent	34	96	12 y.	Ce1	T	IO
35	I		E	No control	20	50	4 y.	Ce10	T	I
36	I		E	No control	20	50	2 y.	Ce10	T	I
37	E	In vitro								
38	E	In vitro								
39	I		E	Comparison: IO materials but no	25	80	28 m.	Ce3 Ce4	T CC	IO

				composite						
40	I		I	Comparison: IO manufacturing	73	270	2.3-5 y.	Gold, 5 Ce, 2 Co	Mostly T, some CC	I
41	E	In vitro								
42	E	In vitro								
43	I		E	In vitro						
44	E	In vitro								
45	E	In vitro								
46	E	Not IO								
47	I		E	No control	28	50	4 y.	Ce5	CC	I
48	E	Review								
49	E	In vitro								
50	E	In vitro								
51	E	In vitro								
52	E	Case report								
53	I		E	In vitro						
54	I		E	No follow up	-	80	0	Co1, Ce1	T	I
55	I		E	In vitro						
56	I		I	Comparison: IO materials	47	94	2 y.	Ce, Co	T	O
57	I		E	Review						
58	I		I	Comparison: IO materials	15	36	75 m.	Ce1, Co4	T	I
59	I		I	Comparison: IO materials	15	36	60 m.	Ce1, Co4	T	I
60	E	In vitro								

61	I		E	Comparison: luting agent	31	94	4 y.	Ce1	T	I
62	I		E	Comparison: luting agent	16	39	6 y.	Ce1	T	I
63	I		E	Comparison: luting agent	34	96	8 y.	Ce1	T	I
64	I		E	Comparison: luting agent	24	57	4 y.	Ce2	T	I
65	I		E	Comparison: luting agent	31	94	8 y.	Ce1	T	I
66	I		E	Comparison: luting agent	34	96	4 y.	Ce1		
67	I		E	In vitro						
68	I		E	Comparison: base material	101	173	0	Ce6	CC	I
69	E	In vitro								
70	I		E	In vitro						
71	I		E	No control	51	99	53 m.	Co4	T	I
72	E	In vitro								
73	I		E	In vitro						
74	E	In vitro								
75	I		E	In vitro						
76	I		E	In vitro						
77	I		I	Comparison: IO materials	45	71	3 y.	Co1 Co2 Co3 Ce1	T	I
78	I		I	Comparison: IO materials	45	71	2 y.	Co1 Co2 Co3	T	I

								Ce1		
79	E	In vitro								
80	I		E	In vitro						
81	I		E	In vitro						
82	E	In vitro								
83	E	In vitro								
84	I		E	Not IO	-	33	8 y.	Cerana	-	inserts
85	I		E	Comparison: IO materials but no composite	20	80	5 y.	Ce1 Ce10 Ce5 gold	T T CC T	I
86	I		E	Comparison: luting agent	25	43	18 m.	Co4	T	IO
87	E	In vitro								
88	I		E	In vitro						
89	I		I		230	?	2 y.	Co8 Co10 Ce11 Ce8	T T T CC	IO
90	E	In vitro								
91	I		E	No control	108	200	10 y.	Ce13	CC	IO
92	I		E	Comparison: IO materials but no composite	16	32	8 y.	Ce7 Ce8	CC	I
93	I		E	Comparison: luting agent	31	62	4 y.	Ce9	T	IO
94	I		E	No control	794	2328	-	Ce5	CC	I
95	E	In vitro								

96	E	In vitro								
97	I		E	In vitro						
98	I		E	In vitro						
99	E	In vitro								
100	E	Not CS								
101	E	In vitro								
102	E	In vitro								
103	I		E	In vitro						
104	E	In vitro								
105	I		E	In vitro						
106	I		I	Comparison: IO materials	45	71	3 y.	Co1 Co2 Co3 Ce1	T	I
107	I		E	In vitro						
108	E	In vitro								
109	I		E	In vitro						
110	I		E	No control	390	810	17.3 m.	Ce1	T	IO
111	I		E	In vitro						
112	E	In vitro								
113	I		E	Comparison: luting agent	27	66	10 y.	Ce7	CC	I
114	I		E	Comparison: luting agent	27	66	5 y.	Ce7	CC	I
115	I		E	Comparison: luting agent	27	66	2 y.	Ce7	CC	I
116	I		E	In vitro						
117	E	In vitro								
118	E	In vitro								

119	E	In vitro								
120	E	In vitro								
121	E	In vitro								
122	E	In vitro								
123	I		E	In vitro						
124	I		E	No control	36	130	2 y.	Ce1	T	IO
125	I		E	Comparison: luting agent	30	83	1 y.	Ce1	T	IO
126	I		I	Comparison: IO materials	37	58	1 y.	Ce5 Co8 Ce12 Co9	CC T T T	I
127	I		I	Comparison: IO materials	37	58	5 y.			
128	I		I	Comparison: IO materials	37	58	10 y.			
129	E	In vitro								
130	E	In vitro								
131	E	In vitro								
132	E	In vitro								
133	I		E	Comparison: luting agent	29	79	5 y.	Ce1	T	I
134	I		E	Comparison: luting agent	50	118	6 y.	Feldspathic ?		
135	I		E	In vitro						
136	I		E	Comparison: luting agent	29	79	2 y.	Ce1	T	I
137	I		E	Comparison: IO materials (heat treatment)	-	30	3 y.	Co	T	I

				but no ceramic						
138	I		E	In vitro						
139	I		E	Comparison: IO materials but no ceramic	?	345	3 y.	Co ? Co4	T	I
140	E	In vitro								
141	I		E	In vitro						
142	E	In vitro								
143	I		E	In vitro						
144	I		E	In vitro						
145	I		E	In vitro						

Restoration: I: inlay or O: onlay or IO: inlay/onlay

I/E: I: inclusion; E: exclusion

Reasons of exclusion: Not IO: intervention does not involve inlays or onlays

Follow-up: m: months, y: years

Material: Ce: ceramics (Ce1: IPS Empress, Ce2: Cergogold, Ce3: e.max Press, Ce4: ProCad, Ce5: Cerec blocks, Ce6: Celay, Ce7: Vita Mk II, Ce8: Dicor, Ce9: IPS Empress 2, Ce10: Mirage 2 (fibre-reinforced), Ce11: Cerinate, Ce12: Vitadur N, Ce13: Vita MkI), Co: composite (Co1: Tetric, Co2: Blend-a-lux, Co3:Pertac-Hybrid Unifil, Co4: Targis, Co5: Paradigm, Co6: Admira, Co7: Grandio, Co8: Brilliant DI, Co9: Estilux, Co10: P-50)

Technique: T: traditional (restoration generally made by a dental technician, else made by the practitioner himself), CC: CAD-CAM

Appendix 6. Record selection on the basis of the full text

Study	Reference no.	Language	I/E	Reason for exclusion
1	28	English	I	
2	40	German	E	In fact a retrospective study: among 407 inlays that had been done with various materials, 260 inlays (made of different 9 materials) were randomly selected to be evaluated after 2 years (and 3 or 5 years for the oldest inlays): “Für den statistischen Vergleich wurden nach dem Zufallsprinzip von jedem Inlay 30 Zähne ausgewählt und im 2-, 3- und 5-Jahresvergleich ausgewertet.”
3	56	English	E	No randomization reported
4	58, 59	French	E	No randomization reported
5	77, 78, 106	English	E	Not true randomization. In smaller cavities: composite randomized; in larger cavities: ceramic.
6	90	English	E	Not a real clinical study since evaluations consist only in impressions and no clinical evaluation was made. Randomization is also unclear: “specimens were selected on a randomized basis”, but 4 inlay systems were used and the number of restorations per system varies greatly (Cerec: 120, Cerinate: 50, Brilliant: 30, P-50: 30). Note that one or more specific cements were used for each inlay system (total= 6 cements).
7	126, 127, 128	English	I	

Appendix 7. Risk of bias tables

Fasbinder trial

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentionned
Allocation concealment (selection bias)	Low risk	"the operator opened the enveloppe containing the random assignment"
Standardization (preparation, adhesive and luting procedure)	Low risk	Random assignment just before milling, same adhesive and luting procedure for both materials.
Blinding of patients (performance bias)	Unclear risk	Not mentionned
Bias of clinical outcome assessment (detection bias)	Low risk	Operators did not participate in baseline evaluation. 1 operator participated in the recall evaluations but there was 2 independent evaluators (then consensus).
Blinding of radiographic outcome assessment (detection bias)	Unclear risk	No radiographic examination mentionned
Incomplete outcome data (attrition bias)	High risk	9 inlays lost to follow-up : 11.25%

Thordrup trial

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not mentionned
Allocation concealment (selection bias)	Unclear risk	Not mentionned
Standardization (preparation, adhesive and luting procedure)	High risk	Preparation differed depending on the material ("greatest divergence of the occlusal walls was required for Brilliant DI and the least for the Cerec group"). "Cementation procedure was similar for all groups"
Blinding of patients (performance bias)	High risk	"No blinding of inlays and patients was possible since each type of inlay material was easily recognized"
Bias of clinical outcome assessment (detection bias)	Unclear risk	1 year report : "Assessments of 3 independent observers as well as 2 independent registrations for one observer were evaluated for the CDA index" 10 year report : "the observer performed 2 independent registrations on 11 inlays."
Blinding of radiographic outcome assessment (detection bias)	Unclear risk	Not mentionned
Incomplete outcome data (attrition bias)	High risk	10.3% inlays lost to follow-up / 10.8% patients lost to follow-up

Appendix 8. The HERMES program: the 3 tabs of the Excel interface

A. The « Homepage » tab

HERMES

HElp for Randomization Methods Evaluation through Simulations

Hélène Fron Chabouis and Francis Chabouis

The **aim** of the HERMES software is to help investigators choose
the most appropriate randomization method when they are planning for a new clinical trial.
The parameters of the clinical trial (e.g. sample size, number of prognostic factors and operators)
are taken into account.
The methods that can be compared are stratification methods (with various block sizes)
and minimization methods (including more or less randomness).

To compare these methods, indicators of balance between treatments
and an indicator of predictability for operators are computed.

How does it work?

1. Fill in the fields of the "Simulations" tab and click on the "Launch" button.
2. Then the results in terms of the method's balance and predictability will appear on the "Results" tab

For more explanations

You can consult the article entitled :
Randomization in clinical trials: stratification or minimization? The HERMES free simulation software
published in *Clinical Oral Investigations* in 2013

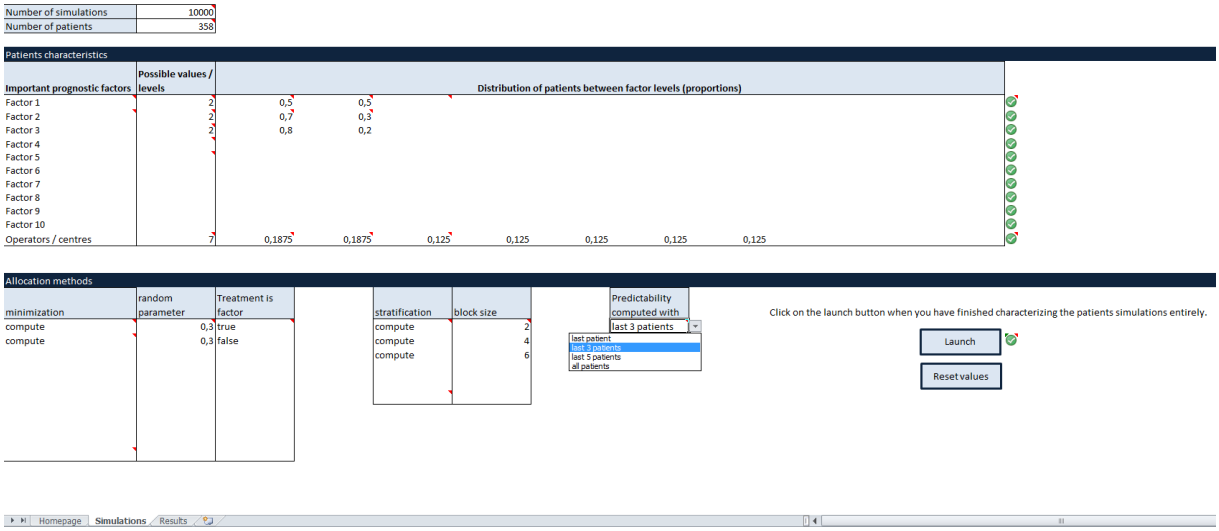
This software can be downloaded at the following address: http://chabouis.fr/helene/hermes/.
If you have any question, please contact Hélène FRON CHABOUIS : helene.fron@parisdescartes.fr

How to cite this work ?
Either : The Hermes program, Version 1.0 (Hélène Fron & Francis Chabouis), downloaded from http://chabouis.fr/helene/hermes/
Or : cite the above mentionned article

Homepage | Simulations | Results

B. The « Simulations » tab

The "Simulations" tab is filled with the characteristics of the Cecoia trial: 358 patients/teeth should be randomized, including an expected 50% inlays and 50% onlays, 30% premolars and 70% molars, 80% vital teeth and 20% non vital teeth.



C. The « Results » tab

	parameters			Predictability		Overall imbalance		Criterias imbalance			
Type	Random Factor	Treatment is Factor	Block Size	Average	standard deviation	Average	standard deviation	Average	standard deviation	min	max
Minimisation	0,3	true		53,54%	2,67%	0,47%	0,48%	3,58%	4,05%	0,00%	57,89%
Minimisation	0,3	false		53,87%	2,73%	0,53%	0,51%	3,29%	3,76%	0,00%	47,06%
Stratification			2	56,59%	2,70%	0,95%	0,76%	2,09%	1,98%	0,00%	20,00%
Stratification			4	53,02%	2,65%	1,38%	1,07%	3,02%	2,72%	0,00%	23,53%
Stratification			6	52,17%	2,71%	1,40%	1,11%	2,84%	2,68%	0,00%	26,98%

Homepage Simulations Results

Appendix 9. VBA code for the simulations.

A. «Main » module

```
'*************************************************************************************************************************************
'*
'*   HERMES software and its VBA code are under a Creative Commons Attribution-NonCommercial-ShareAlike 3.0 Unported License
'*   (2013-...)
'*
'*************************************************************************************************************************************
Option Explicit
Option Base 0
Sub MainSub()
Dim nbMinimisation, nbStratification, nbSimulations, simulation, allocationMethod, blocksize, memory, totalGlobalAverage, criteria, criteriaValue, nbOverallUnexistentBalance, nbCriteriaUnexistentBalance As Long
Dim randomFactor, nbAllocationMethods, prediction, balance As Double
Dim predictAverage(), predictStdev(), overallBalanceAverage(), overallBalanceStdev(), criteriaBalanceAverage(), criteriaBalanceStdev(), minBalance(), maxBalance() As Double
Dim treatmentIsFactor As Boolean
If Range("check") <> 1 Then
    MsgBox ("Incorrect inputs. Patients characteristics must be correct and at least one randomization method selected.")
Else
nbMinimisation = count("minimisation")
nbStratification = count("stratification")
nbAllocationMethods = nbMinimisation + nbStratification
ReDim predictAverage(nbAllocationMethods)
ReDim predictStdev(nbAllocationMethods)
ReDim overallBalanceAverage(nbAllocationMethods)
ReDim overallBalanceStdev(nbAllocationMethods)
ReDim criteriaBalanceAverage(nbAllocationMethods)
ReDim criteriaBalanceStdev(nbAllocationMethods)
ReDim minBalance(nbAllocationMethods)
ReDim maxBalance(nbAllocationMethods)
memory = predictionSetting(Range("predictSetting"))
nbSimulations = Range("nbSimulations")
Call setEqualConstant(minBalance, 1)
Call setEqualConstant(maxBalance, 0)

Application.ScreenUpdating = False
Call clearResultsSheet
Call initialisation
totalGlobalAverage = sumInArray(criteriasPossibleValues) * nbSimulations
For simulation = 0 To nbSimulations - 1
    Call launchSimulation
    For allocationMethod = 0 To (nbAllocationMethods - 1)
        If allocationMethod <= nbMinimisation - 1 Then
            randomFactor = Range("minimisation").offset(allocationMethod, 1)
            treatmentIsFactor = Range("minimisation").offset(allocationMethod, 2)
            Call minimisationAlloc(randomFactor, treatmentIsFactor) 'minimisation is called !
        Else
            blocksize = Range("stratification").offset(allocationMethod - nbMinimisation, 1)
            Call stratificationAlloc(blocksize) 'stratification is called !
        End If
        prediction = predict(allocation, memory)
        predictAverage(allocationMethod) = predictAverage(allocationMethod) + prediction / nbSimulations
        predictStdev(allocationMethod) = predictStdev(allocationMethod) + prediction ^ 2 / nbSimulations
        balance = balancePerCriteria("null", 0)
        If balance = -1 Then
            balance = 0
            nbOverallUnexistentBalance = nbOverallUnexistentBalance + 1
        End If
        overallBalanceAverage(allocationMethod) = overallBalanceAverage(allocationMethod) + balance / nbSimulations
        overallBalanceStdev(allocationMethod) = overallBalanceStdev(allocationMethod) + balance ^ 2 / nbSimulations
        For criteria = 0 To nbCriteria - 1
            For criteriaValue = 0 To criteriasPossibleValues(criteria) - 1
                balance = balancePerCriteria(criteria, criteriaValue)
                If balance = -1 Then
                    balance = 0
                    nbCriteriaUnexistentBalance = nbCriteriaUnexistentBalance + 1
                End If
                criteriaBalanceAverage(allocationMethod) = criteriaBalanceAverage(allocationMethod) + balance / totalGlobalAverage
                criteriaBalanceStdev(allocationMethod) = criteriaBalanceStdev(allocationMethod) + balance ^ 2 / totalGlobalAverage
                If balance < minBalance(allocationMethod) Then minBalance(allocationMethod) = balance
                If balance > maxBalance(allocationMethod) Then maxBalance(allocationMethod) = balance
            Next criteriaValue
        Next criteria
    Next allocationMethod
Next simulation
Call computeStdev(predictAverage, predictStdev, predictStdev)
If nbOverallUnexistentBalance <> 0 Then Call multiplyByScalar(overallBalanceAverage, nbSimulations / (nbSimulations - nbOverallUnexistentBalance))
If nbCriteriaUnexistentBalance <> 0 Then Call multiplyByScalar(criteriaBalanceAverage, totalGlobalAverage / (totalGlobalAverage - nbCriteriaUnexistentBalance))
Call computeStdev(overallBalanceAverage, overallBalanceStdev, overallBalanceStdev)
Call computeStdev(criteriaBalanceAverage, criteriaBalanceStdev, criteriaBalanceStdev)
For allocationMethod = 0 To (nbAllocationMethods - 1)
    If allocationMethod <= nbMinimisation - 1 Then
        Range("result").offset(allocationMethod, 0) = "Minimisation"
        Range("result").offset(allocationMethod, 1) = Range("minimisation").offset(allocationMethod, 1)
        Range("result").offset(allocationMethod, 2) = Range("minimisation").offset(allocationMethod, 2)
    Else
        Range("result").offset(allocationMethod, 0) = "Stratification"
        Range("result").offset(allocationMethod, 3) = Range("stratification").offset(allocationMethod - nbMinimisation, 1)
    End If
    Range("result").offset(allocationMethod, 4) = predictAverage(allocationMethod)
    Range("result").offset(allocationMethod, 5) = predictStdev(allocationMethod)
    Range("result").offset(allocationMethod, 6) = overallBalanceAverage(allocationMethod)
    Range("result").offset(allocationMethod, 7) = overallBalanceStdev(allocationMethod)
    Range("result").offset(allocationMethod, 8) = criteriaBalanceAverage(allocationMethod)
    Range("result").offset(allocationMethod, 9) = criteriaBalanceStdev(allocationMethod)
    Range("result").offset(allocationMethod, 10) = minBalance(allocationMethod)
    Range("result").offset(allocationMethod, 11) = maxBalance(allocationMethod)
Next allocationMethod
Application.ScreenUpdating = True
Range("result").Select
End If
End Sub
```

