T**R**adit**i**onal or minimal intervention **E**ndodontics **FO**r managing ca**R**ious teeth with sy**M**ptomatic pulpitis **(REFORM**): A pragmatic randomised trial in general dental practice in Northern Ireland

**Chief Investigator**

Dr Ikhlas El Karim: Senior Lecturer and Consultant in Restorative Dentistry, the Wellcome-Wolfson Institute for Experimental Medicine. Dr El Karim will oversee, support and supervise the delivery of the clinical trial in the dental practices.

**Co-Investigators**

Professor Mike Clarke: Trial Methodologist and Director of the Northern Ireland Clinical Trials Unit and the Northern Ireland Methodology Hub. Professor Clarke will assist in trial design and methodology and statistical analysis.

Dr Fionnuala Lundy: Reader in Oral Sciences in the Wellcome-Wolfson Institute for Experimental Medicine. Dr Lundy will assist in the measurement and analysis of the pulpal inflammatory biomarkers.

Professor Ciaran O’Neil. Professor of Health Economics at the Centre for Public Health. Prof O’Neill will assist with cost effective analysis of the interventions

Ms Siobhan Cushley, Student. Ms Cushley is a current PhD student with a background in General Dental Practice. Ms Cushley will coordinate recruitment, perform data collection, analysis and report writing

Sponsor: Queen’s University Belfast

**Summary of the research**

**Aim:** The aim of the trial is to compare the clinical and radiographic outcome and cost-effectiveness of two management techniques for the treatment of irreversible pulpitis (IP) in an NHS general dental practice over a 12month period. The trial is set to answer the question: Is the minimally invasive treatment complete pulpotomy (Cp) **(I)** as clinically effective and cost effective **(O)** as conventional root canal treatment (RCTx) **(C)** for managing infected tooth pulps when carried out in general practice **(P)** and can objective measures of inflammation be utilised to determine pulpal diagnosis and subsequent treatment need?

**Design:** 2 arm single blinded randomised controlled trial

**Setting**: NHS General Dental Practices within NI

**Population**: Patients aged 18 years and older registered with a GDP in NI and who are eligible for treatment under General Dental Services (GDS) contract.

**Health interventions**: In the intervention arm, participants will undergo complete pulpotomy (Cp) a procedure in which only the pulp (the living centre ‘nerve’) within the crown of the tooth is removed. The remaining tissue is sealed with a calcium silicate cement prior to placement of a direct restoration to complete the treatment. In the control arm, root canal treatment (RCTx) will be carried out whereby all of the pulp of the tooth is removed and a root filling placed followed by restoration of the tooth.

**Primary outcome:** A composite measure, which requires the absence of pain, absence of apical periodontitis and absence of internal root resorption to be confirmed by history, clinical examination and radiographic assessment.

**Secondary outcomes:** Absence of pain (3-7 days post-operatively), structural integrity of tooth, no further interventions during the 12month follow-up period, no adverse events; a health economic evaluation to include incremental cost-effectiveness; process evaluation (patients’ and practitioners’ satisfaction with the procedure) and identification of facilitators and barriers; concentration of inflammatory biomarkers within infected pulpal tissue.

**Statistical analysis and sample size:** A sample size of n=164 will achieve 80% power at a 5% significance level to establish a 17% difference between the proportion of successful Cp over RCTx. This accounts for a 12% attrition over 12 month and allocation on a 1:1 basis.

**Outcome and impact**: The outcome of this study if successful will change the way in which teeth with IP will be managed in General Dental Practice (GDP) and will provide evidence for the utility of biomarkers in case selection for Minimal Intervention (MI) endodontics.

**Background
The problem:** Dental caries is the most common infectious disease in the world (1) and is a frequent reason for adult patients in the United Kingdom (UK) to seek medical assistance for pain relief (2). Caries is a chronic disease that results in demineralisation of the hard surfaces of the tooth leading to cavitation. If left untreated dental caries will progress, inducing severe inflammation in the dental pulp (tooth nerve) which causes severe pain. This is clinically diagnosed as irreversible pulpitis (IP) (3). IP is traditionally treated by conventional root canal treatment (RCTx), a multi-visit procedure, which involves the removal of all pulpal tissue content and subsequent management of the pulp space. Inherent in the RCTx procedure is loss of dental hard tissue and subsequent weakening of the treated tooth, making teeth more prone to fracture (4-6).

