

PROTOCOL TITLE:

“The survival of teeth and/or restoration following root canal treatment with varying degrees of tooth structure loss restored with CAD CAM restorations”

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CONTENTS

1. Background & Rationale.....	5
2 Trial Objectives, Design and Statistics	7
2.1. Trial Objectives.....	7
2.2 Trial Design & Flowchart	7
2.3 Trial Flowchart.....	8
2.4 Trial Statistics	9
2.4.1 Sample Size.....	9
2.4.2 Recruitment and Retention.....	9
2.4.3 Randomisation	10
2.4.4 Analysis.....	10
3 Selection and Withdrawal of Subjects	10
3.1 Inclusion Criteria	10
3.2 Exclusion Criteria	11
3.3 Withdrawal of Subjects.....	11
4 Assessment of Efficacy	11
4.1 Efficacy Parameters	11
4.1.1 Primary Efficacy Parameters	11
4.1.2 Secondary Efficacy Parameters	11
4.2 Procedures for Assessing Efficacy Parameters.....	12
5 Assessment of Safety	12
6. Definition of the End of Trial.....	13
7. Direct Access to Source Data and Documents	13
8. Ethics and Regulatory Approvals	13
9. Quality Assurance, Data Handling, Publication Policy and Finance.....	14
10. References.....	14

Study Synopsis

Title of clinical trial	The success and survival of teeth and restoration following root canal treatment with varying degrees of tooth structure loss restored with CAD CAM restorations.
Protocol Short Title/Acronym	Survival of root canal treated tooth restored using ceramic onlays
Sponsor name	King's College London
Chief Investigator	Prof. Francesco Mannocci
REC number	17/NW/0594
Medical condition or disease under investigation	Investigation of endodontically treated teeth's success and survival rate at 1-2 years post treatment.
Purpose of clinical trial	To compare the success and survival rate of endodontically treated teeth and restoration with varying degrees of tooth structure loss restored with CAD CAM restorations
Primary objective	To investigate whether varying amounts of residual tooth structure have an influence on the success and survival rate of endodontically treated teeth and restoration at 1-2 years post treatment restored using CAD CAM restorations
Secondary objective (s)	To assess the survival of the CAD CAM restorations on root canal treated teeth and determine the main types of failure.
Trial Design	Case control
Sample Size	120patients
Summary of eligibility criteria	Patients either male or female over the age of 18 in good general health needing root canal treatment.
Version and date of final protocol	Version 1.6 date: 29-06-2017

1. Background & Rationale

Enlargement and shaping of the root canal space are the main objectives of root canal treatment, then sealing it in 3 dimensions to avoid any infection in the future [1, 2]. Wide range of instruments and techniques have been used to accomplish root canal treatment [3].

Although initial root canal therapy has been shown to be a predictable procedure with a high degree of success [4-7], failures can occur after treatment. Recent publications reported failure rates of 14%–16% for initial root canal treatment [4, 6-8].

Lack of healing is attributed to persistent intraradicular infection residing in previously uninstrumented canals, dentinal tubules, or in the complex irregularities of the root canal system [9-12]. The extraradicular causes of endodontic failures include periapical actinomycosis [13], a foreign body reaction caused by extruded endodontic materials [14, 15], an accumulation of endogenous cholesterol crystals in the apical tissues [16], and an unresolved cystic lesion [17, 18]. The preferred treatment of failing endodontic cases is nonsurgical retreatment. According to [6, 19-22] this treatment usually results in successful outcomes.

Conflicting results are present in the literature in relation to the survival of endodontically re-treated teeth. Well controlled trials at 4 years [23] did not find any significant difference between survival of root canal treated and root canal re-treated teeth, whereas the comparison of epidemiologic studies conducted on the survival of teeth following primary and secondary endodontic treatment in dental practices [7, 24] shows that many more re-root canal treated teeth are extracted in the long term. The only information available on the effect of the restoration type on the survival of re-root canal treated teeth is that teeth restored with a cast restoration and teeth not requiring a post for the retention of the crown survive longer. Advances in technology, materials and techniques offer more contemporary ways to restore endodontically treated teeth. One of them is the computer aided design and computer aided manufacturing of ceramic onlays and crown. While this is an established and successful treatment for vital teeth, there are no randomised clinical trials showing its efficacy in endodontically treated teeth.

Cone beam computed tomography (CBCT) is a contemporary, radiological imaging system designed specifically for use on the maxillofacial skeleton. The system overcomes many of the limitations of conventional radiography by producing undistorted, three-dimensional images of the area under examination. These properties make this form of imaging particularly suitable for use in endodontics [25]. Recent laboratory and clinical investigations have revealed that periapical disease may be detected sooner using CBCT compared with periapical views and the true size, extent, nature and position of periapical and resorptive lesions can be assessed [26].