B. . « Simulation » module

```
Option Explicit
Option Base 0
Public patients(), criteriasProbas(), allocation(), criteriasPossibleValues(), nbPatients, nbCriteria, nbOperators As Long
Sub initialisation()
Dim i, j, check, nbCriteriaGlobal As Long
nbPatients = Range("nbPatients")
ReDim allocation(nbPatients - 1)
check = 0
nbCriteria = 0
nbCriteriaGlobal = 0 '=nbCriteria + (1 if nbOperators>1)
nbOperators = Range("operator")
For i = 1 To 10
    If Range("characteristics").offset(i - 1, 0) > 0 Then
        If check = 0 Then
            nbCriteria = nbCriteria + 1
        Else
            MsgBox ("No holes are allowed between criterias")
            End
        End If
    Else
        check = 1
    End If
Next i
nbCriteriaGlobal = nbCriteria
If (nbOperators > 1) Then nbCriteriaGlobal = nbCriteriaGlobal + 1
ReDim criteriasProbas(9, nbCriteriaGlobal - 1)
ReDim criteriasPossibleValues(nbCriteriaGlobal - 1)
ReDim patients(nbPatients - 1, nbCriteriaGlobal - 1)
For i = 0 To 9
    For j = 0 To nbCriteria - 1
        criteriasProbas(i, j) = Range("characteristics").offset(j, i + 1)
    Next j
    If (nbOperators > 1) Then criteriasProbas(i, nbCriteria) = Range("operator").offset(0, i + 1)
Next i
For i = 0 To nbCriteria - 1
    criteriasPossibleValues(i) = Range("characteristics").offset(i, 0)
Next i
If (nbOperators > 1) Then criteriasPossibleValues(nbCriteria) = Range("operator")
nbCriteria = nbCriteriaGlobal
End Sub
```

```
Function randomAlloc(table As Variant, column As Long)
Randomize
Dim i As Long
Dim random, value As Double
random = Rnd
i = 0
value = table(0, column)
While random > value
    i = i + 1
    value = value + table(i, column)
Wend
randomAlloc = i
End Function
```

```
Public Sub launchSimulation()
Dim patient, criteria As Long
For patient = 0 To nbPatients - 1
    For criteria = 0 To nbCriteria - 1
        patients(patient, criteria) = randomAlloc(criteriasProbas, criteria)
    Next criteria
Next patient
End Sub
```

C. « Minimisation » module

```
Option Explicit
Option Base 0
```

```
Sub transformPatientForMini(ByVal patient As Long, result As Variant)
Dim i, value, sum As Long
sum = 0
value = 0
result(0) = 0
For i = 0 To nbCriteria - 1
    value = patients(patient, i)
    result(value + sum + 1) = 1
    sum = sum + criteriasPossibleValues(i)
Next i
End Sub
```

```
Sub minimisationAlloc(ByVal randomFactor As Double, treatmentIsFactor As Boolean)
Dim patient, treatmentP1(), treatmentM1(), treatmentP1hypothesis(), treatmentM1hypothesis(), patientCharac(), temp() As Long
Dim lenght, unbalanceP1, unbalanceM1, treatment As Long
lenght = sumInArray(criteriasPossibleValues)
ReDim treatmentP1(lenght)
ReDim treatmentM1(lenght)
ReDim treatmentP1hypothesis(lenght)
ReDim treatmentM1hypothesis(lenght)
ReDim patientCharac(lenght)
ReDim temp(lenght)
For patient = 0 To nbPatients - 1
    Call transformPatientForMini(patient, patientCharac)
    Call sumArray(treatmentP1, patientCharac, treatmentP1hypothesis)
    Call sumArray(treatmentM1, patientCharac, treatmentM1hypothesis)
    If treatmentIsFactor Then
        treatmentP1hypothesis(0) = treatmentP1hypothesis(0) + 1
        treatmentM1hypothesis(0) = treatmentM1hypothesis(0) + 1
    End If
    Call diffArray(treatmentP1hypothesis, treatmentM1, temp)
    unbalanceP1 = squaredNorm(temp)
    Call diffArray(treatmentM1hypothesis, treatmentP1, temp)
    unbalanceM1 = squaredNorm(temp)
    treatment = 1
    If unbalanceP1 > unbalanceM1 Then
        treatment = -1
    End If
    If unbalanceP1 = unbalanceM1 Then
        If bernouilli(0.5) Then
            treatment = -treatment
        End If
    ElseIf bernouilli(randomFactor) Then
        treatment = -treatment
    End If
    If treatment = 1 Then
        Call setEqualArray(treatmentP1hypothesis, treatmentP1)
    Else
        Call setEqualArray(treatmentM1hypothesis, treatmentM1)
    End If
    allocation(patient) = (treatment + 1) / 2
    Call setEqualArray("null", temp)
    Call setEqualArray("null", patientCharac)
Next patient
End Sub
```

D. « Stratification » module

```
Option Explicit
Option Base 0
```

```
Function blockGeneration(blocksize As Long) As Variant
Dim block() As Long
ReDim block(blocksize - 1)
Dim value As Double
If (blocksize Mod 2 <> 0) Then
    MsgBox ("Incorrect parameter, block size must be even")
    End
Else
    Dim remainingAlloc, remainingSize, i As Long
    remainingAlloc = blocksize / 2
    remainingSize = blocksize
    For i = 0 To blocksize - 1
        value = bernouilli(remainingAlloc / remainingSize)
        block(i) = value
        If value = 1 Then remainingAlloc = remainingAlloc - 1
        remainingSize = remainingSize - 1
    Next i
End If
blockGeneration = block
End Function
```

```
Function nextCharacteristic(ByVal currentCharacteristic As Double, criteriasPossibleValues As Variant) As Double   'd
Dim size, cc, test As Double   'd
cc = currentCharacteristic
size = UBound(criteriasPossibleValues, 1)
Dim i As Long
i = 0
cc = cc + 10 ^ (size + 1)
While i <= size
    test = Mid(cc, size - i + 2, 1)
    If (test + 1 < criteriasPossibleValues(size - i) And test <> 9) Then
        cc = cc + 10 ^ i
        nextCharacteristic = cc - 10 ^ (size + 1)
        Exit Function
    Else
        cc = cc - (criteriasPossibleValues(size - i) - 1) * 10 ^ i
        i = i + 1
    End If
Wend
nextCharacteristic = 0 '0 is returned if the last alloc is reached
End Function
```

```
Sub stratificationAlloc(ByVal blocksize As Long)
Dim i, nbAlloc, flexibleSize, patient, patientCharacteristics, nbPossibleCharac As Long
nbPossibleCharac = 1
Dim stratificationTable(), availableRows, characteristicsList(), currentAlloc() As Double  'd
availableRows = 0
For i = 0 To nbCriteria - 1


    nbPossibleCharac = nbPossibleCharac * criteriasPossibleValues(i)
Next i
ReDim currentAlloc(nbPossibleCharac)
ReDim characteristicsList(nbPossibleCharac)
characteristicsList(0) = 0
For i = 1 To nbPossibleCharac - 1 'characteristics references are filled
    characteristicsList(i) = nextCharacteristic(characteristicsList(i - 1), criteriasPossibleValues)
Next i
For i = 0 To nbPossibleCharac - 1
    currentAlloc(i) = 1
Next i
ReDim stratificationTable(nbPossibleCharac - 1, 0) ' this table is transposed compared to others, as redim works only on the last dimension
For patient = 0 To nbPatients - 1
    patientCharacteristics = getPatientCharacteristics(patient)
    i = 0
    While patientCharacteristics <> characteristicsList(i)
        i = i + 1
    Wend
    If currentAlloc(i) > availableRows Then
        Call fillOneBlock(stratificationTable, blocksize)
        availableRows = availableRows + blocksize
    End If
    allocation(patient) = stratificationTable(i, currentAlloc(i))
    currentAlloc(i) = currentAlloc(i) + 1
Next patient
End Sub
```

```
Sub fillOneBlock(table As Variant, blocksize As Long)
Dim nbRows, nbColumns, i, j As Long
Dim newBlock As Variant
nbRows = UBound(table, 1)
nbColumns = UBound(table, 2)
ReDim Preserve table(nbRows, nbColumns + blocksize)
For i = 0 To nbRows
    newBlock = blockGeneration(blocksize)
    For j = 0 To blocksize - 1
        table(i, j + nbColumns + 1) = newBlock(j)
    Next j
Next i
End Sub
```

E. « Balance » module

```
Option Explicit
Option Base 0
Function balancePerCriteria(criteria As Variant, ByVal criteriaVal As Long) As Double 'criteria="null" <=> treatment balance regardless of any criteria
Dim alloc, total, patient As Double
Dim countAll As Boolean
countAll = False
If VarType(criteria) = 8 And criteria = "null" Then
    criteria = 0
    countAll = True
End If
For patient = 0 To nbPatients - 1
    If patients(patient, criteria) = criteriaVal Or countAll Then
        total = total + 1
        If allocation(patient) = 1 Then
            alloc = alloc + 1
        End If
    End If
Next patient
If total <> 0 Then
    balancePerCriteria = 2 * Abs((alloc / total) - 0.5)   'calculates balance difference between treatments 0 and 1
Else
    balancePerCriteria = -1
End If
End Function
```

F. « Prediction » module

```
Option Base 0
Public Function predict(ByRef allocation As Variant, ByVal memory As Long) As Double 'memory=0 <=> "all patients"
Dim temp(), tempOffset() As Long
Dim offset, i, patient, sum, prediction, CorrectPrediction, proportionOf1, unpredictable, nbUnpredictable, operator As Long
Dim oneOperator, firstPatient, goToNextPatient As Boolean
ReDim temp(nbPatients - 1)
ReDim tempOffset(nbPatients - 1)
CorrectPrediction = 0
unpredictable = 0
nbUnpredictable = 0
firstPatient = True
If nbOperators <= 1 Then oneOperator = True
For operator = 0 To nbOperators - 1
    For patient = 0 To nbPatients - 1
        If patients(patient, nbCriteria - 1) = operator Or oneOperator Then
            If firstPatient = True Then
                sum = allocation(patient)
                firstPatient = False
                i = 0
                goToNextPatient = True
                nbUnpredictable = nbUnpredictable + 1
            End If
            If goToNextPatient = False Then
                i = i + 1
                temp(i) = sum
                If memory <> 0 Then
                    If (i + memory <= nbPatients - 1) Then tempOffset(i + memory) = temp(i)
                    proportionOf1 = (temp(i) - tempOffset(i)) / min(i, memory)
                Else
                    proportionOf1 = (temp(i) - tempOffset(i)) / i
                End If
                If proportionOf1 > 0.5 Then
                    prediction = 0
                ElseIf proportionOf1 < 0.5 Then
                    prediction = 1
                Else
                    prediction = 0
                    unpredictable = 1
                    nbUnpredictable = nbUnpredictable + 1
                End If
                If prediction - allocation(patient) = 0 And unpredictable <> 1 Then
                    CorrectPrediction = CorrectPrediction + 1
                End If
                sum = sum + allocation(patient)
                unpredictable = 0
            Else
                goToNextPatient = False
            End If
        End If
    Next patient
    firstPatient = True
    sum = 0
Next operator
predict = CorrectPrediction / (nbPatients - nbUnpredictable)
End Function
```

G. « Useful functions » module

```
Option Explicit
Option Base 0
```

```
Public Function min(ByVal a As Double, ByVal b As Double)
If a <= b Then
    min = a
Else
    min = b
End If
End Function
```

```
Function bernouilli(p As Double) As Long
Randomize
Dim random As Double
random = Rnd
If random < p Then
    bernouilli = 1
Else
    bernouilli = 0
End If
End Function
```

```
Sub setEqualArray(source As Variant, destination As Variant)
Dim i, lenght As Long
lenght = UBound(destination, 1)
If VarType(source) = 8 Then 'if string => 0
    For i = 0 To lenght
        destination(i) = 0
    Next i
ElseIf lenght = UBound(source, 1) Then
    For i = 0 To lenght
        destination(i) = source(i)
    Next i
End If
End Sub
```

```
Sub setEqualConstant(vector As Variant, constant As Double)
Dim i, lenght As Long
lenght = UBound(vector, 1)
For i = 0 To lenght
    vector(i) = constant
Next i
End Sub
```

```
Sub multiplyByScalar(vector As Variant, scalar As Double)
Dim i, lenght As Long
lenght = UBound(vector, 1)
For i = 0 To lenght
    vector(i) = vector(i) * scalar
Next i
End Sub
```

```
Sub sumArray(a As Variant, b As Variant, result As Variant)
Dim i, lenght As Long
lenght = UBound(a, 1)
If (lenght = UBound(b, 1) And lenght = UBound(result, 1)) Then
    For i = 0 To lenght
        result(i) = a(i) + b(i)
    Next i
End If
End Sub
```

```
Sub diffArray(a As Variant, b As Variant, result As Variant)
Dim i, lenght As Long
lenght = UBound(a, 1)
If (lenght = UBound(b, 1) And lenght = UBound(result, 1)) Then
    For i = 0 To lenght
        result(i) = a(i) - b(i)
    Next i
End If
End Sub
```

```
Function squaredNorm(a As Variant) As Double
Dim i, lenght, result As Long
lenght = UBound(a, 1)
result = 0
For i = 0 To lenght
    result = result + a(i) ^ 2
Next i
squaredNorm = result
End Function
```

```
Function sumInArray(a As Variant) As Double
Dim i, lenght, result As Long
lenght = UBound(a, 1)
result = 0
For i = 0 To lenght
    result = result + a(i)
Next i
sumInArray = result
End Function
```

```
Public Function getPatientCharacteristics(ByVal patient As Long)
Dim i As Long
Dim value As Double
value = 0
For i = 0 To nbCriteria - 1
    value = value + patients(patient, nbCriteria - 1 - i) * 10 ^ i
Next i
getPatientCharacteristics = value
End Function
```

```
Function predictionSetting(excelLabel As String)
If excelLabel = "last patient" Then
    predictionSetting = 1
ElseIf excelLabel = "last 3 patients" Then
    predictionSetting = 3
ElseIf excelLabel = "last 5 patients" Then
    predictionSetting = 5
Else
    predictionSetting = 0
End If
End Function
```

```
Function count(cellName As Variant)
Dim i, nb As Long
i = 0
nb = 0
While Range(cellName).offset(i, 0) = "compute"
    nb = nb + 1
    i = i + 1
Wend
count = nb
End Function
```

```
Sub clearResultsSheet()
Sheets("Results").Select
Range("A3:L65536").Select
Selection.ClearContents
End Sub
```

```
Sub computeStdev(average As Variant, squarredAverage As Variant, result As Variant)
Dim i, lenght As Long
lenght = UBound(average, 1)
If (lenght = UBound(squarredAverage, 1) And lenght = UBound(result, 1)) Then
    For i = 0 To lenght
        result(i) = (squarredAverage(i) - average(i) ^ 2) ^ 0.5
    Next i
End If
End Sub
```

```
Sub ResetValues()
    Sheets("Simulations").Select
    Range("B4:B5").Select
    Selection.ClearContents
    Range("B9:L19").Select
    Selection.ClearContents
    Range("A24:C33").Select
    Selection.ClearContents
    Range("E24:F29").Select
    Selection.ClearContents
    Range("H24").Select
    Selection.ClearContents
End Sub
```

Appendix 10. Estimated budget of the CECOIA trial

PROJET 2011

PHRC National, Détail de la demande financière

Département de la Recherche Clinique et du Développement AP-HP

CODE PROJET :	AOM11206
NOM & TITRE INVESTIGATEUR :	Pr Jean-Pierre ATTAL
ETABLISSEMENT & SERVICE :	Service d'Odontologie, Hôpital Charles FOIX
TITRE DE L'ETUDE :	Essai randomisé multicentrique comparant la céramique et le composite dans le traitement des pertes de substance dentaires par inlays-onlays réalisés par CFAO : essai CECOIA
NOM DU CORRESPONDANT DRCD :	Moufida DABBECH
CREDITS ALLOUES :	236 700,00

Essai Médicament Non

0,00
à positionner

TYPES DE DEPENSES			DETAIL	e-OTP	2011	2012	2013	2014	TOTAL PROJET	Dont crédits gérés par l'URC N°
REMUNERATIONS DU PERSONNEL										
Personnel Médical	I	Temps médical (demi-journées)	sur CFX équivalent de 75 vacations de Prat. Attaché en année 1		7 500,00				7 500,00	
Personnel Non Médical	I	Coordinateur d'étude clinique	1 mois pour mise en place + 0,8 mois par année de projet		6 890,00	3 827,00	3 827,00	3 828,00	18 372,00	
Personnel Non Médical	I	Technicien de recherche clinique	5% ETP / an * 3 ans			1 861,00	1 861,00	1 862,00	5 584,00	
Personnel Non Médical	I	Assistant de Recherche Clinique	5% ETP / an * 3 ans			1 861,00	1 861,00	1 862,00	5 584,00	
Personnel Non Médical	I	Data Manager	1 mois					3 627,00	3 627,00	
Personnel Non Médical	I	Biostatisticien	2 mois					7 655,00	7 655,00	
Personnel Non Médical	I	Autre:	Opérateur de saisie : 1 mois					2 500,00	2 500,00	
SOUS TOTAL GROUPE I					14 390,00	7 549,00	7 549,00	21 334,00	50 822,00	0,00
DEPENSES MEDICALES										
FOURNITURES	II	Fournitures médicales	Kit d'évaluateur = 240€ / kit * 40 kits. Livraison centralisée sur CFX		9 600,00				9 600,00	
FOURNITURES	II	Fournitures de laboratoire	consommable pour CEREC par patient : 14 euros. A intégrer dans les conventions de reversement au pro-rata des patients inclus		3 612,00				3 612,00	
SOUS TOTAL GROUPE II					13 212,00	0,00	0,00	0,00	13 212,00	0,00
DEPENSES HOTELIERES ET GENERALES										
DIVERS	III	Fournitures de bureau	suivi du projet		1 251,00				1 251,00	
DIVERS	III	Frais d'impression et de publication	publications en open access et traduction d'un ou deux articles					3 000,00	3 000,00	
DIVERS	III	Affranchissements	1 lettre par patient par an=358 + 10 courriers 50g par opérateur		303,00	280,00	280,00	280,00	1 143,00	
DIVERS	III	Location d'équipement	location d'une unité CEREC pour CFAO : 30 000€ sur 3 ans : prise en charge par le service de l'année 1 et par le projet en année 2 et 3 (répartition en fonction du temps-machine consacré au projet sur 3 ans)				10 000,00	10 000,00	20 000,00	
SOUS-TRAITANCE	III	Cahier d'observation	358 patients - impression de 400 cahiers * 20 €		8 000,00				8 000,00	
SOUS-TRAITANCE	III	Randomisation	randomisation par chaque cabinet sur interface web		1 000,00				1 000,00	
DEPLACEMENTS	III	Missions (congrès, déplacements, ouvertures de centres)	1 réunion investigateurs / an : 5 personnes de Province + 6 personnes de Paris		948,00	948,00	948,00		2 844,00	
CONVENTION	III	Missions (congrès, déplacements, ouvertures de centres)	2 évaluateurs sur Lyon et Toulouse, 1 déplacemenet de 2 jours par mois, sur 3 ans		11 040,00	11 040,00	11 040,00		33 120,00	
CONVENTION	III	Missions (congrès, déplacements, ouvertures de centres)	4 personnes pour un congrès international					6 000,00	6 000,00	
CONVENTION	III	Missions (congrès, déplacements, ouvertures de centres)	1 déplacement par centre pour ouverture et pour fermeture des centres et un déplacement en année 2		900,00	900,00	900,00		2 700,00	
CONVENTION	III	Missions (congrès, déplacements, ouvertures de centres)	en début de projet + 2 investigateurs pour présentation attentes du projet		1 008,00				1 008,00	
SURCOUTS	III	Prestations médicales	pour les centres de ville (tps d'occupation du praticien hors activité libérale pour l'évaluation) : **100 €** par patient pour 208 patients. Pas de demande de Toulouse en termes de compensation		20 800,00				20 800,00	
SURCOUTS	III	Prestations médicales	Evaluateur : 60jours pour 358 patients à 200€ / jour x 3 ans			12 000,00	12 000,00	12 000,00	36 000,00	
PATIENTS	III	Indemnités versées aux volontaires sains / patients	358 patients à 100 euros par patient pour les 3 venues					35 800,00	35 800,00	
DIVERS	III	*FRAIS D'ASSURANCE*							0,00	
SOUS TOTAL GROUPE III					45 250,00	25 168,00	35 168,00	67 080,00	172 666,00	0,00
SOUS TOTAL (G1+G2+G3)					72 852,00	32 717,00	42 717,00	88 414,00	236 700,00	0,00
FRAIS DE GESTION (pris en charge par MERRI - part variable)					0,00				0,00	
GESTION PHARMACEUTIQUE DES ESSAIS CLINIQUES (pris en charge par MERRI - part variable)					0,00				0,00	
TOTAL GENERAL (Sous-total + Frais de gestion)					72 852,00	32 717,00	42 717,00	88 414,00	236 700,00	0,00

Appendix 11. Appendix document submitted to the call for proposals (PHRC national 2011)

PHRC 2011

Appel à projets national **DRCI : Île-de-France** **Projet n° _____**

Il est rappelé (cf. annexe 3) qu'un projet déposé dans le cadre de l'appel à projet national ne peut être déposé dans le cadre des appels à projets interrégionaux.