Although successful if carried out well (7,8), conventional RCTx is destructive, expensive, technically challenging, time-consuming and weakens the remaining tooth (9). The provision of RCTx in general dental practice (GDP) is difficult to undertake successfully, with recent United Kingdom (UK) data highlighting that a large proportion of RCTx were technically inadequate, with a high prevalence of associated apical infection and disease (10). In Northern Ireland (NI) the prevalence of dental caries is the highest in the UK and data obtained from the Business Services Organisation (BSO) showed high annual provision of root canal treatment in general dental practice **(Table 1)**. As root canal treatment is technically difficult to carry out in general dental practice, large number of root canal treatment cases are referred to secondary care. Data collected from the Department of Restorative Dentistry at Belfast Dental School showed that endodontic referrals constitute a significant financial burden to Northern Ireland’s Health and Social Care (HSC) secondary care services **(Figure 1).**

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| **Table 1: Number RCTx completed NI** |
| 2014-2015 | 48497 |
| 2015-2016 | 49662 |
| 2016-2017 | 49461 |

**Figure 1: Proportion of endodontic referrals for RCTx to the Department of Restorative Dentistry at Belfast Dental Hospital.**

The dental pulp responds to caries by a complex inflammatory response that is currently described in a simple dichotomous way as reversible or irreversible pulpitis. According to the American Association of Endodontists’ (AAE 2013) classification, reversible pulpitis is a clinical diagnosis based upon subjective and objective findings indicating that the inflammation should resolve following appropriate management of the aetiology. Irreversible pulpitis on the other hand, indicates an inflamed pulp that is incapable of healing and for which RCTx is indicated. Such a diagnosis is however, based on crude diagnostic tools that do not accurately represent the true pathological state of the pulp (11). Histological and microbiological studies have shown that the inflammation and microbial presence in teeth traditionally diagnosed with irreversible pulp disease is limited to the coronal pulp tissue and that there is an absence of bacterial invasion and inflammation in the radicular pulp (12). These findings have challenged the established classifications and led to the introduction of new diagnostic terms and management strategies (13). Critically, it has been proposed that removal of the whole pulp and RCTx may not be necessary in teeth with signs or symptoms indicative of irreversible pulpitis (13). Instead, the pulp in these teeth should be preserved with minimal interventions such as pulpotomy (13,14).

**Proposed solution:** Complete pulpotomy (Cp) is a minimally invasive procedure whereby the inflamed/diseased pulp tissue is removed from the coronal pulp chamber of the tooth leaving healthy pulp tissue, which, is dressed with a dental biomaterial that maintains vitality and promotes repair (ESE 2006). The complete pulpotomy procedure involves the removal of the entire coronal pulp leaving the radicular pulp intact (**Figure 2).** In mature permanent teeth, Cp has been successfully reported as an emergency pain relief procedure prior to RCTx (15). However, with the development of bioactive materials and improved biocompatibility (16,17), pulpotomy has been reinvestigated as a definitive treatment of permanent teeth with pulpitis (18). A systematic review on the outcome of Cp from pooled studies with diagnoses of reversible and irreversible pulpitis, showed an overall favourable outcome of the procedure (19).



**Figure 2A** Diagram illustrating irreversible pulpitis in a carious tooth and the current management with root canal treatment. All pulp tissue is removed from the crown and roots of the tooth before cleaning, shaping and sealing the root canal system and filling the tooth and placement of a crown.

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**Figure 2B**: Diagram illustrating irreversible pulpitis in a carious tooth and the proposed management with pulpotomy. **(A)** Deep carious lesion exposing the pulp with inflammation limited to localised area beneath the carious lesion. In such a tooth, the patient will present with symptoms indicative of irreversible pulpitis and the dentist will treat such a tooth with removal of the whole dental pulp to carry out root canal treatment as shown in Figure 2A above. **(B)**The proposed alternative to root canal treatment is complete pulpotomy involving removal of the inflamed coronal but leaving intact dental pulp in the root of the tooth. The remaining pulp is then dressed with pulpotomy material to aid healing prior to placement of a permanent filling without need for a crown