This CBCT study will compare the success and survival rate of endodontically treated teeth with varying degrees of tooth structure loss restored with CAD CAM (Computer Aided Design Computer Aided Manufacturing) restorations, which are routinely used for the clinical care of patients.

This will be carried out at KCL Dental Institute at Guy's Hospital and will form part of the routine dental treatment done at the dental clinics. Potential volunteers will be given written information about the process (see attached information sheet) and be given time to consider participation. Once any questions have been answered, fully informed written consent will be obtained if they are interested in taking part.

Patients requiring endodontic treatment with varying degrees of tooth structure loss will be detected and diagnosed and treated by endodontic MclinDent postgraduate students at Guy's hospital using suitable clinical techniques.

Immediately after root canal treatment has been completed and at patients' review appointments in addition to the conventional radiograph we would also take an additional specialised 3-dimensional Cone Beam Computed Tomography (CBCT) scan of the tooth. Clinical evaluation and radiographic assessment including dental periapical radiograph and Cone Beam Computed Tomography (CBCT) scans will be done at baseline, 12 months and 24 months.

There are no side effects of taking part in this study other than those expected from exposure to ionising radiation taken during routine operative dental care. Every exposure to ionising radiation carries a risk, but due to the low doses of radiation from dental radiology including CBCT, this risk is negligible. The effective dose of a conventional radiograph and a cone beam computed scan is 5 μ Sv and 66 μ Sv (micro Sieverts) respectively, equivalent to 0.19% and 2.43% annual background radiation respectively.

The total radiation dose corresponds to approximately 28 days equivalent natural background radiation, where background radiation is approximately 2.7 mSv per year in the UK.

This clinical trial will be conducted in compliance with the principles of the Declaration of Helsinki. The protocol will be submitted for approval to an NHS Research Ethics Committee.

2. Trial Objectives, Design and Statistics

2.1. Trial Objectives

Aims and Objectives:

The clinical trial aims to investigate whether varying amounts of residual tooth structure have an influence on the success and survival rate of endodontically treated teeth and/or restoration at 1-2 years post treatment by using Cone Beam Computed Tomography (CBCT).

Primary and Secondary endpoints:

The principal outcome of the study is to assess the success and survival of endodontically treated teeth and restoration at 1 and -2 years post treatment restored using CAD CAM restorations. The secondary outcome measure is to assess the survival of the CAD CAM restorations on root canal treated teeth and determine the main types of failure.

2.2 Trial Design & Flowchart

The study is a case control comparing the success and survival rate of endodontically treated teeth with varying degrees of tooth structure loss restored using CAD CAM restorations.

Patients requiring endodontic treatment will be assessed clinically and radiographically and divided into groups defined according to the residual coronal dentin after root canal treatment into four groups (less than 33% , 33%-50%, 50%-66% and more than 66% of tooth structure remaining). The endodontic treatment and final restoration will be accomplished by Endodontic MclinDent Postgraduates Students (Endodontic Postgraduate Unit, Guy's Hospital, Guy's & St. Thomas' NHS trust) who will be trained

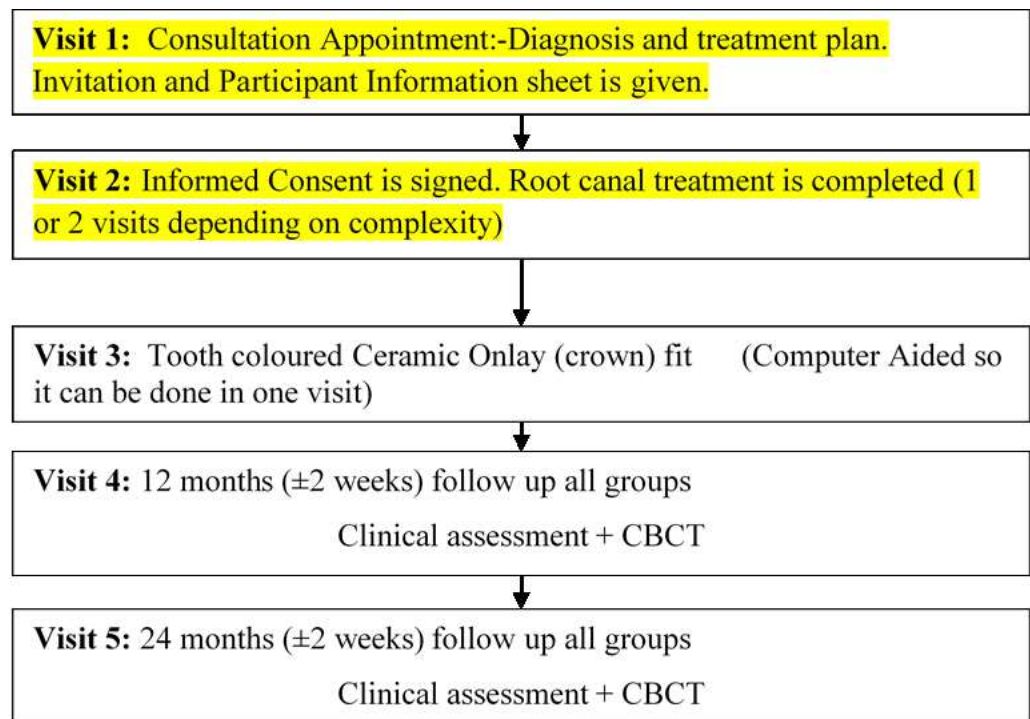
to ensure standardisation of the endodontic and operative procedures by using one of the indirect/direct restorations.