RESUME DU PROJET DE RECHERCHE

NB : La forme du dossier complet détaillant le projet est libre mais ce formulaire type doit être **obligatoirement** renseigné.

INVESTIGATEUR COORDONNATEUR : **Jean-Pierre ATTAL Foix**
(MCU-PH)

Téléphone : 01.58.07.68.02
Télécopie : 01.58.07.68.99
Courriel : jean-pierre.attal@parisdescartes.fr

ETABLISSEMENT PROMOTEUR : **APHPCharles Foix**

POLE D'ACTIVITE ou SERVICE :
Pôle : ASTA de l'hôpital Charles Foix
Service : Odontologie

Responsable de pôle ou chef de service
(Pr Louis Maman)
Signature pour aval

INVESTIGATEURS ASSOCIES :	POLES D'ACTIVITE ou SERVICES :	ETABLISSEMENTS DE SANTE :
- Hélène Fron (AHU)	- Odontologie	- Charles Foix (CSERD Ivry sur Seine)
- Cathy Nabet (MCU-PH)	- Odontologie	- Rangueil (CSERD de Toulouse)
- *Dr Christian Moussally*	- *Odontologie*	- *Cabinet (dentiste libéral, Paris)*
- *Dr Cyril Fonteneau*	- *Odontologie*	- *Cabinet (dentiste libéral, Paris)*
- *Dr Stéphane Cazier*	- *Odontologie*	- *Cabinet (dentiste libéral, Paris)*
- *Dr Caroline Prot*	- *Odontologie*	- *Cabinet (dentiste libéral, Lyon)*

Le cas échéant, préciser le nom du (ou des) METHODOLOGISTE(S) : Florence Gillaizeau, Gilles Chatellier et Pierre Durieux

Implication d'une structure de recherche clinique : **OUI ☑** NON ☐
Si OUI : CIC-P ☑ CIC-EC ☑ CIC-BT ☐ CIC-IT ☐ CTRS / RTRS *(préciser lesquels)*☐
Unité de recherche clinique ☑ Autres ☐

TITRE du projet de recherche : Essai randomisé multicentrique comparant la céramique et le composite dans le traitement des pertes de substance dentaires par inlays-onlays réalisés par CFAO : essai CECOIA

Durée du projet : 3 ans

Montant total demandé sur 4 ans arrondi au millier d'€ : / 239 000 € /
(détailler la demande en p.6)

Ce projet comporte-t-il l'utilisation ou la préparation de produits de thérapie cellulaire, de thérapie génétique ou de thérapie cellulaire xénogénique, ou la mise en œuvre ou l'évaluation de thérapeutiques mettant en œuvre de telles thérapies, ou l'utilisation, à des fins thérapeutiques, d'organes ou de tissus d'origine animale ?
OUI ☐ **NON ☑**

MOTS CLES :	Discipline médicale (*)	Maladie concernée	Axe prioritaire (**)
	/ Odontologie /	/ Maladie carieuse /	/ **2** Programme Blanc /

(*) : discipline de l'investigateur principal

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RESUME

Introduction La prévalence de la carie dentaire dans le monde est estimée à plus de 90% des adultes par l'OMS. Quand la perte de substance liée à la carie est de petit volume, un soin simple est réalisé. Lorsque la perte de substance est importante, les praticiens ont l'habitude de réaliser des couronnes qui présentent l'inconvénient d'être mutilantes. Il existe toutefois une technique intermédiaire, les inlays-onlays, de plus en plus employés, car très respectueux des tissus dentaires. Le métal étant rejeté par la population (corrosion, inesthétique, biocompatibilité), le praticien a le choix entre 2 matériaux : le composite et la céramique. La céramique est un matériau biocompatible et résistant à l'usure, mais cassant. Le composite est moins cassant, mais s'use.

Hypothèses Les études publiées dans la littérature ne permettent pas de choisir entre céramique et composite pour réaliser des inlays-onlays : défauts méthodologiques et absence d'essai clinique comparant ces deux matériaux. Ainsi, le choix entre inlay-onlay en composite ou en céramique varie en fonction des pays sans raison valable (en France, c'est souvent le composite qui est préféré, contrairement aux USA par exemple).

Objectifs. Principal : Comparer les performances cliniques des inlays-onlays en céramique et en composite.
Secondaire(s) : 1) Recherche des facteurs pronostiques du succès clinique des deux types de restaurations. 2) Evaluation des propriétés métrologiques de l'instrument international FDI d'évaluation des restaurations dentaires.

Critères d'évaluations. Principal : L'évaluation des inlays-onlays est réalisée avec l'instrument construit par la fédération dentaire internationale (FDI) à la suite d'une conférence de consensus. Il est composé de 3 dimensions (biologique, fonctionnelle et esthétique), composées chacune de plusieurs items qui sont évalués par examen clinique selon des échelles de Likert à 5 modalités. Certains items sont évalués de façon quantitative, d'autres de façon visuelle (un site internet permet la calibration des évaluateurs). **Secondaires** : Survie d'une restauration, EVA de la qualité globale de la restauration. **Recueil** : Tous les critères de jugement sont recueillis 1 semaine, 1 an et 2 ans après la restauration, par 2 évaluateurs (non opérateurs) indépendants.

Critères d'éligibilité : Patient âgé de 18 à 80 ans, capable de tolérer les procédures restauratrices nécessaires, mettant moins de 45mn à se rendre au centre, disponible pour la période de suivi ; présentant une dent postérieure nécessitant un inlay-onlay**. Critères de non éligibilité :** allergie à l'un des matériaux employés, bruxisme, maladie parodontale ou carieuse aiguë ou sévère, hygiène orale insuffisante ; dent support de prothèse adjointe, avec mobilité dentaire > II ou poches parodontales > 3mm. **Critère d'inclusion :** dent nécessitant un inlay-onlay après préparation**. Critères de non inclusion :** limites sous gingivales après préparation, isolation par champ opératoire (digue) impossible. **Critère d'exclusion** : inlay-onlay modifié par un dentiste ne participant pas à l'essai.

Méthodologie : Essai multicentrique randomisé ouvert en groupes parallèles.

Randomisation : Randomisation individuelle des traitements (composite ou céramique) par minimisation (allocation de façon dynamique), avec un élément aléatoire de 30%, afin de minimiser à la fois le déséquilibre entre les groupes et la prédictibilité de l'allocation. Les facteurs pronostiques principaux retenus à l'issue d'une revue de littérature sont : inlay/onlay, prémolaire/molaire, dent pulpée/dépulpée, opérateur. Une pré-étude a été réalisée à l'aide de 2 questionnaires (patient et opérateur) visant à vérifier l'acceptabilité de la randomisation pour les opérateurs et l'acceptabilité de l'inclusion et du suivi pour les patients. Les critères d'éligibilité ont été conçus afin de minimiser le nombre de perdus de vue (profils à risque).

Déroulement de l'étude : La randomisation sera réalisée immédiatement après l'inclusion. Les restaurations seront réalisées par CFAO (Conception et fabrication assistée par ordinateur), car cette technique est intéressante dans le cadre d'un essai clinique puisqu'elle permet de standardiser nombre de paramètres techniques et de supprimer la variabilité liée au prothésiste. Par ailleurs, c'est une technique d'avenir car elle permet de réaliser l'inlay-onlay en une seule séance au fauteuil. Le suivi des sujets est prévu sur 2 ans, avec recueil des critères de jugement lors de 3 rendez-vous de suivi (1 semaine, 1 an, 2 ans après l'inclusion).

Nombre de sujets nécessaires : 358 **Nombre d'opérateurs :** 10 358 sujets (179 dans chaque groupe) permettront de mettre en évidence une taille d'effet de 0,31 avec une puissance de 80%, un risque alpha de 1,7% (alpha global=5% pour 3 tests liés aux 3 dimensions), en tenant compte de l'effet opérateur (coefficient de corrélation intraclasse=0,02; 10 opérateurs). 0,31 correspond à la taille d'effet attendue du critère (item) le plus discriminant de la dimension biologique de l'instrument FDI (puissance suffisante pour les 2 autres dimensions car leurs critères les plus discriminants ont des tailles d'effet attendues>0.31).

Nombre de centres participant : 6 (2 CSERD et 4 dentistes libéraux). Le choix d'inclure des dentistes libéraux a pour but d'augmenter la validité externe de l'essai. Cette démarche prend de plus en plus d'importance aujourd'hui, dans le cadre de ce que nous appelons la « Practice based research ».
Nombre moyen d'inclusions par mois par centre : 5
Durée totale de l'étude : 3 ans **Période d'inclusion :** 1 an **Durée de participation pour un patient :** 2 ans

Perspectives : La mise en œuvre de cet essai constituerait une avancée considérable en dentisterie restauratrice, car il s'agirait du premier véritable essai clinique dans cette discipline (vrai calcul du NSN et randomisation…).

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Recherche biomédicale au sens de l'article L. 1121-1 du code de la santé publique OUI ☐ NON ☑

Si OUI : Identité du promoteur :

Si NON :

Recherche « non interventionnelle » mentionnée au 1° de l'article L. 1121-1 et à l'article R. 1121-2 du code de la santé publique OUI ☐ NON ☑

Recherche portant sur des « soins courants » mentionnée au 2° de l'article L. 1121-1 et à l'article R. 1121-3 du code de la santé publique **OUI ☑** NON ☐

Dans le cas où il s'agirait d'un projet d'essai thérapeutique portant sur des produits mentionnés à l'article L. 5311-1 du code de la santé publique, préciser les items suivants :

Essai réalisé sur des :

Patients ☐ Personnes ne présentant aucune affection et se prêtant volontairement à la recherche (volontaires sains)
☐ ou personnes malades pour lesquelles l'objet de la recherche est sans rapport avec leur état pathologique

Médicamenteux OUI ☐ **NON ☑**
Randomisé **OUI ☑** NON ☐

Phase (1, 2, 3 ou 4) / 3 – 4 /

Le risque encouru est justifié par :

Le bénéfice escompté pour la personne qui se prête à la recherche ☑
Le bénéfice escompté pour d'autres personnes ☑
Indemnisation en compensation des contraintes subies OUI ☐ NON ☐

Nombre de personnes dont l'inclusion est prévue dans le cadre du protocole de recherche : / 358 /

PROJET MULTICENTRIQUE **OUI ☑** NON ☐

Si OUI précisez les centres associés :

CHU : Charles Foix (Ivry) et Hôtel Dieu (Toulouse)

CLCC :

CHG, CHS :

ou le cas échéant médecins libéraux correspondants : *Dr Christian Moussally, Dr Cyril Fonteneau, Dr Alexandre Gaucher, Dr Caroline Prot*

PROJET MULTIDISCIPLINAIRE OUI ☐ **NON ☑**

Si OUI , disciplines concernées : /_____/ /_____/ /_____/

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CO-FINANCEMENT(S)

Le projet a-t-il été présenté à un autre financement : **OUI** ☑ NON ☐

Si OUI : ☐ PHRC (préciser le ou lesquels)

☐ Autre(s) (préciser le montant de la demande)

Le projet a-t-il obtenu un autre financement : **OUI** ☑ NON ☐

Le CSERD de Toulouse (Rangeuil) avait demandé et obtenu un financement Activité nouvelle pour faire une évaluation médico-économique des restaurations réalisées par CFAO directe. Celui-ci permet de dédommager les praticiens libéraux qui viennent comme attachés au centre pour réaliser les restaurations. Ce financement couvrira 7500 euros des dépenses occasionnées lors de la période d'inclusion pour les vacations des opérateurs.

Identité du ou des co-financeurs (s'il y a lieu) :

Nom :

Adresse :

Montant du co-financement :

Les industriels se sont engagés à fournir gracieusement les matériaux nécessaires (cf. annexe pages 36 à 39).

Association avec les organismes de recherche (préciser : Inserm, CNRS, CEA, INRA…) :

OUI ☐ **NON** ☑

Si OUI : nom et adresse de l'organisme :

Montant et destination du financement accordé par l'organisme de recherche :

Le projet a-t-il débuté : OUI ☐ **NON** ☑

Si OUI, quand ?

Appendix 12. Case report form (main pages)

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

CECOIA

Essai clinique randomisé multicentrique comparant la céramique et le composite dans le traitement des pertes de substance dentaires par inlays-onlays réalisés par CFAO : essai CECOIA

Essai AOM 11206 / Code Promoteur P110129/N° IDRCB : 2011-A01658-33

Cahier d'observation Version v1-0 du 14/08/2012	
N° du centre :	|0|0|__|
N° d'inclusion :	|0|__|__|__|
Nom :	|__| (1ère lettre du nom)
Prénom :	|__| (1ère lettre du prénom)
Dent :	|__|__|
Opérateur :	|__|__|__|

Investigateur coordonnateur :
Dr Jean-Pierre ATTAL
Service d'Odontologie, Hôpital Charles Foix
7 Avenue de la République, 94200 Ivry-sur-Seine
Tél : 01.58.07.68.02 ; 01.58.07.67.25
Email : jean-pierre.attal@parisdescartes.fr

Promoteur :
Assistance Publique – Hôpitaux de paris
Moufida DABBECH/Karine GOUDE
Direction de la Recherche Clinique et du Développement
Carré historique de l'hôpital Saint-Louis
1, avenue Claude Vellefaux, 75010 PARIS
Tel : 01.44.84.17.37 / 17.22

Responsable scientifique :
Dr Hélène FRON
Service d'Odontologie, Hôpital Charles Foix
7 Avenue de la République, 94200 Ivry-sur-Seine
Tél : 01.58.07.67.25 / 06 22 78 72 64
Email : helene.fron@parisdescartes.fr

Coordination de l'étude :
Inès KHABTHANI BEN JABALLAH
Unité d'Epidémiologie et de Recherche Clinique
Hôpital Européen Georges Pompidou
20-40 rue Leblanc, 75908 Paris Cedex 15
Tel : 01.56.09.20.31

Technicien d'étude clinique :

Attaché de recherche clinique :
Renaud BOYER
Unité d'Epidémiologie et de Recherche Clinique
Hôpital Européen Georges Pompidou
20-40 rue Leblanc, 75908 Paris Cedex 15
Tel : 01.56.09.56 38
renaud.boyer@egp.aphp.fr

URC HEGP CECOIA	|0|0|__| |0|__|__|__| |__| |__|	Inclusion
	n° centre n° inclusion Nom Prénom	

FORMULAIRE D'INCLUSION

Date d'inclusion : |__|__| / |__|__| / |__|__|__|__|

Sexe : ☐ Homme ☐ Femme

Date de naissance : |__|__| / |__|__| / |__|__|__|__|

Accord de participation à l'étude : ☐ oui ☐ non

---------- **Critères d'inclusion** ----------

PATIENT	OUI	NON
être âgé de 18 à 70 ans,		STOP
avoir signé le consentement éclairé,		STOP
être capable de tolérer les procédures restauratrices nécessaires (ouverture buccale et coopération suffisantes),		STOP
pouvoir bénéficier d'une antibioprophylaxie en cas de risque d'endocardite infectieuse,		STOP
être disponible pendant la période de suivi et mettre moins de 45 minutes à se rendre au centre dentaire.		STOP

DENT ATTEINTE	OUI	NON
postérieure (prémolaire ou molaire),		STOP
présentant une perte de substance occluso-proximale de volume modéré à important, ne pouvant pas être restaurée avantageusement par une technique de restauration par composite directe et ne justifiant pas une préparation périphérique,		STOP
une radiographie rétro-coronaire pré-opératoire confirme a priori l'indication d'une restauration de type inlay-onlay., faite dans l'année précédent l'inclusion		STOP
présente une mobilité <1mm dans le sens VL		STOP
présente une profondeur de poche < 3mm		STOP

Radio

Date de la radio : |__|__| / |__|__| / |__|__|__|__|

Format : ☐ argentique ☐ numérique

1

URC HEGP CECOIA	|0|0|__| n° centre |0|__|__|__| n° inclusion |__| Nom |__| Prénom	Inclusion

---------- Critères de non inclusion ----------

PATIENT	OUI	NON
allergie à l'un des matériaux employés dans le protocole,	STOP	☐
bruxisme important *(facettes d'abrasion importantes, antécédents multiples de fracture de prothèses ou rapport d'épisodes de bruxisme fréquents et/ou sévères),*	STOP	☐
maladie parodontale aiguë *(inflammation et/ou saignements parodontaux)* ou sévère *(atteinte radiologique supérieure à la moitié de la hauteur radiculaire touchant plus du tiers des sites)*,	STOP	☐
hygiène orale insuffisante *(présence de plaque et tartre visibles à l'œil nu),*	STOP	☐
maladie carieuse sévère *(4 restaurations primaires ou secondaires ou plus dans l'année précédente),*	STOP	☐
contre-indication à la lidocaïne *(hypersensibilité aux anesthésiques locaux à liaison amide, porphyries, troubles de la conduction auriculoventriculaire nécessitant un entraînement électrosystolique permanent non encore réalisé, épilepsie non contrôlée par un traitement),*	STOP	☐
non affiliation à un régime de sécurité sociale *(bénéficiaire ou ayant droit).*	STOP	☐

DENT	OUI	NON
implication dans le support d'une prothèse adjointe partielle,	STOP	☐
mobilité dentaire > II *(1 mm dans le sens vestibulo-lingual)*,	STOP	☐
poches parodontales de > 3mm,	STOP	☐
les limites de la perte de substance seront a priori intra-sulculaires ou sous gingivales et empêcheront la pose de la digue.	STOP	☐

PATIENT INCLUS : ☐ **OUI** ☐ **NON**

- **Le patient présente un risque d'endocardite infectieuse :**
  - ☐ non
  - ☐ oui → Prescrire une antibioprophylaxie pour le rendez-vous du traitement

2

URC HEGP CECOIA	|0|0|__| n° centre	|0|__|__|__| n° inclusion	|__| Nom	|__| Prénom	Randomisation

FORMULAIRE DE RANDOMISATION

Date de randomisation : |__|__| / |__|__| / |__|__|__|__|

1. Vous allez commencer la préparation.

- **La dent présentait déjà une restauration :** ☐ oui ☐ non
  Si oui, de quel type : ☐ amalgame ☐ composite direct ☐ inlay métallique ☐ inlay composite ☐ inlay céramique ☐ Autre, préciser : _____
- **Quel type de guidage existe en latéralité :** ☐ fonction canine ☐ fonction de groupe
- **Les courbes occlusales et l'occlusion sont :** ☐ correctes ☐ légèrement perturbées ☐ très perturbées
- **Teinte pour un bloc composite :** ☐ A1 ☐ A2 ☐ A3
- **Teinte pour un bloc céramique :** ☐ A1 ☐ A2 ☐ A3

Enregistrement de l'antagoniste par : ☐ mordu ☐ cliché vestibulaire

Avez-vous réalisé une base intermédiaire : ☐ oui ☐ non

Réponse de la dent traitée au test au froid :
☐ Comparable aux dents adjacentes ☐ Augmentée, avec rémanence
☐ Augmentée, sans rémanence ☐ Diminuée ☐ Absente

Réponse de la dent traitée au test de percussion axiale :
☐ Normale ☐ Légèrement sensible ☐ Douloureuse

Réponse de la dent traitée au test de percussion latérale :
☐ Normale ☐ Légèrement sensible ☐ Douloureuse

2. Vous avez fini la préparation, pris l'empreinte optique et en êtes à insérer le bloc pour l'usinage.

Combien de cuspides ont été recouvertes ? ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4
Si prémolaire, lesquelles : ☐ P/L ☐ V
Si molaire : ☐ MP/ML ☐ DP/DL ☐ MV ☐ DV

Dent :
- nécessite une restauration par inlay-onlay ☐ oui ☐ non

Cavité :
- ne présente pas des limites sous gingivales ☐ oui ☐ non
- permet la pose de la digue ☐ oui ☐ non
- toutes les cuspides ne sont pas recouvertes ☐ oui ☐ non

3

URC HEGP CECOIA	|0|0|__| |0|__|__|__| |__| |__|	Randomisation
	n° centre n° inclusion Nom Prénom	

PATIENT RANDOMISÉ : ☐ **OUI** ☐ **NON**

Dent : ☐ prémolaire ☐ molaire

Vitalité : ☐ pulpée ☐ dépulpée

Restauration : ☐ inlay ☐ onlay

La cavité présente : ☐ Aucune fissure ou fêlure ☐ 1 petite fissure
☐ Plusieurs petites fissures ☐ 1 ou plusieurs grosses fissures

RANDOMISATION : ☐ **composite** ☐ **céramique**

3. Vous pouvez lancer l'usinage.

Avez-vous pu réaliser l'inlay dans la séance :

☐ oui ☐ non → Pourquoi ? :……..