In line with the transition to minimally invasive (MI) therapies, the European Society of Endodontology (ESE) convened an expert panel to synthesise the evidence base on the ‘management of deep caries and the exposed pulp’ and propose treatment strategies. The panel issued a position statement with key recommendations for adopting MI endodontic procedures to preserve the vitality of the dental pulp where it is possible (14). The ESE position paper recommended Cp as a definitive treatment option for the cariously exposed pulp but acknowledged the limitation of existing evidence. It highlighted that the success of the procedure is based on heterogeneous studies with high risk of bias. Most of the studies were carried out in secondary care making it difficult to extrapolate their findings to general dental practice where most irreversible pulpitis cases are treated. Another important recommendation from the ESE position statement is the development of appropriate tests to diagnose the inflammatory status of the pulp. Implementation of these MI therapies requires accurate diagnosis of the pulpal status, ideally using biomarkers. Currently, clinicians diagnose pulp condition based on pain symptoms which are subjective as well as clinical investigations that have been shown to be not fit for purpose (11).

A recent systematic review based on data solely relating to the diagnosis of irreversible pulpitis as defined by the AAE classification answered the research question: What is the success rate of complete coronal pulpotomy in treating carious mature permanent teeth with signs and symptoms indicative of irreversible pulpitis and what is the success rate of coronal pulpotomy compared with the success rate of root canal treatment in such teeth (21)? Results showed the average success rate for complete coronal pulpotomy was 97.4% for clinical assessment and 95.4% for radiographic assessment at 12 month follow-up. At 36 months, the success rates were 94.0% and 88.4% for clinical and radiographic assessments respectively. Results from the only comparative clinical trial showed pulpotomy to have comparable success to RCTx at 12, 24 and 60- month follow-up (22). These results however are based on heterogeneous studies of only fair quality and with high risk of bias, highlighting the need for well designed, adequately powered trials to produce evidence to change clinical practice. Pain is the principal subjective symptom for which patients seek endodontic treatment (23). Presence of pre-operative pain is the major predictor of post-operative pain (24). The mean post-operative pain scores were found to be significantly lower for Cp than for RCTx (25). The subjective nature of pain however makes it a less predictable diagnostic tool for the inflammatory status of the pulp. To implement an MI approach, it is important to establish a biological marker that could indicate whether Cp is appropriate or if RCTx is required. Therefore, combining success with biomarkers may be a better approach to identify the most appropriate intervention for teeth with irreversible pulpitis.

**Aims and Objectives**

**Aims:**

The aim of the trial is to compare the clinical and radiographic outcomes and cost-effectiveness of two management techniques for the treatment of IP in an NHS general dental practice over a 12month period. The trial is set to answer the question: Is the minimally invasive treatment complete pulpotomy (Cp) **(I)** as clinically effective and cost effective **(O)** as conventional root canal treatment (RCTx) **(C)** for managing infected tooth pulps when carried out in general practice **(P)** and can objective measures of inflammation be utilised to determine pulpal diagnosis and subsequent treatment need?

**Objectives:**

1. Undertake a pragmatic individually randomised controlled trial in general dental practice to determine the clinical effectiveness of Cp in the management of IP in symptomatic adult teeth. The primary outcome will be a composite measure which requires absence of pain, absence of apical periodontitis and absence of internal root resorption to be confirmed by clinical and radiographic assessment. Secondary outcome measures include short-term post-operative pain relief (3-7 days); structural integrity of teeth and no evidence of adverse events or need for further interventions at 12month follow-up. Secondary outcomes also include health economic, process evaluation and laboratory analysis of inflammatory proteins.
2. Undertake a parallel cost-effectiveness analysis from an NHS perspective to examine the potential long-term costs and benefits of the intervention. This will be an incremental cost-effectiveness analysis undertaken from the perspective of a publicly funded third party payer. Incremental costs will be related to the composite outcome measure in a primary analysis.
3. Undertake a process evaluation to assess the acceptability of the intervention to both patients and general dental practitioners, while exploring the barriers and enablers to implementation. A realist informed process evaluation will be undertaken alongside the trial to study acceptability for patients and dentists and treatment fidelity. It will also capture the contextual factors that shape the intervention, mechanisms that sustain or potentiate effects and unexpected pathways and consequences.
4. Undertake laboratory analysis of inflammatory proteins to test the feasibility of using biomarkers for pulpal diagnosis and subsequent treatment need.