Dental periapical radiograph and Cone Beam Computed Tomography (CBCT) scans will be taken at baseline, 12 months and 24 months. The patients will be sent a reminder to attend the follow up by email, letter or SMS. Clinical assessment and radiographical evaluation of Cone Beam Computed Tomography (CBCT) scans will be carried out immediately after endodontic treatments have been accomplished and 1 and 2 years post operatively and will be assessed independently by a group of examiners.

Four examiners (Endodontists n=2, Radiologists n=2) will view the randomised images under standardised conditions. The examiners will also be trained on how to interpret CBCT data before looking at images. The restorations will be assessed clinically.

2.3 Trial Flowchart:-

STUDY FLOWCHART



2.4 Trial Statistics

2.4.1 Sample Size

The sample size calculation for this study was based on chi-test for testing the association between tooth surface lost (<33%, 33-66% and >66%) and Root Canal Treatment status (Success or Failure). A study with an effect size of 0.3 and a power of 80% will require a total sample of 108 to test the association at 5% levels using two tailed test. The power calculation was carried out using Gpower 3.1.7.

In a previous study by Ferrari et al. (2012), a sample of 345 patients provided 6 groups of 60 premolars each in need of endodontic treatment. Groups were classified according to the number of remaining coronal walls before abutment build-up. Within each group, teeth were allocated to one of three subgroups: (A) no post retention; (B) prefabricated post; or (C) customized posts (N = 20). The authors found that failure risk was lower in teeth restored with prefabricated ($p = 0.001$) than with customized posts ($p = 0.009$). Teeth with one ($p = 0.004$), two ($p < 0.001$), and three coronal walls ($p < 0.001$) had significantly lower failure risks than those without ferrule and similar failure risks existed for teeth without coronal walls, regardless of the presence/absence of ferrule ($p = 0.151$). Sample size calculation for this study was based on comparing success rates for the four groups using chi-square test. This study designed to have 80% power to detect the difference in success rates between the four groups at 5% level of significance with an effect size of 0.35 using a two-tailed test. Assuming a dropout rate of 25% at the end (after 2 years of root canal re-treatment), it requires a sample size of 120

2.4.2 Recruitment and Retention

Patients who have been referred to the Endodontic Postgraduate Unit or assessment clinics at King's College Dental Institute at Guy's Hospital for root canal treatment will first undergo an examination at the assessment clinic to diagnose and treatment plan their problem by the postgraduate students under supervision of the Consultants in charge of the Endodontic clinic. This is to check if the tooth is indicated for root canal treatment or extraction.

If they are indicated for root canal treatment and satisfies the inclusion criteria of the clinical trial, they will be given the invitation letter and Patient Information Sheet.

They then have about two weeks, before their scheduled appointment to decide if they want to take part in the study or not. If they express an interest, at this appointment, they will then be explained the study by the treating post graduate student, who is part of the research team and thereby begin the informed consent process. Consented patients will be allocated an anonymised number.

If they do not wish to take part, they will still receive routine treatment as planned at the assessment clinic

2.4.3 Randomisation

Randomisation is not applicable, as the patients will be divided according to the number of tooth structure lost.

2.4.4 Analysis

Descriptive statistics will be used to summarise the sample characteristics and baseline measurements. Chi square test for association will be used to test whether there is any relationship between success rate and different groups. The difference in success rate over a period of time will be analysed using survival analysis. This will involve Kaplan-Meier graph and cox regression predictors of failure rate. All analysis will be carried out by using SPSS version 20.

3. Selection and Withdrawal of Subjects

3.1 Inclusion Criteria

- 1) Patients either male or female over the age of 18 (who can consent for themselves) in good general health.
- 2) The selected teeth needed to be in occlusal function with a natural tooth and in interproximal contact with two adjacent natural teeth.

- 3) Molar or premolar teeth with suspected endodontic problems that require root canal treatment.
- 4) Teeth should not be mobile and must be restorable.