4. Ajustez le point de contact et retirez l'ergot.

- **Pesez l'inlay-onlay :** |__|, |__|__| g

5. Vous pouvez maquiller / polir l'inlay-onlay puis l'assembler.

- **Avez-vous vérifié l'occlusion avant de coller l'inlay-onlay ?** ☐ oui ☐ non
- **Avez-vous pu mettre la digue au moment du collage ?** ☐ oui ☐ non
  Si non, préciser pourquoi :……
- **Finitions de l'inlay**
  - Si céramique : ☐ glaçage ☐ glaçage + maquillage ☐ polissage
  - Si composite, maquillage: ☐ oui ☐ non
- **Y a-t-il eu une étape où vous n'avez pas pu suivre le protocole** ☐ oui ☐ non

  Si oui, précisez : …….

4

EVALUATION A 1 SEMAINE
(au maximum 1 mois après la randomisation)

URC HEGP CECOIA	|0|0|__| |0|__|__|__| |__| |__|	1 semaine
	n° centre n° inclusion Nom Prénom	

FORMULAIRE D'EVALUATION (OPERATEUR)

Date : ____ / ____ / _____

Critères de jugement FDI

1. Brillance	☐1	☐2	☐3	☐4	☐5
2a. Colorations de surface	☐1	☐2	☐3	☐4	☐5
2b. Colorations marginales	☐1	☐2*	☐3*	☐4*	☐5*

* Quelle proportion de la longueur totale de la limite est colorée ? |__|__|__| %

* Les portions de la limite qui sont colorées se trouvent au niveau :

☐ O ☐ proximal ☐ V/P/L

3. Teinte	☐1	☐2	☐3	☐4	☐5
4. Forme anatomique	☐1	☐2	☐3	☐4	☐5
5. Fractures du matériau et rétention	☐1	☐2	☐3	☐**4***	☐**5***

** Ne pas oublier de prendre une empreinte de la dent fracturée*

6. Adaptation marginale	☐1	☐2*	☐3*	☐4*	☐5*

* Quelle proportion de la longueur totale de la limite permet le passage de la sonde ? |__|__|__| %

* Les portions de la limite qui permettent le passage de la sonde se trouvent au niveau :

☐ O ☐ proximal ☐ V/P/L

7. Anatomie occlusale et usure	☐1	☐2	☐3	☐4	☐5
8a. Forme anatomique proximale (point de contact)	☐1	☐2	☐3	☐4	☐5
8b. Forme anatomique proximale (contour)	☐1	☐2	☐3	☐4	☐5
9. Examen radiographique	☐1	☐2	☐3	☐4	☐5
10. Opinion du patient	☐1	☐2	☐3	☐4	☐5
11. Sensibilité/ vitalité pulpaire	☐1	☐2	☐3	☐4	☐5
12. Caries secondaires, érosion, abfraction	☐1	☐2*	☐3*	☐4*	☐5*

* Avez-vous remarqué une zone de :

☐ carie secondaire ☐ érosion ☐ abfraction

* Quelle proportion de la longueur totale de la limite est atteinte ? |__|__|__| %

* Les portions atteintes se trouvent au niveau :

☐ O ☐ M ☐ D ☐ V ☐ P/L

13. Intégrité dentaire (fêlures, fractures)	☐1	☐2	☐3	☐4	☐5
14. Réponse parodontale	☐1	☐2	☐3	☐4	☐5
15. Muqueuse adjacente	☐1	☐2	☐3	☐4	☐5
16. Santé orale et générale	☐1	☐2	☐3	☐4	☐5

5

URC HEGP CECOIA	|0|0|__| |0|__|__|__| |__| |__|	1 semaine
	n° centre n° inclusion Nom Prénom	

Qualité globale de la restauration (cocher) :

☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

1 2 3 4 5 6 7 8 9 10

Inacceptable (à remplacer immédiatement) *Excellente*

Réponse de la dent traitée au test au froid :

☐ Comparable aux dents adjacentes ☐ Augmentée, avec rémanence

☐ Augmentée, sans rémanence ☐ Diminuée ☐ Absente

Réponse de la dent traitée au test de percussion axiale :

☐ Normale ☐ Légèrement sensible ☐ Douloureuse

Réponse de la dent traitée au test de percussion latérale :

☐ Normale ☐ Légèrement sensible ☐ Douloureuse

La surface de la dent antagoniste en contact avec l'inlay-onlay est :

☐ Intacte ☐ Restaurée ☐ Absente

Si elle est restaurée, est-ce par :

☐ alliage précieux ☐ alliage non précieux

Si non précieux, type de restauration :

☐ composite ☐ céramique feldspathique

☐ vitrocéramique enrichie à la leucite ☐ vitrocéramique enrichie au disilicate de lithium

EVALUATION A 1 AN
(après la date de randomisation +/- 3 mois)

- Prendre une radiographie rétro-alvéolaire
- Chaque opérateur remplit indépendamment le formulaire d'évaluation
- Les 2 opérateurs remplissent le formulaire de consensus
- Les 2 opérateurs mesurent l'indice de plaque, l'indice de saignement puis prennent une empreinte sectorielle en mordu puis 2 empreintes optiques (dent traitée et antagoniste)

Les formulaires d'évaluation à 2 ans sont identiques à ceux de l'évaluation à 1 an.

URC HEGP CECOIA	|0|0|__| |0|__|__|__| |__| |__|	1 an
	n° centre n° inclusion Nom Prénom	

FORMULAIRE D'EVALUATION (CONSENSUS)

Date : ____ / ____ / _____

Critères de jugement FDI

1. Brillance	☐1	☐2	☐3	☐4	☐5
2a. Colorations de surface	☐1	☐2	☐3	☐4	☐5
2b. Colorations marginales	☐1	☐2*	☐3*	☐4*	☐5*

* Quelle proportion de la longueur totale de la limite est colorée ? |__|__|__| %

* Les portions de la limite qui sont colorées se trouvent au niveau :

☐ O ☐ proximal ☐ V/P/L

3. Teinte	☐1	☐2	☐3	☐4	☐5
4. Forme anatomique	☐1	☐2	☐3	☐4	☐5
5. Fractures du matériau et rétention	☐1	☐2	☐3	☐**4***	☐**5***

** Ne pas oublier de prendre une empreinte de la dent fracturée*

6. Adaptation marginale	☐1	☐2*	☐3*	☐4*	☐5*

* Quelle proportion de la longueur totale de la limite permet le passage de la sonde ? |__|__|__| %

* Les portions de la limite qui permettent le passage de la sonde se trouvent au niveau :

☐ O ☐ proximal ☐ V/P/L

7. Anatomie occlusale et usure	☐1	☐2	☐3	☐4	☐5
8a. Forme anatomique proximale (point de contact)	☐1	☐2	☐3	☐4	☐5
8b. Forme anatomique proximale (contour)	☐1	☐2	☐3	☐4	☐5
9. Examen radiographique	☐1	☐2	☐3	☐4	☐5
10. Opinion du patient	☐1	☐2	☐3	☐4	☐5
11. Sensibilité/ vitalité pulpaire	☐1	☐2	☐3	☐4	☐5
12. Caries secondaires, érosion, abfraction	☐1	☐2*	☐3*	☐4*	☐5*

* Avez-vous remarqué une zone de :

☐ carie secondaire ☐ érosion ☐ abfraction

* Quelle proportion de la longueur totale de la limite est atteinte ? |__|__|__| %

* Les portions atteintes se trouvent au niveau :

☐ O ☐ M ☐ D ☐ V ☐ P/L

13. Intégrité dentaire (fêlures, fractures)	☐1	☐2	☐3	☐4	☐5
14. Réponse parodontale	☐1	☐2	☐3	☐4	☐5
15. Muqueuse adjacente	☐1	☐2	☐3	☐4	☐5
16. Santé orale et générale	☐1	☐2	☐3	☐4	☐5

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URC HEGP CECOIA	|0|0|__| |0|__|__|__| |__| |__|	1 an
	n° centre n° inclusion Nom Prénom	

Radiographie

La radiographie montre :

- ☐ aucune particularité
- ☐ un petit excès de colle en proximal
- ☐ un gros excès de colle en proximal
- ☐ un petit défaut d'adaptation en proximal
- ☐ un gros défaut d'adaptation en proximal
- ☐ une radioclarté entre dent et restauration (qui n'est pas située en proximal)
- ☐ une image radioclaire à l'apex
- ☐ un léger élargissement desmodontal
- ☐ autre, préciser : ……

Vous avez modifié la restauration pour résoudre une petite anomalie observée à la radio :

☐ oui ☐ non

- **Indice de plaque (IP) :** |__|__| %
- **Indice de saignement (nombre de sites):** ☐0 ☐1 ☐2 ☐3 ☐4
- **La surface de la dent antagoniste en contact avec l'inlay-onlay est :**
  ☐ Intacte ☐ Restaurée ☐ Absente
- **Si elle est restaurée, est-ce par :** ☐ alliage précieux ☐ alliage non précieux
- **Si non précieux, est-ce par :** ☐ composite ☐ céramique
- **Avec un papier articulé, déterminer si les points de contact sur la restauration sont :**
  ☐ Faibles ☐ Un peu trop forts ☐ Trop forts ☐ Absents
- **Vous avez modifié la restauration pour résoudre une petite anomalie observée à l'aide du papier articulé :**
  ☐ oui ☐ non

Prendre une empreinte sectorielle en mordu et une empreinte optique de la dent et de l'antagoniste

Remarques :_____

_____

_____

_____

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URC HEGP CECOIA	|0|0|__| |0|__|__|__| |__| |__|	E.I.
	n° centre n° inclusion Nom Prénom	

FORMULAIRE D'EVENEMENT INDESIRABLE

Date : ____ / ____ / _____

** Se reporter au protocole en cas de fracture de la dent ou de l'inlay-onlay

1-Evènement entrainant l'extraction de la dent (cause principale)		
1-1 Reprise de carie		Date de l'extraction : ___ / ___ / _____
1-2 Infection parodontale		
1-3 Fracture dentaire		
2-Evènement bénin entrainant la modification de l'inlay-onlay		
2-1 Fracture de la restauration**		Date : ___ / ___ / _____ Quelle a été la modification ? ☐ Réparation au composite ☐ Remarginage au composite fluide ☐ Polissage ☐ Autre. Préciser : _____
2-2 Fracture de la dent**		
2-3 Usure du joint		
2-4 Inadaptation proximale		
2-5 Sensibilités/douleurs		
2-6 Modification de l'anatomie occlusale de l'antagoniste		
3-Evènement bénin n'entrainant pas la modification de l'inlay-onlay : Sensibilités		
Sensibilités		Nombre de jours : |__|__|__|
		Nombre de jours : |__|__|__|
4-Autre événement en lien avec l'inlay-onlay		
Préciser : _____ _____		Date : ___ / ___ / _____ A entrainé : ☐ l'extraction de la dent ☐ la dépose de l'inlay-onlay ☐ la modification de l'inlay-onlay - Si oui, préciser …… ☐ aucune modification de l'inlay-onlay

URC HEGP CECOIA	|0|0|__| |0|__|__|__| |__| |__|	E.I.
	n° centre n° inclusion Nom Prénom	

FORMULAIRE D'EVENEMENT INDESIRABLE GRAVE

Date : ____ / ____ / _____

Evènement	Cocher *toutes les cases pertinentes*	Préciser obligatoirement :
5-Evènement grave lié à la réalisation de l'inlay-onlay		
5-1 Choc anaphylactique		Date : ___ / ___ / _____ Heure : ____h
5-2 Urticaire local ou « géant »		
5-3 Œdème de Quincke/angio-œdème		
5-4 Syncope		
5-5 Vertiges		Date de début : ___ / ___ / _____ Date de fin: ___ / ___ / _____
5-6 Nausées		
5-7 Réaction cutanéo-muqueuse		Préciser laquelle : _____ Date de début : ___ / ___ / _____ Date de fin: ___ / ___ / _____
5-8 Autre réaction allergique		
5-9 Inhalation		Date : ___ / ___ / _____ Heure : ____h
5-10 Ingestion		

Cet événement a entrainé :		
Décès		Date : ___ / ___ / _____
Coma		Date de début : ___ / ___ / _____ Date de fin: ___ / ___ / _____
Hospitalisation *Envoyer le fax d'EIG au :* *01 44 84 17 99*		Date de début : ___ / ___ / _____ Date de fin: ___ / ___ / _____ Hôpital : _____ Service : _____
Radiographie(s)		Date : ___ / ___ / _____
Autre. Préciser : _____		Date : ___ / ___ / _____

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URC HEGP CECOIA	|0|0|__| |0|__|__|__| |__| |__|	E.I.
	n° centre n° inclusion Nom Prénom	

PROTOCOLE A SUIVRE EN CAS DE FRACTURE DE L'INLAY-ONLAY / DE LA DENT TRAITEE

(SE REPORTER AU PROTOCOLE AU DOS DE L'INTERCALAIRE « E.I»)

N° opérateur : |__|__|__| **Date** : ____ / ____ / _____

Dent : |__|__|

Date de la fracture (le plus précisément possible) : ____ / ____ / _____

Comment le patient décrit-il la survenue de la fracture ?

☐ en mastiquant normalement ☐ en croquant sur quelque chose de dur
☐ pendant la nuit ☐ ne sait pas
☐ autre : _____

Appendix 13. Contract with an industry partner of the CECOIA trial

CONTRAT DE FOURNITURE DE PRODUIT DE SANTE (DISPOSITIF MEDICAL) POUR UNE RECHERCHE MENEE DANS LE CADRE D'UN APPEL D'OFFRES

***[*MED n° 12.010*]-[P110129]-[*N°VAL 2012/2012-139/02]**

ENTRE :

L'ASSISTANCE PUBLIQUE – HOPITAUX DE PARIS, Etablissement public de santé, dont le siège est situé au 3, Avenue Victoria, Paris 4ème, représentée par sa Directrice Générale, Madame Mireille Faugère,

Représentée par : M. Christophe Misse, Directeur du Département de la Recherche Clinique et du Développement, en application des arrêtés de délégation n° 2010-0232 du 23 septembre 2010, et n°2010-0718 du 5 novembre 2010 l'habilitant à signer le présent contrat,

ci-après désignée par l'« AP-HP»

D'une part,

ET

La Société **KERR** (forme juridique de la société) au capital de …….. €, immatriculée au registre du commerce et des sociétés de …….. sous le numéro ……., dont le siège social est ……., représentée par M. Fayçal IRATNI (directeur), dument habilité à l'effet des présentes,

ci-après désignée par le **« Partenaire »**

D'autre part,

Ensemble désignés individuellement « la Partie » et collectivement « les Parties »

VU les dispositions du Code de la Santé Publique,

IL EST PREALABLEMENT EXPOSE QUE :

Dans le cadre de l'appel d'offres : **Programme Hospitalier de Recherche Clinique** 2011, le Ministère de la Santé a accordé un financement pour la réalisation du projet de recherche clinique intitulé **" Essai randomisé multicentrique comparant la céramique et le composite dans le traitement des pertes de substance dentaires par inlays-onlays réalisés par CFAO : essai CECOIA"** ci-après dénommé « la Recherche », sous la responsabilité du **Dr Jean-Pierre ATTAL,** Service d'Odontologie, Hôpital Charles Foix, 7 Avenue de la République, 94200 Ivry-sur-Seine, ci après dénommé « l'Investigateur ».

Le résumé de la Recherche, promue par l'AP-HP, figure en annexe 1 du présent contrat.

La Recherche a été qualifiée de recherche biomédicale, au sens de l'article L.1121-1 du Code de la santé publique. Elle a été autorisée par l'autorité compétente en date du 22/05/2012, et a reçu l'avis favorable du comité de protection des personnes le 14/05/2012.

Compte tenu de l'intérêt potentiel des résultats de la Recherche exprimé par le Partenaire, ce dernier accepte d'apporter une contribution à la réalisation de la Recherche.

EN CONSEQUENCE LES PARTIES SONT CONVENUES DE CE QUI SUIT :

ARTICLE 1 - OBJET DU CONTRAT

Le présent contrat a pour objet de définir :

- les conditions d'approvisionnement en produits nécessaires à la réalisation de la Recherche listés dans le tableau suivant :
-

Produit	Quantité
Colle : NX3	40
Adhésif : Optibond XTR	500
Composite fluide : Premise flowable	24
teintier et kit de maquillantsKolor + (5 flacons)	6

ci après désigné « les Produits »,

- les droits et obligations qui résultent de cette contribution pour chacune des Parties.

ARTICLE 2– OBLIGATIONS DES PARTIES

2-1 Obligations du Partenaire

2-1-1 Fourniture du Produit

Le Partenaire s'engage à fournir à titre gracieux les produits nécessaires à la réalisation de la Recherche dans les conditions définies dans l'annexe technique, annexe 2 du présent contrat, qui détermine les responsabilités et engagements des Parties sur les aspects concernant les Produits.

Cette annexe précise notamment :

- Le statut du Dispositif médical vis-à-vis du marquage CE,
- Le positionnement de l'usage du DM dans la recherche par rapport- à celui revendiqué par le fabricant
- La constitution et la conservation des dossiers de lot de fabrication et de conditionnement
- La fourniture des documents nécessaires à la réalisation de la Recherche
- L'information du promoteur en cas de modifications des caractéristiques du Dispositif médical et le nécessaire aval du promoteur dans ces situations
- Les modalités de gestion d'éventuels rappels de lot,
- Les obligations relatives à la matériovigilance,

- Les modalités d'étiquetage / contre-étiquetage
- Les modalités de commande et de livraison permettant d'optimiser les quantités mises à disposition
- La gestion des échanges pour péremption ou pour défaut
- Le devenir des Dispositifs médicaux à la fin de la Recherche.

Au plus tard à la date de dernière signature du présent contrat, le Partenaire s'engage à transmettre à l'AP-HP la notice d'instruction actualisée des Produits concernés par le présent contrat.