**Outcome measures**

**Primary outcome:**

The primary outcome of the trial is a composite measure which is defined as:

 1) Absence of pain at 12 months

 2) Absence of swelling or sinus around the tooth indicative of acute or chronic periapical infection

3) No radiographic evidence of periapical radiolucency or internal resorption.

Primary end point analysis will be success or failure of the composite outcome measure at 12 months. This will be defined by achieving all 3 criteria. Failure of any single criteria within the composite will indicate a treatment failure. The choice of the success criteria as primary outcomes for Cp and RCTx was based on guidance by the ESE position papers.

**Secondary outcome:**

The secondary outcome measures will be:

1. Absence of pain 3-7 days post-operatively
2. Structurally integral tooth with an intact, non-defective restoration at 12 months
3. No further interventions during the 12month follow-up period or adverse events
4. Health economic evaluation to include incremental cost effectiveness analysis
5. Process evaluation (patients’ and practitioners’ satisfaction with the procedure) and identification of facilitators and barriers
6. Concentration of inflammatory biomarkers collected from pulpal tissue samples

**Planned interventions**

Each participant will be asked about their pre-operative pain using the numeric rating scale (NRS) prior to the intervention.

The proposed interventions, Cp and RCTx, will not deviate from recognised current clinical practice for the management of patients with IP in a permanent posterior tooth. Although Cp is not routinely performed as a definitive treatment for patients with IP, the technical procedure itself forms the first stage of conventional RCTx that is regularly undertaken in practice. The technicality of the interventions will not be new to the dentists.

**RCTx (control):** Following adequate anaesthesia and isolation, an access cavity will be prepared using a diamond bur in a high speed hand-piece with water coolant. Caries will be excavated using a stainless steel bur in a slow speed handpiece and the pulp chamber deroofed. A sample of pulp tissue will be removed using an excavator and placed in a specimen pot prior to refrigeration and subsequent freezing. The entire pulp will be extirpated and working length determined. The canals will be chemo-mechanically debrided prior to placement of a temporary restoration to seal the tooth. The patient will return within 6 weeks to have the root canal treatment completed and a permanent restoration placed either at this visit or at a subsequent visit. At the routine 12month examination appointment a clinical and radiographic examination of the tooth will be completed. A paralleling technique and film holder device will be used to take the periapical radiograph which must include apical tissues beyond the root tip (>3mm) with no evidence of distortion, overlap or processing errors.

**Complete Pulpotomy (Cp) (intervention):** Initial operative procedures will be as described for RCTx but only the coronal pulp tissue will be removed to the depth of the root canal orifices. The resultant bleeding from the pulp wound will be controlled with a cotton pellet soaked in 2.5% sodium hypochlorite solution applied for up to 5 minutes. (If haemostasis is not achieved within 5 minutes, RCTx will be carried out). The pulp stump will then be covered with Biodentine (Septodont, France), which will restore the entire cavity as a provisional restoration. The tooth will be permanently restored within 6 weeks at the 2nd visit. The temporary restoration will be removed to leave a minimum depth of 3mm of Biodentine and the tooth permanently restored. The radiograph procedure will be as described for RCTx.

**Sample size calculation:** Based on meta- analysis from previous studies the success rate of RCTx in vital teeth clinically and radiographically was 82% (CI 74-91%) (7,8). However, the success rate was considerably lower for treatment carried out by general dental practitioners 66% (CI 56-75%) (7). The European position statement on vital pulp treatment recommended that pulpotomised teeth be reviewed by patient history, clinical examination and periapical radiograph after 12 months (14). According to a systematic review the pooled success rate for pulpotomy in patients with signs and symptoms of irreversible pulpitis was 95% (range 92-98%) after 12 months (21). To date there is only one non inferiority randomised clinical trial comparing pulpotomy with RCTx of vital teeth with IP but it is considered to be at high risk of bias (22). Based on a 17% difference between the proportion of successful pulpotomy (92%) and RCTx (75%) a sample of 142 participants allocated on a 1:1 basis will achieve 80% power at the 5% significance level. In determining the assumed success rates for both interventions we have adopted a conservative approach by using the lower bound of the 95% CI for pulpotomy and the upper bound for the RCTx. Accounting for a 12% attrition at 12 months following recruitment, we will recruit and randomise 164 participants. This attrition rate is realistic at 12 months.