3.2 Exclusion Criteria

- 1) Pregnant women, in view of requirements for radiographs (or if they could possibly be pregnant). To be confirmed by the Medical History Questionnaire.
- 2) Patients younger than 18.
- 3) Patients unable to give consent.
- 4) Teeth with probing periodontal depths greater than 5 mm.
- 5) Non-restorable teeth.
- 6) Not involving patients from prisons.
- 7) Not involving patients who cannot read, write or understand English

3.3 Withdrawal of Subjects

The participant would be withdrawn from the study if he or she no longer wishes to participate in the study or has relocated and will be unable to attend. Data or tissue, which is not identifiable to the research team, may be retained. Any identifiable data or tissue would be anonymised or disposed of.

4. Assessment of Efficacy

4.1 Efficacy Parameters

Parameters used to assess efficacy of the study will depend upon the participant's signs and symptoms, clinical examination and radiographical assessment.

4.1.1 Primary Efficacy Parameters

The primary efficacy parameter will be the success of teeth in relation to the absence of any signs and symptoms, endodontic or restorative failures.

4.1.2 Secondary Efficacy Parameters

The survival of teeth and or restoration in the oral cavity.

4.2 Procedures for Assessing Efficacy Parameters

Patients will be recalled after 12 and 24 months for clinical and radiographical assessments. Four examiners other than the operator independently performed evaluation of success or failure.

Clinical examination should reveal the absence of the following events which considered if present as 'relative' failures: restoration debonding, restoration fracture, failure of the core portion requiring a new coronal restoration, and no mobility of the teeth or tenderness to percussion. While root fractures leading to tooth extraction were considered as 'absolute' failures.

CBCT scans assessment should reveal the absence or reduction of any radiolucencies or widening of the apical periodontal ligament space and vertical or horizontal root fracture.

5. Assessment of Safety

5.1 Specification, Timing and Recording of Safety Parameters

Measures that will be taken to ensure the subject's safety during the study are the same as with any routine dental procedure.

5.2 Adverse Event (AE)- Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product

- Syncope/ transient loss of consciousness during dental procedure or medical emergencies of a mild nature that are managed at chair side.

5.3 Adverse Drug Reaction (ADR) - Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

- Sodium hypochlorite used in root canal treatment is known to cause an adverse reaction of pain/ swelling if accidentally extruded beyond the root apex. These are rare and not expected to be reported

5.4 Serious Adverse Event or Reaction (SAE/SAR) - A serious adverse event is defined as an adverse experience that results in any of the following outcomes:-

- death
- a life-threatening adverse experience (any adverse experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death)
- inpatient hospitalisation or prolongation of existing hospitalization
- a persistent or significant disability/incapacity (a substantial disruption of a

- person's ability to conduct normal life functions)'
- a congenital anomaly/birth defect.

Where GSTT is the Sponsor and the SAE is related (that is, it resulted from administration of any of the research procedures), to the study procedures or is an unexpected occurrence (that is, the type of event is not listed in the protocol as an expected occurrence) then it must be reported immediately upon knowledge of the event to R&D and always within 24 hours. For all other AEs these must be reported to GSTT when copied into the Annual Progress Report.

The definition of “serious” may be defined differently within the protocol and it is the responsibility of the research team to adhere to the protocol definition in terms of SAE reporting. Additionally the protocol and other documentation may identify SAEs that do not need immediate reporting and SAEs falling under these categories should be recorded and reported according to the protocol. Where GSTT is the Sponsor and an SAE occurs that does not require immediate reporting, this SAE should be reported in the Annual Progress Report and copied to R&D. All adverse events that are to be reported to R&D Directorate must be signed and dated and completed by the Investigator.

6. Definition of the End of Trial

The end of trial is after the end of visit five (twenty fourth month follow-up). Following that, patients will be reviewed normally either at their GDP or at Guy's Hospital.

7. Direct Access to Source Data and Documents

The investigators and KCL will permit trial-related monitoring, audits, REC review, and regulatory inspections (where appropriate) by providing direct access to source data and other documents such as patients' case sheets and notes.

8. Ethics & Regulatory Approvals

The study will be conducted in compliance with the principles of the Declaration of Helsinki and the principles of GCP. Any subsequent protocol amendments will be submitted to the REC, and the REC will be provided with progress reports, and a copy of the Final Study Report.

9. Quality Assurance, Data Handling, Publication Policy and Finance

Patients will be allocated a unique identification number. The Principal Investigator will maintain a database of the patient's personal data, clinical notes and treatment records. This will be stored in the office of the Chief Investigator Prof Francesco Mannocci in Room 309, Floor 25, Tower Wing, Guy's Hospital. Only the chief investigator and researchers will have access to the participants' personal data during the study. The personal data will be stored for 6 months and the research data for 3 years after the study has ended. The trial will be registered on the GSTFT NHS R&D database and a public database: clinicaltrials.gov. The results of the study will be published in peer reviewed scientific journals, internal reports and in conference presentations. The study is self-funded.

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