Afin de respecter les obligations légales et réglementaires de pharmacovigilance, le Partenaire s'engage à transmettre à l'AP-HP toutes informations nouvelles ou faits nouveaux concernant le Produit, dans les meilleurs délais après en avoir eu lui-même connaissance.

2-2 Obligations de l'AP-HP et des Investigateurs

L'aide apportée par le Partenaire à la Recherche ne dispense ni l'AP-HP, ni l'Investigateur d'assumer l'intégralité des obligations qui leur reviennent au titre de la législation et de la réglementation applicables.

A ce titre, l'AP-HP s'engage à obtenir, préalablement au démarrage de la Recherche, toutes les autorisations nécessaires à sa réalisation.
L'AP-HP s'engage également à souscrire une assurance garantissant sa responsabilité civile ainsi que celle de tout intervenant à la Recherche, conformément à l'article L.1121-10 du Code de la santé publique, ainsi qu'à se conformer aux obligations relatives au traitement informatique de données personnelles opéré dans le cadre d'une recherche.

L'AP-HP et ses représentants sont seuls autorisés à se rendre sur les sites où se déroulera la Recherche, à avoir accès aux données et à les recueillir.

A la signature du présent contrat, l'AP-HP transmettra au Partenaire, qui accepte d'en maintenir le contenu confidentiel, un exemplaire du protocole dans sa version actualisée.

ARTICLE 3 – CONFIDENTIALITE

Sauf autorisation écrite préalable de l'AP-HP, le Partenaire est tenu de garder confidentiels, à l'égard de toute personne non autorisée, les faits, informations, connaissances, documents, protocoles, résultats, ou tout autre élément auquel il a eu accès ou dont il a eu connaissance dans le cadre de la Recherche.

L'AP-HP s'engage à maintenir confidentielles et à ne pas divulguer à des tiers les informations et données liées au Produit qui lui seraient communiquées par le Partenaire et désignées comme confidentielles.

Cependant ne sont pas soumis à ces obligations de confidentialité et d'usage restreint, les informations :
- qui sont accessibles au public ou qui le deviendront sans faute de la Partie,
- qui seraient transmises à l'une des Parties par un tiers non tenu par une obligation de confidentialité vis-à-vis de l'autre Partie, à l'exclusion de toute personne ayant accès aux données sources [investigateurs, assistants de recherche clinique...].

Le Partenaire impose le respect de la confidentialité à ses agents, salariés, collaborateurs et sous-traitants éventuels.

Le Partenaire s'engage, pour lui-même et pour son personnel, à ne pas utiliser à des fins autres que celles de l'exécution du contrat et à ne divulguer à des tiers aucun fait, information, connaissance, document, protocole, résultat ou autre élément dont il aurait reçu communication ou pris connaissance à l'occasion de l'exécution du contrat.

Les présentes dispositions restent en vigueur cinq années après l'arrivée à échéance du présent contrat, ou sa résiliation anticipée

ARTICLE 4 – COMMUNICATIONS ET PUBLICATIONS

L'AP-HP se réserve la maîtrise de la communication et de la publication des résultats de la Recherche. Le Partenaire sera informé des projets de communication et de publication.

L'AP-HP s'engage à demander à l'Investigateur de mentionner, dans ses publications et ses communications, le soutien apporté par le Partenaire à la réalisation de la Recherche, en faisant figurer la mention : "Les matériaux nécessaires à cette Recherche ont été fournis en partie par la société **KERR**".

Les présentes dispositions restent en vigueur cinq années après l'arrivée à échéance du présent contrat, ou sa résiliation anticipée.

ARTICLE 5– PROPRIETE ET EXPLOITATION DES RESULTATS

L'AP-HP est propriétaire des données et résultats obtenus dans le cadre de la Recherche et s'en réserve l'exploitation exclusive.

Rapport Final de la Recherche : Le Partenaire aura la possibilité de se voir communiquer le rapport final de la Recherche en contrepartie du versement d'une somme forfaitaire correspondant à 15% du budget de la Recherche soit 35505 Euros.

Communication des données brutes de la Recherche : Dans le cas où le Partenaire souhaite avoir accès à l'intégralité des données brutes de la Recherche à des fins de R&D interne ou d'utilisation commerciale, notamment dans le cadre d'un dossier destiné aux Autorités de Santé françaises ou étrangères (dossier d'enregistrement, dossier de validation, dossier de remboursement, dossier de publicité...), cet accès pourra être envisagé si le Partenaire rembourse à l'AP-HP l'intégralité des coûts directs et indirects supportés par l'AP-HP pour la réalisation de cette Recherche comprenant notamment le budget alloué au titre du Programme Hospitalier de Recherche Clinique 2011 (déduction faite, le cas échéant, de la somme forfaitaire déjà versée au titre de la remise du rapport final) ainsi qu'une somme correspondant à la valorisation de l'expertise des équipes de l'AP-HP. Dans ce cas, le montant exact dû par le Partenaire, ainsi que les modalités de cet accès aux données seront déterminées dans le cadre d'un contrat spécifique ultérieur.

Dans le cas où le Partenaire souhaite disposer d'un délai visant à évaluer l'intérêt des données brutes et des résultats de la Recherche, le Partenaire pourra disposer d'un droit d'option (l'« Option ») lui permettant l'accès et la consultation des données brutes et des résultats de la Recherche.

Le Partenaire disposera ainsi d'un délai (le « Délai d'Option ») de six (6) mois à compter de la date de remise du rapport final de la Recherche pour informer l'AP-HP de son intention de lever l'option.
L'AP-HP garantit pendant le Délai d'Option qu'aucun tiers n'aura accès aux données brutes et aux résultats de la Recherche à l'exception des collaborateurs académiques impliqués dans la Recherche et soumis à une obligation de confidentialité dans ce cadre.

Si le Partenaire décide d'utiliser son droit d'Option d'accès aux données brutes et résultats de la Recherche, l'AP-HP s'engagera à assurer la collaboration de son personnel en garantissant l'accès aux dossiers originaux des patients et la mise à disposition des documents requis, dans le respect de la législation applicable sur la protection des données personnelles des participants à la Recherche, ainsi que du secret médical et professionnel.

Dans le cas contraire ou à défaut d'une réponse du Partenaire à échéance du délai d'Option, l'AP-HP se réserve le droit d'autoriser l'accès aux données et résultats de la Recherche à tout tiers de son choix.

Les présentes dispositions restent en vigueur après l'arrivée à échéance du présent contrat, ou sa résiliation anticipée.

ARTICLE 6 – DATE D'EFFET ET DUREE - DENONCIATION

Le présent contrat entre en vigueur à la date de dernière signature.

Le contrat est conclu pour toute la durée de la Recherche, et prend fin le 31/12/2019.

Il prend fin de plein droit, sans intervention judiciaire et sans indemnité, si l'autorité compétente en interdit le déroulement.
Dans l'hypothèse où l'AP-HP décide d'arrêter la Recherche pour des motifs méthodologiques, éthiques ou liés à la sécurité du patient, le contrat sera résilié, sans intervention judiciaire ni indemnités. Dans ce cas, les sommes non utilisées par l'AP-HP seront restituées au Partenaire.
Sans contradiction avec les paragraphes précédents, les articles relatifs à la confidentialité, aux publications et communications, ainsi qu'à la propriété des données et résultats de la Recherche, resteront en vigueur après l'échéance du contrat ou sa résiliation, pour la durée prévue par chacun de ces articles.

ARTICLE 7 – NOTIFICATIONS

Toute notification relative au contrat est effectuée par écrit et mentionne le numéro du contrat. Les notifications sont envoyées aux adresses suivantes:

Pour l'AP-HP:
Aspects concernant la Recherche :
Pôle Promotion
Département de la Recherche Clinique et du Développement
Carré Historique de l'hôpital Saint-Louis – Secteur Gris - Porte 23
1, avenue Claude Vellefaux
75475 Paris Cedex 10

Aspects contractuels :
Office de Transfert de Technologies & Partenariats Industriels
Département de la Recherche Clinique et du Développement
Carré Historique de l'hôpital Saint-Louis – Secteur Gris - Porte 23
1, avenue Claude Vellefaux
75475 Paris Cedex 10

Pour la Société :
M. Fayçal IRATNI
Directeur
[Dénomination sociale]
[Adresse officielle complète]

ARTICLE 8 - DISPOSITIONS GENERALES

RESPONSABILITES DE L'INVESTIGATEUR : L'apposition du visa de l'Investigateur, ce dernier s'engageant à titre personnel, vaut acceptation de l'ensemble des conditions et obligations lui incombant au titre du présent contrat et notamment, mais non exclusivement, celles relatives à la confidentialité, aux publications et communications, ainsi qu'à la propriété des données et résultats de la Recherche. Par conséquent, l'Investigateur s'engage expressément à ne causer aucun préjudice à la protection et l'exploitation des résultats de la Recherche au travers de toutes sortes de diffusion de ceux-ci.

MODIFICATIONS: Le présent contrat annule et remplace tout accord antérieur entre les Parties et l'Investigateur relatif à l'objet des présentes. Le présent contrat ne pourra être modifié que par écrit, toute modification devant être signée par un représentant habilité de chacune des Parties. Aucune entente formulée oralement ne peut lier les Parties à cet effet.

INCESSIBILITE - INTUITU PERSONAE : Aucune des Parties ne peut céder en tout ou partie le présent contrat à un tiers sans l'accord préalable écrit de l'autre Partie, qui ne saura refuser son consentement sans juste motif.
En cas de fusion, d'absorption, de cession, de transfert d'activités à une société ou de toute autre transformation du Partenaire visant à modifier les caractéristiques intuitu personae prises en compte pour la conclusion du présent contrat, le présent contrat ne pourra être transféré qu'avec le consentement préalable et écrit de l'AP-HP, qui devra

intervenir dans le délai maximum de soixante (60) jours à compter de la demande, consentement qui ne pourra être refusé sans motif légitime.
Il est entendu que ladite société sera en tout état de cause soumise aux mêmes obligations que celles mises à la charge du Partenaire dans le cadre des présentes à moins que les Parties n'en conviennent autrement ensemble.
Dans tous les cas, un avenant au présent contrat devra être élaboré entre l'AP-HP et ladite société simultanément à l'opération réalisée avec le Partenaire qui définira les obligations respectives desdites Parties conformément au paragraphe précédent.

FORCE MAJEURE: Chaque Partie sera excusée de ne pas satisfaire à ses obligations et ne pourra être tenue responsable ni redevable de dommages intérêts envers l'autre Partie, si l'inexécution est due à un cas de force majeure, tel que prévue à l'article 1148 du Code Civil, et ses applications jurisprudentielles.

CO-CONTRACTANTS INDEPENDANTS: Le présent contrat ne doit en aucun cas être interprété comme créant une relation d'association ou une société de fait entre les Parties, chacune d'elles devant être considérée comme co-contractant indépendant.

NON-ABANDON DE DROITS: Si, en cas de violation par l'une ou l'autre des Parties de ses obligations résultant du présent contrat, la Partie non fautive ne se prévaut pas de ses droits résultants pour elle de ladite violation, le non-exercice de ses droits ne saura être interprété comme une renonciation à exercer lesdits droits dans le futur ou à l'occasion d'une nouvelle violation similaire par la Partie fautive de ses obligations résultant du présent contrat.

ARTICLE 9 - LISTE DES ANNEXES

Le présent contrat comporte les annexes suivantes, lesquelles font partie intégrante de celui-ci :
Annexe 1 : Résumé de la Recherche
Annexe 2 : Annexe technique

ARTICLE 10 - CLAUSE DE COMPETENCE JURIDICTIONNELLE - LITIGE

Le présent contrat est soumis au droit français.

Les Parties s'engagent à tenter de résoudre à l'amiable tout différend susceptible d'intervenir entre elles. A défaut de règlement amiable, attribution de juridiction est faite aux tribunaux compétents de Paris.

Fait à Paris, en deux (2) exemplaires originaux.

POUR L'ASSISTANCE PUBLIQUE - HOPITAUX DE PARIS	**POUR LE PARTENAIRE**
Par délégation Le Directeur du Département de la Recherche Clinique et du Développement,	Le Directeur
Christophe MISSE [cachet – date – signature]	M. Fayçal IRATNI [cachet – date – signature]

Vu l'Investigateur, le Docteur Jean-Pierre ATTAL qui déclare reconnaître :

- avoir lu l'ensemble des dispositions et annexes du présent contrat et notamment l'Article 8 « Responsabilités de l'Investigateur »;
- avoir approuvé les obligations lui incombant au titre de l'apposition de son visa au présent contrat

Docteur Jean-Pierre ATTAL

Appendix 14. Technical appendix to the contract with an industry partner of the CECOIA trial

ANNEXE TECHNIQUE
au contrat [MED n° 12.009]-[P110129]-[N°VAL 2012/2012-139/01]

ARTICLE I -OBJET

Cette annexe technique a pour objet de préciser les conditions dans lesquelles la Société **IVOCLAR VIVADENT** fournira les dispositifs médicaux non stériles nécessaires à la recherche visée ci-dessous.
Elle vient en complément du contrat établi pour les besoins de l'essai clinique cité dans l'article II, passée entre le promoteur AP-HP et la société et ne peut s'en dissocier.

La présente annexe est signée, au titre de promoteur par Mr C. MISSE Directeur du DRCD/ DIRC Ile de France et pour la Société **IVOCLAR VIVADENT**, par M. Henri ROCHET en qualité de Président de la SAS Ivoclar Vivadent France.

ARTICLE II-CARACTERISTIQUES DE LA RECHERCHE

L'AP-HP prend l'initiative de réaliser une recherche biomédicale, dont le titre est : **«*Essai randomisé multicentrique comparant la céramique et le composite dans le traitement des pertes de substance dentaires par inlays-onlays réalisés par CFAO : essai CECOIA*, codes *CECOIA*, P110129.**

Les caractéristiques de l'étude sont les suivantes :

Investigateur coordonnateur : Docteur Jean-Pierre ATTAL, service d'odontologie du Pr. MAMAN de l'hôpital Charles Foix

Type d'essai : prospectif, randomisé, ouvert, multicentrique

Durée prévue de l'essai : 36 mois (dont 12 mois d'inclusion)

Nombre de centres au démarrage de l'essai : 6 centres

Nombre de patients maximum : 400 (200 par bras)

La société a décidé d'apporter son aide à la réalisation de cette recherche, il a été convenu ce qui suit :

ARTICLE III - DESCRIPTION DES DISPOSITIFS MEDICAUX NECESSAIRES A LA REALISATION DE L'ESSAI

1- Dispositifs médicaux :

Les Produits **mis à disposition à titre gracieux** par la société **IVOCLAR VIVADENT** aux Centres investigateurs pour cette recherche sont selon les quantités suivantes :

Produit	Quantité
Optragate	400
Blocs céramique (Empress CADMulti)	270
Silane Monobond S	12

IPS Object fix putty	25
Optrafine et Optrafine polishing paste (coffrets)	12

Produit	Composition	Classe du DM
Optragate	Styrol-Ethylen-Butylen-Styrol (SEBS) > 95%	I
Blocs céramique (Empress CAD)	> 98 % SiO_2, BaO, Al_2O_3, CaO, CeO_2, Na_2O, K_2O, B_2O_3 ; < 2 % TiO_2 et pigments	IIa
Silane Monobond S	Ethanol 50-100% ; méthacrylate de 3-triméthoxysilylpropyle ≤ 2,5%	IIa
IPS Object fix putty	Pâte en aluminium oxyde, quartz, eau et hydroxyéthylcellulose.	*
Optrafine et Optrafine polishing paste (coffrets)	Poudre de diamant, glycérine, propylene glycol, sodium, lauryl sulphate	I

* Produit n'étant pas mis en contact avec le corps du patient.

Fabricant/distributeur
Société IVOCLAR VIVADENT
219 route de la Chapelle du Puy 74410 Saint Jorioz
Tél : 0450886400

Liste des centres participants : Les dispositifs seront donnés aux centres suivants dans le cadre de l'essai :

Dr Attal, Jean-Pierre Dr Fron Chabouis, Helène	Service d' Odontologie du Pr. Maman Hôpital CHARLES FOIX 12 AV DE LA REPUBLIQUE 94205 IVRY SUR SEINE CEDEX
Pr Nabet, Catherine Dr Nasr, Karim Dr Chabreron, Olivier Dr Arcaute, Bertrand	CENTRE HOSPITALIER UNIVERSITAIRE DE TOULOUSE HOTEL DIEU SAINT JACQUES 2 RUE VIGUERIE 31052 TOULOUSE
Dr Prot, Caroline	CABINET DENTAIRE Dr Caroline PROT 18 Rue SERVIENT 69003 LYON
Dr Fonteneau, Cyril	CABINET DENTAIRE Dr Cyril FONTENEAU 37 Rue des ACACIAS 75017 PARIS
Dr Moussally, Christian	CABINET DENTAIRE Dr Christian MOUSSALLY 7, Rue Alexandre CABANEL

	75015 PARIS
Dr Cazier, Stéphane	CABINET DENTAIRE Dr Stéphane CAZIER 44 Bd de REUILLY 75012 PARIS

Liste des documents livrés avec les produits

- 1 bon de livraison
- 1 brochure technique en français pour chaque dispositif médical
- le marquage CE

ARTICLE IV - QUALITE / PERFORMANCES / SECURITE D'EMPLOI

La société est responsable de la qualité et de la sécurité d'emploi des dispositifs médicaux, fournis.

Elle garantit le maintien de cette qualité pour la durée totale de l'essai, sous réserve d'une utilisation dans les conditions spécifiées.

Une copie du marquage CE et un exemplaire de la notice d'utilisation pour ***les produits*** seront transmis à la DIRC Ile de France (DRCD) avant le début de la recherche.

Des copies des dossiers de lot de fabrication seront livrées avec les dispositifs livrés. Elles seront conservées par l'investigateur principal (Faculté de chirurgie dentaire, Montrouge).
En cas d'évolution de la réglementation ou du référentiel normatif applicable, la Société est tenue de se mettre en conformité avec les nouvelles dispositions à compter de leur date d'effet.

ARTICLE V – SERVICE / MAINTENANCE / ECHANGE

La société assurera le **transport** et la **livraison** des ***produits*** à la faculté de chirurgie dentaire de Montrouge.

ARTICLE VI - RAPPELS DE LOT / MATERIO-VIGILANCE /PHARMACOVIGILANCE

En cas d'anomalie constatée, ou portée à la connaissance de la Société, après livraison, la société s'engage à avertir immédiatement :

- le promoteur : Département de la Recherche Clinique et du Développement (DRCD), télécopie : 01. 44. 84. 17. 99.
- la surveillante du service d'investigation dans lequel le dispositif médical est livré
- l'investigateur coordonnateur

La Société communiquera à l'AP-HP (DRCD), dans les meilleurs délais, une copie de toutes les notifications de matério-vigilance, ainsi que toute information concernant les dispositifs fournis susceptible de remettre en question la sécurité des patients se prêtant à la Recherche Biomédicale portées à sa connaissance durant la réalisation de la Recherche pour les dispositifs concernés par la présente convention.

Nom et coordonnées du correspondant matério-vigilance de la société :
M. Patrik OEHRI
Tel : +423 / 235 35 35 ou 373 40 40
(Ivoclar Vivadent AG, FL-9494 Schaan, Liechtenstein)
e-mail : patrik.oehri@ivoclarvivadent.com

Le cas échant, la Société s'engage à faire son possible pour assurer le remplacement des dispositifs concernés afin de permettre à la recherche d'être conduite à son terme.

ARTICLE VII - DOCUMENTATION/DOSSIERS DE LOT

La Société s'engage à conserver à la disposition des Autorités de Tutelle, durant la période prévue par la réglementation pharmaceutique pour les produits destinés à des recherches biomédicales, les dossiers de lot de fabrication des dispositifs livrés.