**Randomisation:**

Following assessment (clinical and radiographic) and subsequent diagnosis of IP, patients who meet the inclusion criteria will be invited to participate in the trial and consent will be obtained prior to randomisation to one of the treatment arms. Randomisation will be by patient using a block randomisation system of concealed envelopes

**Eligibility criteria**

Inclusion criteria:

1. Patients 18 years or older with symptoms of IP affecting a mature, permanent posterior tooth. Symptomatic IP may include sharp pain upon thermal stimulus, lingering pain, spontaneity (unprovoked pain) and referred pain (AAE 2017)
2. Tooth should be responsive to sensibility tests
3. Tooth should be restorable and can be adequately isolated during treatment.

Exclusion criteria:

1. Teeth with active periodontal disease (pocket depth >5 mm)
2. Participants with complex medical histories that may affect their caries experience and healing ability
3. Inability to provide consent
4. History of trauma to tooth
5. Presence of apical radiolucency or ligament enlargement on radiograph
6. Pregnant or breast-feeding patient

**Recruitment of practices:**

The trial will be open to GDPs in NI with NHS registered patients. The practices will have to demonstrate evidence of registered patients eligible for inclusion and the organisational skills required to deliver the trial. Using local audit data collected from individual practices, 7 practices (10 dentists) will be recruited who are able to demonstrate that they could recruit sufficient eligible patients.

**Training of participants:**

The participating dentists will complete fundamental clinical trial training including Good Clinical Practice training in addition to the intervention training. The intervention training will be shaped by the findings of previous qualitative data. Training will be undertaken to validate that the recruited dentists can carry out the pulpotomy interventions and RCTx to a competent standard expected of any GDP. As part of training dentists will perform Cp under controlled conditions using a simulated set-up to assure the standard. Any procedural issues identified will be rectified with further training before the dentist starts treating patients in the trial. Training will be facilitated by Northern Ireland Medical and Dental Training Agency (NIMDTA) in association with QUB.

**Statistical analysis:**

**Primary outcome:** Primary end-point analysis will be success or failure of the composite outcome at 12 months. This will be defined as achieving all three criteria. Failure of any single criteria within the composite will indicate a failure. The primary analysis model will be logistic regression adjusting for variables. Treatment effect estimates will be presented with 95% confidence intervals. Other potential factors that could affect the results will be determined a priori and considered for inclusion in the model.

**Secondary outcomes:** Binary secondary outcomes will be assessed using the same model as for the primary endpoint. Analysis models of the individual elements of the composite outcome will also be calculated to aid interpretation of the overall primary model and to establish if the effect is being driven by one particular element of the composite. Continuous secondary outcomes will be analysed using mixed effects regression models. Exploratory analysis using marginal models with generalised estimating equations with information sandwich estimates of the standard error, specifying the correlation structure as exchangeable may be used to consider the possibility of within general practice or centre correlation.

**Biomarkers analysis and validation.**

A major challenge of treating painful pulpitis with conservative approaches such as pulpotomy is the inability to accurately diagnose the state of pulpal health at chairside. The currently employed diagnostic tests are poor measures of inflammation (11) and as a result it is difficult for the dentist to accurately determine the degree of pulpal health/degeneration prior to treatment and offer the most suitable treatment modality. New tests to diagnose the health of the remaining pulp tissue are therefore required (32). A number of studies have reported on the level of inflammatory cytokines and inflammatory mediators both at gene and protein expression in pulp tissue of healthy and inflamed dental pulps (32,33,34). In this part of the study the biological pulp samples collected during the clinical interventions outlined above will be analysed in the laboratory for the elucidation of biomarkers. The choice of biomarkers will be decided through discussion by the consensus group as part of another approval. Results of the biomarker analysis will be linked to the outcome of the treatment and if a correlation is detected between specific biomarkers and clinical outcome then this could guide development of the next generation of chair side diagnostic tests for future case selection.