La Société assurera une échantillothèque, qui sera à la disposition des autorités de tutelle, et représentative de chacun des lots de produit fini, conditionné et étiqueté, livrés dans le cadre de l'essai. Ils ne pourront être détruits sans autorisation écrite du promoteur (DRRC). Les échantillons de chaque lot seront conservés pour une durée au moins égale à la durée réglementaire prévue pour les médicaments en essais cliniques. La Société conservera, à la disposition des autorités de tutelle également les dossiers de fabrication et de conditionnement de chacun des lots fournis dans le cadre de l'essai, pour une durée au moins égale à la durée réglementaire prévue pour les médicaments en essais cliniques.

L'investigateur principal étiquettera les boîtes de Dispositifs Médicaux–avant utilisation afin de les identifier comme réservés à l'étude sur les centres.

ARTICLE VIII - APPROVISIONNEMENT / LIVRAISONS /FORMATION/ / ENLEVEMENT

Les besoins globaux de la recherche sont évalués pour les 6 centres à :

Produit	Quantité totale
Optragate	400
Blocs céramique (Empress CAD Multi)	270
Silane Monobond S	12
IPS Object fix putty	25
Optrafine et Optrafine polishing paste (coffrets)	12

Si ces besoins devaient être dépassés, les parties conviennent d'en discuter dans le cadre d'un nouvel accord permettant à la recherche d'être conduite à son terme.

Demande d'approvisionnement

L'approvisionnement en Produits nécessaires pour la Recherche, se fera par la Société, **en une seule fois**, avant le démarrage de la Recherche. Le partenaire s'engage à faire en sorte qu'un produit donné provienne d'un seul lot de fabrication (autant que possible).

La demande d'approvisionnement sera adressée à la Société après signature du présent contrat. **Aucune expédition ne sera réalisée par la Société avant réception à son niveau du document attestant de la libération réglementaire** de l'essai par le DRCD de l'AP-HP.

Les cartons seront livrés à la faculté de chirurgie dentaire de Montrouge, au service de biomatériaux (avec la mention CECOIA).

Livraisons

La société **IVOCLAR VIVADENT** assurera la livraison directe du service concerné. Le délai d'approvisionnement est de 7 jours ouvrés.

IVOCLAR VIVADENT s'engage à ce que les Produits livrés aient une durée de péremption compatible avec leur utilisation dans le cadre de la Recherche et au minimum de 12 mois à livraison.

Les **Produits**, fournis gratuitement, seront dédiés à la recherche. Ils ne peuvent en aucun cas être utilisés en dehors du cadre de cette recherche pendant toute la durée de la recherche.

Les dispositifs médicaux non stériles sont fournis à titre gracieux par la Société, franco de port et de taxes.

Pour les dispositifs médicaux, chaque emballage livré comportera l'étiquetage commercial, la notice d'utilisation et le nom du destinataire (cf article III).

L'investigateur principal apposera, après réception, un étiquetage spécifique de la Recherche Clinique, de dimension suffisante pour éviter toute erreur d'affectation des produits et comportant au minimum les informations suivantes :

Assistance Publique Hôpitaux de Paris DRCD, Hôpital Saint Louis, 75010 Paris **CECOIA** pour Recherche Biomédicale uniquement

Un **avis d'expédition/AR** sera joint à chaque livraison et sera retourné par fax par le service du centre à la société **IVOCLAR VIVADENT**

Devenir des produits sur les sites

En cours de recherche, tout dispositif médical défectueux sur un site d'investigation sera conservé jusqu'au passage de l'ARC de l'étude qui en gérera le retour vers la société **IVOCLAR VIVADENT** au moyen de la « fiche de demande d'échange » (document associé au présent circuit) et fera l'objet d'un échange à titre gracieux.

A la fin de la Recherche, le promoteur informera la société de la fin de la recherche, les

dispositifs médicaux non utilisés seront conservés par les centres investigateurs, pour une éventuelle utilisation hors essai, à l'exception des blocs Cérec qui seront restitués au partenaire.

ARTICLE IX- CONDITIONS D'APPLICATION

La présente annexe entre en vigueur à la date de signature de la convention à laquelle elle se rattache. Il est précisé qu'aucune commande ou livraison ne pourra être effectuées avant cette date.

Signataires :

Pour Ivoclar Vivadent	Pour l'AP-HP
Date:	Date :
Président de la SAS Ivoclar Vivadent France Henri ROCHET	Le Directeur du DRCD/ DIRC Ile de France Christophe MISSE

Appendix 15. Additional document submitted to the committee for the protection of persons (CPP)

	Numéro d'enregistrement de la recherche : IDRC 2011-A01658-33
	Titre complet de la recherche : Essai randomisé multicentrique comparant la céramique et le composite dans le traitement des pertes de substance dentaires par inlays-onlays réalisés par CFAO : essai CECOIA
	Justification et analyse critique de la pertinence de la recherche : La prévalence de la carie dentaire dans le monde est estimée à plus de 90% des adultes par l'OMS. Quand la perte de substance liée à la carie est de petit volume, un soin simple est réalisé. Lorsque la perte de substance est importante, les praticiens ont l'habitude de réaliser des couronnes qui présentent l'inconvénient d'être mutilantes. Il existe toutefois une technique intermédiaire, les inlays-onlays (le DM étudié), de plus en plus employés, car très respectueux des tissus dentaires. Le métal étant rejeté par la population (corrosion, inesthétique, biocompatibilité), le praticien a le choix entre 2 matériaux : le composite et la céramique. La céramique est un matériau biocompatible et résistant à l'usure, mais cassant. Le composite est moins cassant, mais s'use. Les études publiées dans la littérature ne permettent pas de choisir entre céramique et composite pour réaliser des inlays-onlays : défauts méthodologiques et absence d'essai clinique comparant ces deux matériaux. Ainsi, le choix entre inlay-onlay en composite ou en céramique varie en fonction des pays sans raison valable (en France, c'est souvent le composite qui est préféré, contrairement aux USA par exemple). Elle concerne de très nombreux patients et une thérapeutique moderne encore trop peu utilisée en France (les inlays-onlays). Aucun véritable essai clinique n'a été réalisé à ce sujet jusqu'à présent. Elle pourrait avoir un impact sur la longévité des restaurations dentaires et plus globalement sur le coût de la prise en charge des restaurations par l'Assurance Maladie.
	Hypothèse principale de la recherche et objectifs : Comparer les performances cliniques des inlays-onlays en céramique et en composite.
	Evaluation des bénéfices et des risques que présente la recherche, notamment les

	bénéfices escomptés pour les personnes qui se prêtent à la recherche et les risques prévisibles liés au traitement et aux procédures d'investigation de la recherche (incluant notamment la douleur, l'inconfort, l'atteinte à l'intégrité physique des personnes se prêtant à la recherche, les mesures visant à éviter et/ou prendre en charge les événements) : - Les patients bénéficieront d'un traitement de grande qualité (protocole opératoire, plateau technique et matériaux optimaux), d'un suivi régulier sur 2 ans ainsi que d'une compensation des contraintes de la recherche. - Les risques prévisibles liés au traitement pour les patients sont très faibles : l'inlay-onlay est un soin courant. Seuls le matériau et la technique justifient d'une recherche biomédicale. Dans le cadre de leur participation à ce projet, s'ils sont inclus puis leur dent randomisée, les patients peuvent bénéficier de traitements qui sont, chacun, utilisés en pratique habituelle. En ce qui concerne leur prise en charge, la participation à la recherche ne leur fait donc courir aucun risque particulier. Les risques encourus lors de la participation à cette recherche sont négligeables et sont identiques à ceux de la prothèse dentaire traditionnelle (allergie à l'un des matériaux utilisés, très rare ; fracture de votre dent ou de la restauration, rare ; reprise de carie, rare si votre hygiène bucco-dentaire est bonne ; sensibilités, rares et le plus souvent juste après le traitement ;…). Le risque de réaction allergique à un composant n'est pas totalement exclu. Les éléments de surveillance propres au protocole de recherche (mesure du critère de jugement principal avec empreintes et photographie) ne présentent que des risques négligeables pour les patients. Lors de l'empreinte sectorielle, le silicone n'est quasiment jamais avalé ou en quantité négligeable, une dent trop mobile pourrait éventuellement être extraite. Les risques encourus lors de l'empreinte optique, nécessaire pour la CFAO, sont quasiment nuls. La poudre d'Optispray, utilisée pour l'empreinte optique, peut éventuellement être avalée en faible quantité).En grande quantité, certains composants de la poudre d'Optispray peuvent provoquer une atteinte des poumons en cas d'ingestion, une irritation en cas de projection dans l'œil, un dessèchement ou des gerçures de la peau en cas d'exposition répétée et somnolence et vertiges en cas d'inhalation de vapeurs. Au vu des quantités utilisées et du mode d'utilisation de la poudre d'Optispray, aucune de ces complications n'a été rapportée à ce jour. Les risques encourus par les patients lors de la participation à cette recherche sont donc négligeables. Cette recherche présente un bon rapport bénéfice / risque.

Justifications de l'inclusion de personnes visées aux articles L. 1121-5 à L. 1121-8 et L. 1122-1-2 du code de la santé publique (ex : mineurs, majeurs protégés etc.…) et procédure mise en œuvre afin d'informer et recueillir le consentement de ces personnes ou de leurs représentants légaux :

Ces personnes ne seront pas incluses.

Description des modalités de recrutement des personnes (joindre notamment tous les supports publicitaires utilisés pour la recherche en vue du recrutement des personnes) :

Les investigateurs proposeront à tous leurs patients nécessitant une restauration par inlay-onlay et répondant aux critères d'éligibilité de participer à l'essai. Dans les salles d'attentes des 6 centres, une affiche permettra d'informer les patients, et des prospectus donneront de plus amples informations.

Procédures d'investigations menées et différences par rapport à la prise en charge habituelle, le cas échéant :

Le suivi impliquera le remplissage d'une grille d'évaluation du DM (instrument de la Fédération Dentaire Internationale) par l'évaluateur en présence du patient et la réalisation de radiographies de contrôle tous les ans (ce qui correspond à la fréquence habituelle du contrôle radiographique), voire de photographies endo-buccales. De plus, une prise d'empreintes (pour étudier l'usure du DM) sera réalisée de façon classique (comme c'est le cas pour la réalisation de toutes les prothèses dentaires conventionnelles) annuellement.

Description des actes et/ou procédures	SOIN	RECHERCHE
Préliminaires (Choix de la teinte…)	x	
Préparation de la cavité	x	
Empreinte optique	x	
Conception assistée par ordinateur	x	
Randomisation		x
Fabrication assistée par ordinateur	x	
Essai clinique de l'inlay-onlay	x	
Maquillage/polissage	x	
Collage	x	
Finitions et réglage de l'occlusion	x	
Evaluation initiale (1 semaine à 1 mois) et Evaluations de suivi (à 1 an et à 2 ans) radiographie grille des critères FDI	x	 x

	Justification de l'existence ou non : - d'une interdiction de participer simultanément à une autre recherche ; - d'une période d'exclusion pendant laquelle la participation à une autre recherche est interdite. Chaque patient est informé sur le fait que sa participation à cette recherche durera 24 mois et que cela implique qu'il devra informer son chirurgien-dentiste de sa participation à une autre recherche, si celle-ci se fait en même temps que l'essai CECOIA A l'issue de la recherche, il n'y a pas de période d'exclusion pendant laquelle la participation à une autre recherche est interdite.
0	Modalités et montant de l'indemnisation des personnes se prêtant à la recherche, le cas échéant : Les inlays-onlays seront gratuits dans les CSERD (alors qu'ils coutent habituellement environ 300 euros après remboursement de la part sécurité sociale) et payants dans les cabinets dentaires (le coût est de l'ordre de 500-600 euros). Tous les patients qui seront venus à leurs 3 rendez-vous de suivis (t= 1 semaine, 1 an, 2 ans) seront indemnisés pour ces 3 déplacements à hauteur de 100 euros.
1	Motifs de constitution ou non d'un comité de surveillance indépendant : Un comité de surveillance indépendant ne parait pas nécessaire pour cet essai, du fait du niveau de risque très faible encouru par les participants.
2	Nombre prévu de personnes à inclure dans la recherche : 400

Appendix 16. Information notice and consent for patients of the CECOIA trial

Essai randomisé multicentrique comparant la céramique et le composite dans le traitement des pertes de substance dentaires par inlays-onlays réalisés par CFAO : Essai CECOIA

Cette recherche est organisée par l'Assistance Publique - Hôpitaux de Paris
Département de la Recherche Clinique et du Développement
1 avenue Claude Vellefaux
75010 Paris

NOTE D'INFORMATION

Madame, Mademoiselle, Monsieur,

Le Docteur..... (nom, prénom), exerçant à l'hôpital .....vous propose de participer à une recherche concernant votre problème dentaire.

Il est important de lire attentivement cette note avant de prendre votre décision ; n'hésitez pas à lui demander des explications.
Si vous décidez de participer à cette recherche, un consentement écrit vous sera demandé.

1) Quel est le but de cette recherche?

Cette recherche porte sur les inlays-onlays. Ce sont des prothèses dentaires (comme des petites couronnes) qui permettent de conserver au maximum les tissus dentaires sains et de restaurer une dent atteinte d'une cavité trop importante pour être bien traitée directement en bouche.

Les inlays-onlays peuvent être réalisés avec 2 matériaux : le composite et la céramique. On sait que ces 2 matériaux sont performants mais on ne sait pas encore lequel est plus performant, et dans quelle situation.
Cette recherche a donc pour but de comparer l'efficacité des matériaux céramique et composite dans le traitement de patients présentant des pertes de substance dentaire.

Pour répondre à la question posée dans la recherche, il est prévu d'inclure 400 personnes nécessitant un inlay-onlay, dans des centres de soins dentaires français et dans des cabinets dentaires français.

2) En quoi consiste la recherche ?

Dans la recherche proposée, nous allons évaluer les performances cliniques des 2 matériaux utilisés pour réaliser des inlays-onlays.

Vous bénéficierez, par tirage au sort soit d'un inlay-onlay en composite soit d'un inlay-onlay en céramique. Ces inlays-onlays seront contrôlés annuellement pendant 2 ans.

Dans cette recherche, la technique choisie pour réaliser les inlays-onlays est la Conception et Fabrication Assistée par Ordinateur (CFAO). Cette technologie permet de concevoir la restauration par ordinateur et de fabriquer la pièce conçue à l'aide d'une machine-outil.

3) Quel est le calendrier de la recherche ?

La recherche durera ~~3~~ 4 ans et votre participation sera de 2 ans.

Visite 1 : lors de la première consultation, votre chirurgien-dentiste vous conseille un traitement par inlay-onlay, vous propose de participer à l'étude et vous donne cette note d'information et un formulaire de consentement (ci-joint).
Visite 2 : lors de la deuxième consultation, si vous avez signé le consentement, l'inlay-onlay est réalisé selon les étapes suivantes :

- Choix de la teinte du matériau
- Anesthésie si nécessaire
- Préparation de la cavité
- Vérification des contacts avec les dents opposées et légère modification éventuelle
- Empreinte optique (enregistrement de la forme de la cavité de votre dent à l'aide d'une caméra)
- Conception de l'inlay-onlay sur l'ordinateur
- Randomisation (tirage au sort) : attribution d'un inlay-onlay soit en composite soit en céramique
- Usinage de l'inlay-onlay, avec une machine-outil qui se trouve dans le cabinet
- Polissage ou maquillage de l'inlay-onlay
- Mise en place du champ opératoire
- Collage de l'inlay-onlay
- Finitions

Visite 3 : un contrôle aura lieu dans le mois qui suit, idéalement à une semaine.
Visite 4 : un contrôle aura lieu 1 an après la réalisation de l'inlay-onlay.
Visite 5 : un contrôle aura lieu 2 ans après la réalisation de l'inlay-onlay.

Dans le cadre de ces visites de contrôle, le dentiste prendra une empreinte classique, une empreinte optique, une radiographie et éventuellement des photographies endo-buccales pour évaluer la qualité de votre restauration dentaire sur les plans esthétique, fonctionnel et biologique.

4) Quels sont les bénéfices et les contraintes liés à votre participation ?

Vous bénéficierez d'un traitement par inlay-onlay de grande qualité, répondant aux concepts actuels de la dentisterie restauratrice moderne.

Votre inlay-onlay sera réalisé par CFAO avec des matériaux et techniques de pointe. La CFAO permet de réaliser la restauration au fauteuil, en direct, en une seule séance sans recourir aux services d'un prothésiste de laboratoire, d'obtenir des matériaux plus résistants car obtenus de façon industrielle et de gagner du temps en supprimant l'étape de temporisation.

La durée de vie d'un inlay-onlay réalisé par CFAO est supérieure à 10 ans (survie de 97% à 5 ans et de 90% à 10 ans).
La durée totale de votre présence dans le centre dentaire sera d'environ 2 à 3 heures pour la pose de l'inlay-onlay puis 30 à 45 minutes pour les visites de contrôle.

De plus, en participant à cette recherche, vous bénéficierez d'un suivi bucco-dentaire étroit et spécifique pour lequel aucun frais supplémentaire ne vous sera demandé. Par ailleurs, par votre participation, vous contribuerez à une meilleure connaissance des matériaux et facteurs favorables à la réalisation des inlays-onlays.

Si vous acceptez de participer, nous vous informons des points suivants à respecter :

- Avoir une bonne hygiène bucco-dentaire (vous devrez respecter les instructions et suivre les recommandations de votre chirurgien-dentiste quant au brossage, ou à l'utilisation du fil dentaire ou des brossettes interdentaires).
- Venir aux rendez-vous. En cas d'impossibilité, nous vous remercions de contacter votre chirurgien-dentiste le plus rapidement possible.
- Ne pas faire modifier l'inlay-onlay qui sera réalisé par un autre chirurgien-dentiste.
- Informer votre chirurgien-dentiste de toute modification de votre état bucco-dentaire ou général pouvant avoir un lien avec la dent qui sera soignée (allergie, grossesse, douleurs dentaires ou buccales, petit morceau de dent ou de prothèse cassé, nouvelles caries ou dents qui bougent…).
- Informer votre chirurgien-dentiste si vous participez à un autre projet de recherche.
- Etre affilié(e) à un régime de sécurité sociale ou être bénéficiaire d'un tel régime.

Pour votre participation à l'étude et en compensation des contraintes de la recherche, votre inlay-onlay sera gratuit. Vous recevrez, au bout de 2 ans, une indemnité d'un montant de 100 euros si vous êtes venu à tous vos rendez-vous.

5) Quels sont les risques prévisibles de la recherche?

L'inlay-onlay sera réalisé par un chirurgien-dentiste spécialisé et expérimenté dans ce domaine.

Dans le cadre de votre participation à ce projet, vous pouvez bénéficier de traitements qui sont, chacun, utilisés en pratique habituelle. En ce qui concerne votre prise en charge, la participation à la recherche ne vous fait donc courir aucun risque particulier.
Les risques que vous encourrez lors de la participation à cette recherche sont négligeables et sont identiques à ceux de la prothèse dentaire traditionnelle (allergie à l'un des matériaux utilisés, très rare ; fracture de votre dent ou de la restauration, rare ; reprise de carie, rare si votre hygiène bucco-dentaire est bonne ; sensibilités, rares et le plus souvent juste après le traitement ;...).
Le risque de réaction allergique à un composant n'est pas totalement exclu.
Les éléments de surveillance propres au protocole de recherche (empreintes et photographie) ne présentent que des risques négligeables pour vous.
Lors de l'empreinte en silicone, le silicone n'est quasiment jamais avalé ou en quantité négligeable, une dent trop mobile pourrait éventuellement être extraite.
Les risques encourus lors de l'empreinte optique, nécessaire pour la CFAO, sont quasiment nuls. La poudre d'Optispray, utilisée pour l'empreinte optique, peut éventuellement être avalée en faible quantité. En grande quantité, certains composants de la poudre d'Optispray peuvent provoquer une atteinte des poumons en cas d'ingestion, une irritation en cas de projection dans l'œil, un dessèchement ou des gerçures de la peau en cas d'exposition répétée et somnolence et vertiges en cas d'inhalation de vapeurs. Au vu des quantités utilisées et du mode d'utilisation de la poudre d'Optispray, aucune de ces complications n'a été rapportée à ce jour.

Les risques encourus lors de votre participation à cette recherche sont donc négligeables.

6) Que vont devenir les prélèvements effectués pour la recherche ?

Il n'y a pas de prélèvement dans cette recherche.

Les modèles en plâtre (issus des empreintes réalisées), photographies, clichés pris avec la caméra et radiographies réalisées dans le cadre de la recherche seront utilisés pour valider les résultats observés et comparer la céramique et le composite dans la réalisation d'inlays-onlays. Ils seront conservés pendant une durée de 5 ans (après la fin de l'étude) sous la responsabilité du Dr Jean-Pierre Attal dans le service de biomatériaux de la faculté de chirurgie dentaire de Montrouge (1 rue Maurice Arnoux, 92120).

Vous avez la possibilité à tout moment de demander à votre chirurgien-dentiste la destruction de ces modèles, photographies et radiographies ou de vous opposer à toute utilisation ultérieure.

7) Quelles sont les éventuelles alternatives médicales?

- Une couronne, qui délabrerait plus la dent.
- Cependant, il est possible que, le jour de la deuxième consultation, le chirurgien-dentiste s'aperçoive qu'un inlay-onlay n'est pas réalisable. Il vous proposera alors le traitement adapté, et vous ne participerez donc pas à la recherche.

8) Quelles sont les modalités de prise en charge médicale à la fin de votre participation?

Votre chirurgien-dentiste pourra décider à tout moment de l'arrêt prématuré de votre participation ; il vous en expliquera les raisons.
Après la fin de votre participation à cette présente recherche, votre prise en charge sera celle qui est effectuée habituellement dans le cadre de votre suivi bucco-dentaire.

9) Si vous participez, que vont devenir les données recueillies pour la recherche ?

Dans le cadre de la recherche biomédicale à laquelle l'AP-HP vous propose de participer, un recueil de vos données personnelles va permettre d'analyser les résultats de la recherche.
Les données administratives et bucco-dentaires vous concernant seront transmises à l'Assistance Publique-Hôpitaux de Paris (en particulier à l'unité de recherche clinique de l'Hôpital Européen Georges Pompidou). Ces données seront identifiées par un numéro de code et vos initiales. Ces données pourront également, dans des conditions assurant leur confidentialité, être transmises aux autorités de santé françaises.

Pour tout arrêt de participation sans retrait de consentement, les données recueillies précédemment à cet arrêt seront utilisées sauf si vous ne le souhaitez pas.

10) Comment cette recherche est-elle encadrée ?

L'AP-HP a souscrit une assurance (N°010051881403320110 52) garantissant sa responsabilité civile et celle de tout intervenant auprès de la compagnie HDI–GERLING par l'intermédiaire de BIOMEDICINSURE dont l'adresse est Parc d'Innovation Bretagne Sud C.P.142 56038 Vannes Cedex.
L'AP-HP a pris toutes les dispositions prévues par la loi relative à la protection des personnes se prêtant à des recherches biomédicales, loi Huriet (n° 88-1138) du 20 décembre 1988 modifiée par la loi de santé publique (n° 2004-806) du 9 août 2004.
L'AP-HP a obtenu l'avis favorable du Comité de Protection des Personnes Ile de France XI pour cette recherche le *14/05/2012* et une autorisation de l'Agence Française de Sécurité Sanitaires des Produits de Santé (Afssaps).

11) Quels sont vos droits ?

Votre participation à cette recherche est entièrement libre et volontaire. Votre décision n'entraînera aucun préjudice sur la qualité des soins et des traitements que vous êtes en droit d'attendre.
Vous pourrez tout au long de la recherche demander des explications sur le déroulement de la recherche au chirurgien-dentiste qui vous suit.
Vous pouvez vous retirer à tout moment de la recherche sans justification, sans conséquence sur la suite de votre traitement ni la qualité des soins qui vous seront fournis et sans conséquence sur la relation avec votre chirurgien-dentiste. A l'issue de ce retrait, vous pourrez être suivi par la même équipe médicale.

Conformément aux dispositions de la CNIL (loi relative à l'informatique, aux fichiers et aux libertés), vous disposez d'un droit d'accès et de rectification. Vous disposez également d'un droit d'opposition à la transmission des données couvertes par le secret professionnel susceptibles d'être utilisées dans le cadre de cette recherche et d'être traitées. Ces droits s'exercent auprès du chirurgien-dentiste en charge de la recherche qui seul connaît votre identité. Vous pouvez également accéder directement ou par l'intermédiaire d'un chirurgien-dentiste de votre choix à l'ensemble de vos données bucco-dentaires en application des dispositions de l'article L 1111-7 du Code de la Santé Publique.
Votre dossier médical restera confidentiel et ne pourra être consulté que sous la responsabilité du chirurgien-dentiste s'occupant de votre traitement ainsi que par les autorités de santé et par des personnes dûment mandatées par l'AP-HP pour la recherche et soumises au secret professionnel.

A l'issue de la recherche et après analyse des données relatives à cette recherche, vous pourrez être informé(e) des résultats globaux par l'intermédiaire du chirurgien-dentiste qui vous suit dans le cadre de cette recherche.

Pendant toute la durée de l'étude, vous pourrez contacter le Dr ATTAL, maître de conférence des universités et praticien hospitalier, par email à l'adresse : jean-pierre.attal@parisdescartes.fr, ou par téléphone : 01 58 07 68 02.

Si vous acceptez de participer à la recherche après avoir lu toutes ces informations et discuté tous les aspects avec votre chirurgien-dentiste, vous devrez signer et dater le formulaire de consentement éclairé se trouvant à la fin de ce document.

FORMULAIRE DE CONSENTEMENT

Je soussigné(e), Mme, Mlle, M. *[rayer les mentions inutiles]* (*nom, prénom*).....
accepte librement de participer à la recherche intitulée :

Essai randomisé multicentrique comparant la céramique et le composite dans le traitement des pertes de substance dentaires par inlays-onlays réalisés par CFAO : essai CECOIA

organisée par l'Assistance Publique - Hôpitaux de Paris et qui m'est proposée par le Docteur (nom, prénom, téléphone)....., chirurgien-dentiste dans cette recherche.

- J'ai pris connaissance de la note d'information version ~~1-0 du 14/03/2012~~ 2-0 du 21/06/2013, (4 pages) m'expliquant l'objectif de cette recherche, la façon dont elle va être réalisée et ce que ma participation va impliquer,
- je conserverai un exemplaire de la note d'information et du consentement,
- j'ai reçu des réponses adaptées à toutes mes questions,
- j'ai disposé d'un temps suffisant pour prendre ma décision,
- j'ai compris que ma participation est libre et que je pourrai interrompre ma participation à tout moment, sans encourir la moindre responsabilité et préjudice pour la qualité des soins qui me seront prodigués. J'indiquerai alors au chirurgien-dentiste qui me suit, si je souhaite ou non que les données recueillies, jusqu'au moment de ma décision, soient utilisées,
- Je suis conscient(e) que ma participation pourra aussi être interrompue par le chirurgien-dentiste si besoin,
- avant de participer à cette recherche, j'ai bénéficié d'un examen médical adapté à la recherche, dont les résultats m'ont été communiqués,
- j'ai compris que pour pouvoir participer à cette recherche je dois être affilié(e) à un régime de sécurité sociale ou bénéficiaire d'un tel régime. Je confirme que c'est le cas,
- j'ai bien été informé(e) que ma participation à cette recherche durera 2 ans, et que j'informerai mon chirurgien-dentiste si je participe à une autre recherche, avant la fin de l'essai CECOIA
- j'ai été informé(e) que mes modèles en plâtre, photographies endo-buccales et radiographies seront conservés et utilisés ultérieurement à des fins de recherche portant sur la dentisterie restauratrice.
- mon consentement ne décharge en rien le chirurgien-dentiste qui me suit dans le cadre de la recherche ni l'AP-HP de l'ensemble de leurs responsabilités et je conserve tous mes droits garantis par la loi.

Signature de la personne participant à la recherche		**Signature du chirurgien-dentiste**	
Nom Prénom :		Nom Prénom :	
Date :	Signature :	Date :	Signature :

Ce document est à réaliser en 3 exemplaires, dont l'original doit être conservé 15 ans par l'investigateur, le deuxième remis à la personne donnant son consentement et le troisième transmis à l'AP-HP sous enveloppe scellée à la fin de la recherche.

Appendix 17. Enregistrement dans le registre clinicaltrials.gov

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Trial record **1 of 1** for: NCT01724827
Previous Study | Return to List | Next Study

Ceramic Versus Composite in the Treatment of Posterior Teeth by Inlays or Onlays (CECOIA)

This study is currently recruiting participants.

Verified May 2012 *by Assistance Publique - Hôpitaux de Paris*

Sponsor:
Assistance Publique - Hôpitaux de Paris

Collaborators:
Ministry of Health, France
Hôpital Charles Foix - Service d'odontologie (APHP)
Hôtel Dieu - Service d'odontologie (Toulouse)
Dental practitionners

Information provided by (Responsible Party):
Assistance Publique - Hôpitaux de Paris

ClinicalTrials.gov Identifier:
NCT01724827

First received: September 10, 2012
Last updated: September 17, 2013
Last verified: May 2012
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer
How to Read a Study Record

Tracking Information	
First Received Date ICMJE	September 10, 2012
Last Updated Date	September 17, 2013
Start Date ICMJE	September 2012
Estimated Primary Completion Date	September 2016 (final data collection date for primary outcome measure)
Current Primary Outcome Measures ICMJE	FDI criteria for dental restorations assessment [Time Frame: at 2 years] [Designated as safety issue: Yes]

(submitted: November 9, 2012)	2 independent evaluators The primary outcome will consist in the FDI instrument for dental restorations assessment, as it was published after consensus in 2007 and updated in 2010 . This instrument is composed of three dimensions (biological, functional and esthetic), each consisting of several items that are assessed by clinical and radiographic examination according to Likert scales of 5 terms. Some items are evaluated quantitatively, others visually.The worst score of all items is retained as the overall score of the restoration, thus resulting in a single (ordinal) primary outcome.
Original Primary Outcome Measures **ICMJE**	*Same as current*
Change History	Complete list of historical versions of study NCT01724827 on ClinicalTrials.gov Archive Site
Current Secondary Outcome Measures **ICMJE** **(submitted: November 9, 2012)**	Restoration survival analysis [Time Frame: at 2 years] [Designated as safety issue: No] The primary outcome will consist in the FDI instrument for dental restorations assessment, as it was published after consensus in 2007 and updated in 2010 . This instrument is composed of three dimensions (biological, functional and esthetic), each consisting of several items that are assessed by clinical and radiographic examination according to Likert scales of 5 terms. Some items are evaluated quantitatively, others visually.The worst score of all items is retained as the overall score of the restoration, thus resulting in a single (ordinal) primary outcome. wear [Time Frame: at 2 years] [Designated as safety issue: No] The primary outcome will consist in the FDI instrument for dental restorations assessment, as it was published after consensus in 2007 and updated in 2010 . This instrument is composed of three dimensions (biological, functional and esthetic), each consisting of several items that are assessed by clinical and radiographic examination according to Likert scales of 5 terms. Some items are evaluated quantitatively, others visually.The worst score of all items is retained as the overall score of the restoration, thus resulting in a single (ordinal) primary outcome. overall quality of the restoration [Time Frame: at 2 years] [Designated as safety issue: No] The primary outcome will consist in the FDI instrument for dental restorations assessment, as it was published after consensus in 2007 and updated in 2010 . This instrument is composed of three dimensions (biological, functional and esthetic), each consisting of several items that are assessed by clinical and radiographic examination according to Likert scales of 5 terms. Some

	items are evaluated quantitatively, others visually.The worst score of all items is retained as the overall score of the restoration, thus resulting in a single (ordinal) primary outcome. FDI instrument validity data [Time Frame: at 2 years] [Designated as safety issue: No] The primary outcome will consist in the FDI instrument for dental restorations assessment, as it was published after consensus in 2007 and updated in 2010 . This instrument is composed of three dimensions (biological, functional and esthetic), each consisting of several items that are assessed by clinical and radiographic examination according to Likert scales of 5 terms. Some items are evaluated quantitatively, others visually.The worst score of all items is retained as the overall score of the restoration, thus resulting in a single (ordinal) primary outcome.
Original Secondary Outcome Measures ICMJE	*Same as current*
Current Other Outcome Measures ICMJE	*Not Provided*
Original Other Outcome Measures ICMJE	*Not Provided*
Descriptive Information	
Brief Title ICMJE	Ceramic Versus Composite in the Treatment of Posterior Teeth by Inlays or Onlays
Official Title ICMJE	Ceramic Versus Composite in the Treatment by Inlays or Onlays of Posterior Teeth Affected by Tooth Substance Loss : a Multicenter Randomized Controlled Trial
Brief Summary	The main purpose of this trial is to determine which material, between ceramic and composite, is best to manufacture dental inlays and onlays in the treatment of moderate dental substance losses, generally due to dental caries. Restorations will be done using direct Computer Assisted Design and Manufacturing (CAD-CAM). Another aim of this study is to determine which factors influence the success of these restorations.
Detailed Description	WHO estimates dental caries prevalence to be over 90% adults worldwide. When tooth substance loss due to the decayed tissue is small, a filling is done by the dentist directly. When the substance loss is important, dentists often treat it with a crown, which presents the disadvantage of further mutilating the tooth. An intermediate technique consists in manufacturing an inlay or an onlay: these restorations become more and more common

	since they are a minimally invasive solution in such cases. Inlays and onlays can be made of metal, ceramic or composite. Patients tend to refuse metallic restorations, so that dentists generally have to choose between composite and ceramic. Composite wears whereas ceramics fracture. Published in vitro studies provide possible answers to which material is most effective but very few clinical studies have been conducted to confirm them. Material\'s choice for inlay manufacturing is thus more country-based than evidence-based (Most french dentists choose composite while US dentists prefer ceramics for example). The main objective of this trial is to compare the clinical performance of ceramic and composite inlays/onlays. Other objectives include looking for the prognostic factors of these restorations and validating the criteria proposed by the World Dental Federation (FDI) to evaluate dental restorations.
Study Type ICMJE	Interventional
Study Phase	Phase 3
Study Design ICMJE	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Open Label Primary Purpose: Treatment
Condition ICMJE	• Dental Caries • Inlays
Intervention ICMJE	• Device: ceramic (Empress CAD, Ivoclar Vivadent) Leucite-reinforced glass ceramic (Empress CAD, Ivoclar Vivadent) • Device: composite (Lava Ultimate, 3M Espe) Nanohybrid composite resin (Lava Ultimate, 3M Espe)
Study Arm (s)	• Active Comparator: ceramic Leucite-reinforced glass ceramic (Empress CAD, Ivoclar Vivadent) Intervention: Device: ceramic (Empress CAD, Ivoclar Vivadent) • Active Comparator: composite Nanohybrid composite resin (Lava Ultimate, 3M Espe) Intervention: Device: composite (Lava Ultimate, 3M Espe)
Publications *	• Hickel R, Roulet JF, Bayne S, Heintze SD, Mjör IA, Peters M, Rousson V, Randall R, Schmalz G, Tyas M, Vanherle G. Recommendations for conducting controlled clinical studies of dental restorative materials. Science Committee

Project 2/98--FDI World Dental Federation study design (Part I) and criteria for evaluation (Part II) of direct and indirect restorations including onlays and partial crowns. J Adhes Dent. 2007;9 Suppl 1:121-47. Review. Erratum in: J Adhes Dent. 2007 Dec;9(6):546.

- Hickel R, Peschke A, Tyas M, Mjör I, Bayne S, Peters M, Hiller KA, Randall R, Vanherle G, Heintze SD. FDI World Dental Federation: clinical criteria for the evaluation of direct and indirect restorations-update and clinical examples. Clin Oral Investig. 2010 Aug;14(4):349-66. Epub 2010 Jul 14.

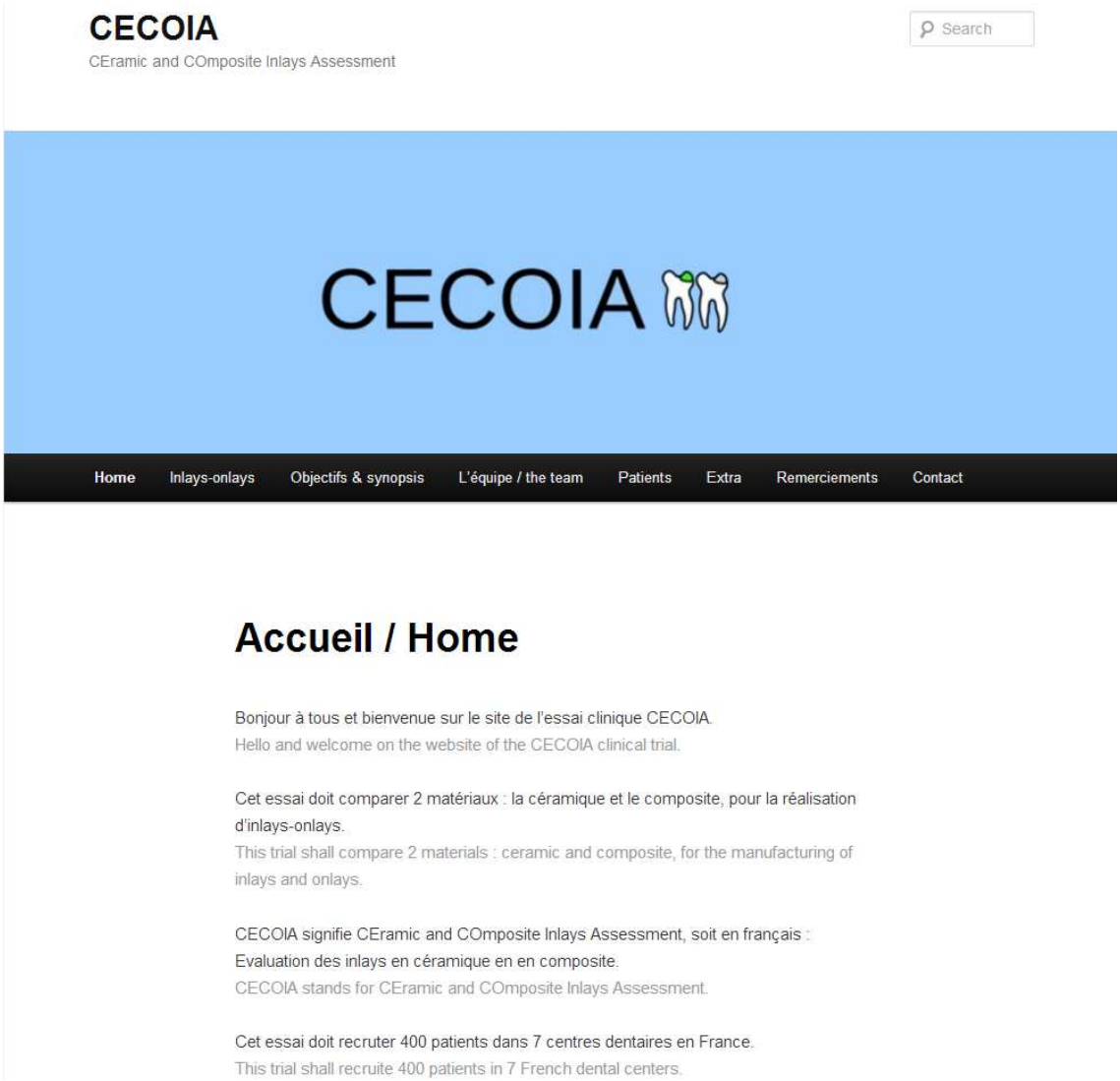
*** Includes publications given by the data provider as well as publications identified by ClinicalTrials.gov Identifier (NCT Number) in Medline.**

Recruitment Information	
Recruitment Status ICMJE	Recruiting
Estimated Enrollment ICMJE	400
Estimated Completion Date	September 2016
Estimated Primary Completion Date	September 2016 (final data collection date for primary outcome measure)
Eligibility Criteria ICMJE	Inclusion criteria : - patient aged 18-70,who tolerates restorative procedures and presents a moderate-sized dental caries or restoration (that needs to be replaced) necessitating an inlay/onlay restoration. Exclusion criteria : - allergy to one of the materials employed, bruxism, severe or acute periodontal or carious disease, poor oral hygiene - Tooth presents a mobility > II, a periodontal socket > 3mm or supports a removable partial denture Randomization criterium : - tooth necessitates an inlay-onlay restoration after caries or former restoration removal Exclusion from randomization criteria : - subgingival margin after cavity preparation, rubber dam cannot be placed, all tooth cuspids need to be covered by the restoration.
Gender	Both

Ages	18 Years to 70 Years
Accepts Healthy Volunteers	No
Contacts ICMJE	Contact: jean-pierre attal, DDS, PhD — 01 58 07 67 82 ext 33 — jean-pierre.attal@parisdescartes.fr
Location Countries ICMJE	France
Administrative Information	
NCT Number ICMJE	NCT01724827
Other Study ID Numbers ICMJE	P110129
Has Data Monitoring Committee	No
Responsible Party	Assistance Publique - Hôpitaux de Paris
Study Sponsor ICMJE	Assistance Publique - Hôpitaux de Paris
Collaborators ICMJE	Ministry of Health, France Hôpital Charles Foix - Service d'odontologie (APHP) Hôtel Dieu - Service d'odontologie (Toulouse) Dental practitionners
Investigators ICMJE	Study Director: hélène fron chabouis, DDS, MSc — APHP, Hôpital Charles Foix, Service d'odontologie, Ivry-sur-Seine, France ; Faculté de chirurgie dentaire, Service de biomatériaux (URB2i EA4462), Université Paris Descartes, Sorbonne Paris Cité, Montrouge, France.
Information Provided By	Assistance Publique - Hôpitaux de Paris
Verification Date	May 2012

ICMJE **Data element required by the International Committee of Medical Journal Editors and the World Health Organization ICTRP**

Appendix 18. Homepage of the cecoia.fr website



Appendix 19. Elements of the systematic review on the bond strength of five machinable esthetic materials to resin cements

Search equation

(((((bond strength*) OR ((adhe* AND MPa)))) AND ((((((Mark2 OR Mk 2 OR Mk2 OR mark 2 OR mkii OR mk ii OR mrakii OR mark ii OR albite*)) OR (emax cad OR (emax AND CAD) OR (lithium* AND *disilicate* AND ceramic*))) OR (empress cad OR empress cad OR (leucite* AND ceramic*))) OR enamic) OR (lava ultimate OR (lava AND ultimate))))) AND ((adhesive*) AND (cement* OR luting*))

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Information retrieved

Ref	**Test**	**Partner 1**	**Adhesive**	**Cement**	**Partner 2**	**Aging**	**Bond strength (MPa)**
1	SBS	Dentin (M3)	1 Step	Illusion	Empress 2	10mn OR 24h 1000TC	13.2-15.9
2	MTBS	Dentin (M)	1 Step +	Duolink	IPS Empress	24h 6000TC	8.6-19.6
3	MTBS	Dentin	XP Bond Enabond ED Primer	Core X Flow Enacem Panavia RelyX Unicem	Composite (Enamel-Plus HFO) Ceramic (Reflex, Wieland)	24h 5000TC	18.29-31.39 4.36-7.16
4	MTBS	Dentin (M)	-	iCem SA Maxcem RelyX Unicem Enacem Panavia F2	Composite IPS Empress		
5	MTBS	Composite (Z250)	-	Single Bond	Leucite reinforced : Omega 900 (Vita)	7day H_2O	10.17-10.19
6	Apparent interfacial fracture toughness	Composite (Z100)	-	-	Empress 2 Empress 1	7 days air (indentation) 24h air	HF 0.31 S 0.13 HFS 0.41 HF 0.26 S 0.23 HFS 0.30
7	MTBS	Composite	Scotchbond	-	Empress 1	30day H_2O	HF 9.9 S 27.2

		(Z100)	MPP		Empress 2		HFS 20.6 HF 41.7 S 30.1 HFS 56.1
8	Vickers indenter method ology		One Step		Ceramic Vitapan 3D master		
9 E							
10	MTBS	Dentin or enamel (M)	One Step +	Duolink ± fiber reinforced composite	Empress 2	6000TC	
11	MTBS	Composite (Tetric EvoCeram)	-	D/E Resin	IPS Empress	?	HF 22.8 HFS 18.5 HFSair 27.8 Sair 28.5 (100°C)
12	SBS				Ceramic specime ns (feldspathic, leucit e, leucite-free, and fluorapatite)		HF 34.11
13	Push-out BS	Dentin (M)	Syntac	Variolink II SpeedCem RelyX Unicem SmartCem 2 iCem	**IPS Empress CAD**	24h or 5000TC+H_2O 6months	7.23 (24h) 9.47
14	SBS	Dentin	Excite DSC Scotchbond MPP	Variolink II Rely X ARC	**Vitablocs Mark II**	24h H_2O	22Hf / 29HfS 22Hf /26HfS
15	MTBS	Composite (Tetric n-Ceram)	-	Rely X ARC	e.max Press	24h H_2O 3000TC 100000FC 2Hz	35.0 24.3 23.9
16	MTBS	Dentin (bovine incisors)	Excite DSC (Clearfil SE Bond)	Variolink II RelyX Unicem wet dentin RU dry dentin RU + Clearfil SE B	IPS Empress esthetic	24h H_2O	19.0 18.5 9.1 24.2
17	TBS	Composite (Multicore	-	Multilink Automix	e.max Press	3 days 150 days	saliva +

		flow)				37500TC	HF/H3PO4 38-49 saliva&silicone +HF 44-50
18	SBS	Composite (Z250)	Scotchbond MP+	-	IPS Empress	24h H_2O	HF9.6%4mn 17.64 polished1200 7.6
19	SBS	*(cement)*	Etching agent/silane+CSEb HF9.5%60s S Heliobond HF9.5% 60s S	Panavia 21 Panavia F RelyX Unicem Variolink 2 Rely X ARC	IPS Empress 2	24h H_2O / 24h H_2O 6000TC	5.8 / 2.4 10.2 / 4.8 6.6 / 3.8 26.0 / 23.2 28.7 / 8.4
20	SBS SCT	IPS e.max Zircad		Resicem Panavia F2 Multilink Resicem Panavia F2 Multilink	IPS Empress CAD (Rocatec, silane, functional primer)	24h H_2O 24h H_2O / 10000TC	28 40 19 39 / 27 40 / 20 40 / 27
21	SBS	Composite (Z250)	Adper single bond	Rely X ARC	IPS Empress 2 (surfacettt + Rely X ceramic primer)	24h H_2O	HF9.5%60s 8.4 Er,Cr :YSGG 3.6-3.8 Polish1000 1.9
22	MTBS	Lithium-disilicate ceramic Dentin (M3)	manufact. Recomm.	Multilink Panavia F Superbond C&B Multilink Panavia F Superbond C&B	Lithium-disilicate ceramic (HF4%+S)	None / 12000TC 150 days H_2O	18 / 18 27 / 16 27 / 27 no sign diff after aging
23	TBS	Dentin (M)	Syntac	TetricCeram	Leucite reinforced ceramic inserts (SonicSys)	24h H_2O	10 (pre etched pre silanated) 10 (HF+S)
24	µSBS (+roughness)			Variolink 2 Linkmax HV Clearfil esth. cem Superbond C&B	Glass ceramic with leucite crystallites	None / 30000TC	
25	SBS	IPS Empress 2	-	Variolink 2 MonobndS+Var2	IPS Empress 2 P=H3PO4	24h H_2O / 100000TC	P14 /0,HF53/47,A31/0 P65/53,HF71/

				Super Bond PorcelainLinM+SB	HF=HF20s A=airabr		61,A65/60 P11/0,HF31/24,A17/0 P36/27,HF35/35,A35/27
26	µSBS	*(cement)*	-	Variolink 2	Empress Esthetic (leucite-reinforced)	24h H_2O	HF60s-S 18 HF40s-S 22[a] HF60s+unfilled resin 25[a]
27 E							
28	MTBS	ProCad	-	Variolink 2	**ProCad**	24h H_2O	H3PO4 19 H3PO4-S 27 HF 37.6 HFS 34.6
29	SBS	Dentin		Variolink 2 Panavia F2 Multilink Rely X Unicem Maxcem	NobelRondo Finesse All-Ceram (leucite) Sinfony (composite)	1week H_2O	xxx
30	SBS	Dentin	Excite DSC ED Primer Multil. A+B - -	Variolink 2 Panavia F2 Multilink Rely X Unicem Maxcem	NobelRondo Finesse All-Ceram (leucite) Sinfony (composite)	1week H_2O	Cf PDF
31	SBS	Composite (Herculite XRV)		(RelyX ARC) Panavia F (Variolink 2) (Compolute) ReyX Unicem	IPS Empress (HFS) IPS Empress 2 (HFS)	30mn / 14days H_2O 1000TC	P 10 / 23 U 13 / 22 P 7 / 10 U 14 / 18
32	Push out BS	Dentin (M3)	Excite	Variolink 2	e.max Press	24h H_2O	17
33	MTBS	Composite (2 different)	Adhesive ?	-	**Vita Mark** II	30days H_2O 7000TC	HFS 30 / 34
34	MTBS	Dentin (M)	Syntac Syntac OptibSolo+ OptibSolo+ (p: pre curing)	Tetric ceram Variolink 2 Prodigy Nexus 2	**Vitablocs Mark** II 2mm / 4mm thick	24h H_2O	16/p19/10/p17 17/p22/14/p28 14/p16/12/p16 18/p22/16/p22

35	SBS	*(Cement)*	-	Rely X Unicem Callibra Variolink 2	**Vita Mark** II	5000TC, 10000TC	Cf table
36	SBS			Variolink 2 Nexus Panavia F2	**Vita Mark** II	24h dry / +5000TC	HF H3PO4 H3PO4
37 E	SBS	Metal bracket			IPS Empress esthetic…		
38	MTBS	Dentin	- ED Primer ED Primer Prime&bon dNT, Excite	Unicem (Maxcem, Monocem, Multilink Sprint) Panavia F2 (Clearfil esthetic cement, Calibra, Variolink 2)	**Vita Mark** II (HF, S, Heliobond)	1week H_2O	20 20
39	PBS	Dentine ? (bovine incisors)	Clearfil SE B		Z250 Esthet-x		
40	MTBS	*(cement)*	-	Variolink 2 RelyX U100 Biscem, Maxcem Elite	**Vita Mark** II (no conditionning) / HFS	Immediate, 12000TC	24/19TC 23/22TC
41	TBS	Dentin	Syntac Syntac	RelyX Unicem Variolink 2 G-Cem, ArtcemGI Variolink 2	**artBloc Temp** (PMMA : no ttt / 50µm Al2O 3 **Vita Mark** II (HF S Heliobond)	Initial, TCL : « a » (6000TC, 1.2millionFC)	0/a0/2.2/a1.9 0/a0/0/a0 7.3/a6.4
42	SBS	composite		??	Leucite reinforced pressed (HF S)	1week H_2O 1000TC / +27500FC	
43	TBS	Enamel / dentine		Vita Cerec ? Panavia 21 TF	**Vita Mark** II (Plat 2 ceramic)		8.9 / 8.5 7.5 / ? poor
44	TBS	Dentin (M3)	ED Primer 2	Clearfil esthetic cement	IPS e.max press	24h H_2O + 6000TC	Median 22.6

Table 8. Information retrieved from the systematic search : bond strength test used, partners of the assembly, aging process and bond strength results

TC = thermocycles FC = fatigue cycles TCL= thermomechanical cyclic loading SCT = Schwickerath crack initiation test

Appendix 20. Machinability of different tooth-colored materials: upper surfaces of machined inlays

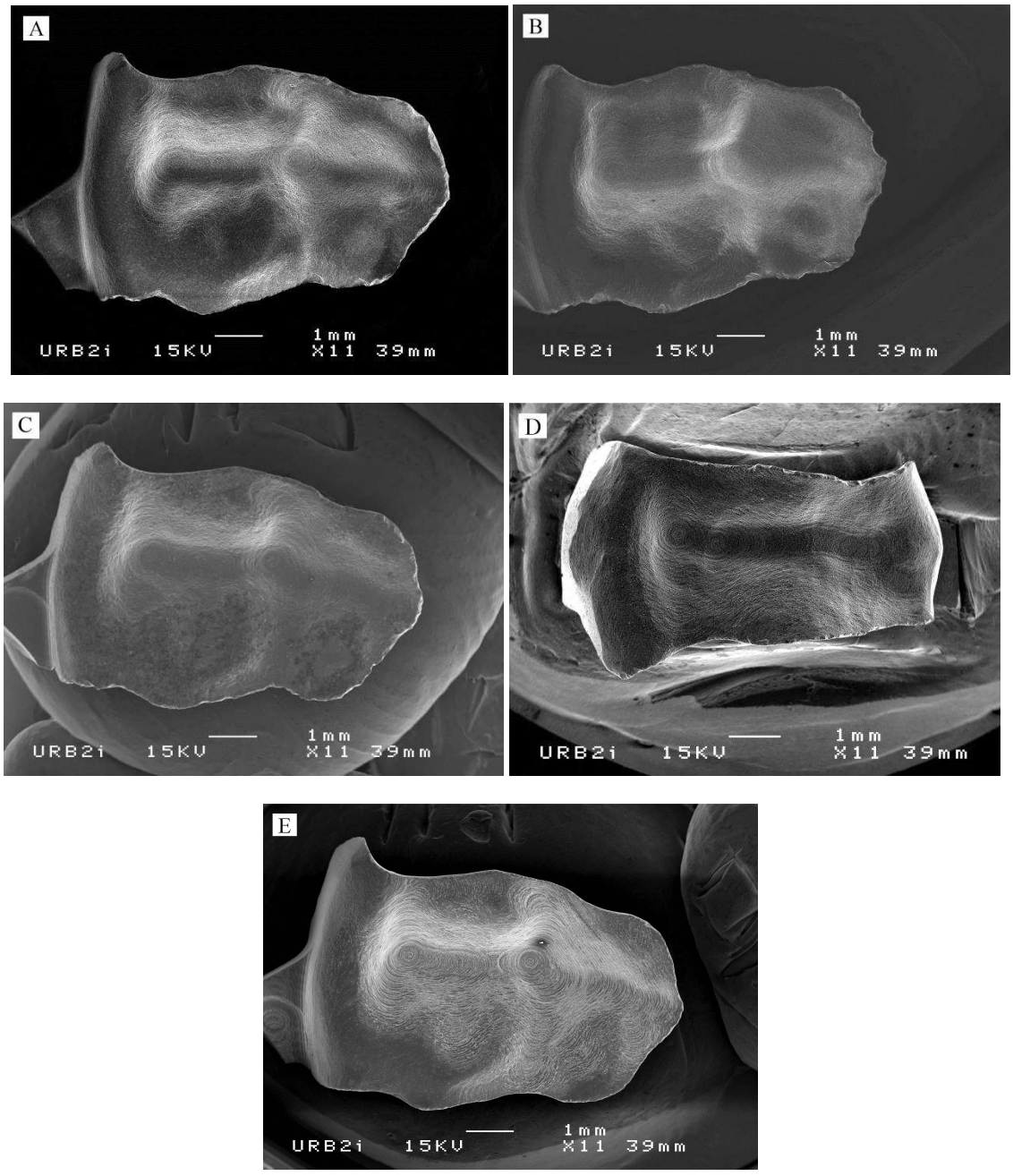

Figure 30. SEM images of the upper surfaces of inlays machined with a milling unit (Cérec MCXL, Sirona) A. MK, B. EMP, C. EM, D. EN, E. LU

Appendix 21. Machinability of different tooth-colored materials: intaglio surfaces of machined inlays

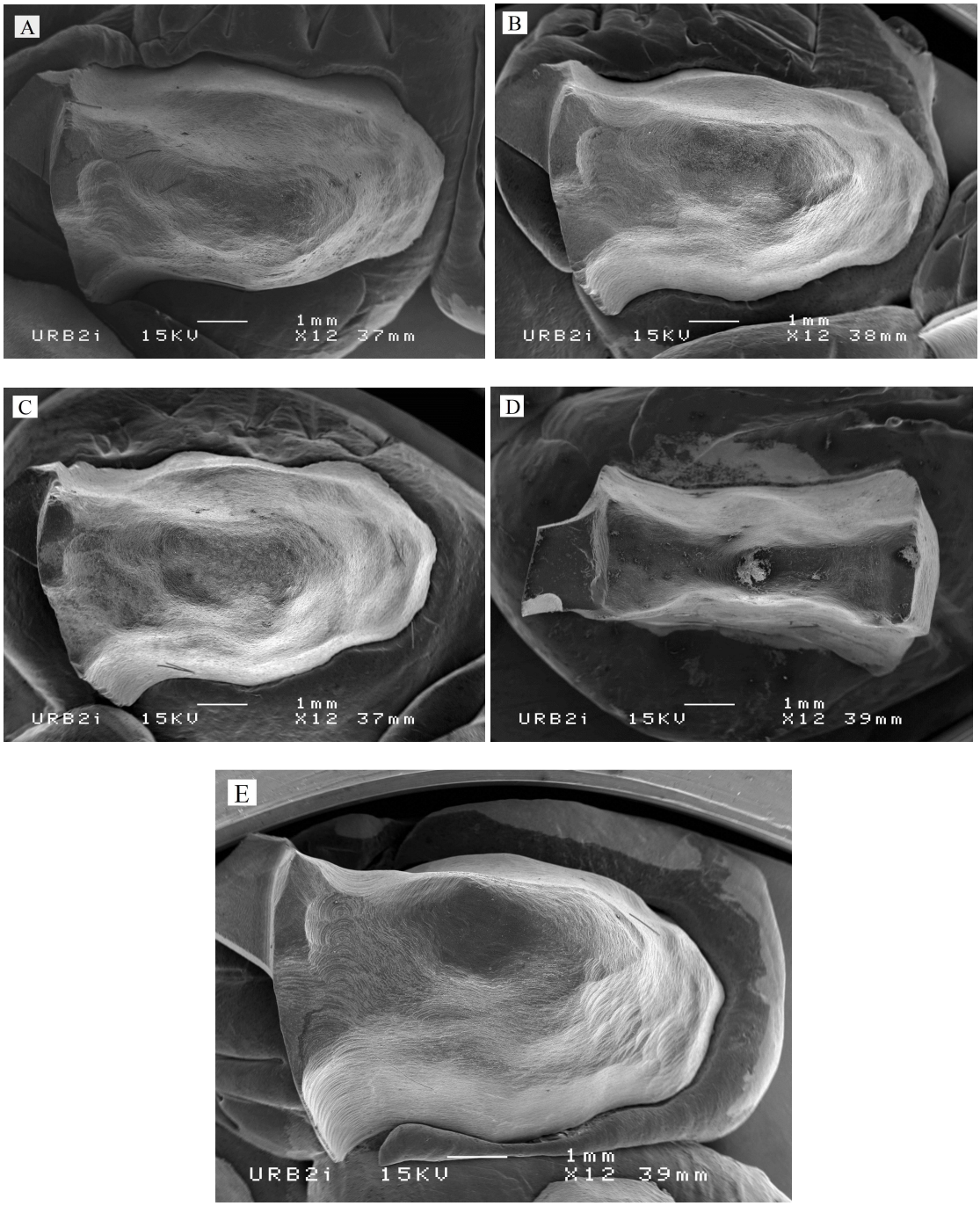

Figure 31. SEM images of the intaglio surfaces of inlays machined with a milling unit (Cerec MCXL, Sirona)
A. MK, B. EMP, C. EM, D. EN, E. LU
(The machining strategy in circular arcs adopted by the Cerec system is objectified, especially for LU)