**Health Economics**

**Economic evaluation:**

An incremental cost- effectiveness analysis will be undertaken from the perspective of a publicly funded third party payer. Incremental costs will be related to the composite measure of pain, signs of infection and periapical radiolucency in a primary analysis. Dental treatment costs will be imputed using the 'Statement of Dental Remuneration' (SDR). The relative value for money of the intervention will be established by comparing the estimated incremental cost- effectiveness ratios (ICERs) against a range of hypothetical willingness to pay thresholds informed by the willingness to pay study and uncertainty around the threshold level explored using cost-effectiveness acceptability curves. For additional analyses, a societal perspective will be adopted for the measurement of costs to examine the potential implications in terms of lost productivity associated with absences from work related to consumption of care and in respect of out- of- pocket expenses. Sub-group analyses will be used to explore differences that may exist between groups differentiated by age. Willingness to pay for hypothetical levels of outcome at baseline and each follow-up point will be determined using a contingent valuation approach. Willingness to pay will be elicited using an iterative bidding game with random starting points to address potential starting point bias.

Data collection:
Data will be collected at baseline and at 12 months after the intervention. Use of non-publicly funded dentists and other aspects of healthcare (General medical practitioners etc.) will be gathered using an amended version of the Client Services Receipt Inventory (CSRI) to capture the potential impact on other parts of the healthcare system whether dental or general medical. The data captured at 12 months will cover the period since the last measurement point. With respect to publicly funded dentists, these will again be captured using the CSRI and as a validation exercise, patients in NI’s use will be compared with that recorded in reimbursement records held with the Business Services Organization. The contingent valuation exercise will be used to establish willingness to pay for the outcome at 12 months by their recipients.

**Economic analysis**:
Costs of dental care and all healthcare from a payer perspective will be aggregated to provide separate measures for the 12month duration of the study – one for dental care only and one for all healthcare. To these, lost production and travel costs will be added to provide an estimate of societal costs. Costs will be analysed using a GLM model to allow for the positive and potentially skewed nature of healthcare costs. The treatment group will be specified as a key covariate in this analysis. Costs will be related to outcomes as an incremental cost effectiveness ratio (ICER) with a Monte Carlo simulation exercise used to establish the mean difference in outcomes divided by the mean difference in costs between intervention and control groups. 10,000 simulations will be used and the 2.5 and 97.5 centile for the estimated ratio will be used to establish confidence intervals around the incremental cost effectiveness ratio. This exercise will be repeated where costs are estimated from a societal perspective. Cost-effectiveness acceptability curves will be used to assess the potential relative value for money of Cp over RCTx at a range of hypothetical values for the composite outcome. This analysis will be informed by the contingent valuation study.

**Estimation of costs**: The costs of all dental services including Cp and RCTx and will be monetised using the Statement of Dental Remuneration for NI. This will reflect the actual costs to the payer associated with the provision of these therapies or are incurred as out of pocket if these services are paid for privately.

Details of other private costs related to for example productivity losses or travel costs will be gathered using surveys of the patients; the former based on time-off related to the consumption of dental care, the latter on estimated distance to usual dentist monetised using Automobile Association estimates of travel costs.

**Process evaluation**

**Realist-informed process evaluation**:
A realist process evaluation will be undertaken alongside the trial to study acceptability for dentists and patients, treatment fidelity and the other elements recommended by contextual factors that shape the intervention; contextual factors that shape implementation; mechanisms that sustain or potentiate effects; and unexpected pathways and consequences. This process evaluation work will be subject to separate ethical approval through QUB MHLS Faculty Research Ethics Committee.

Realist principles will be used to underpin the evaluation to provide a theory-driven approach to understanding contingencies; what works about the intervention, why, how and under which circumstances. The realist approach will be used to develop a theoretical framework of intervention impacts and successful implementation. The initial framework will then be tested and refined, using further mixed methods (interviews and video diaries). Semi- structured interviews will be undertaken with a purposive sample of participants, General dental practitioners, Consultants in Restorative Dentistry, Endodontists (a sub-specialty of Restorative Dentistry), Consultants in Dental Public Health and NHS commissioners to “provide valuable insight into why an intervention fails or has unexpected consequences, or why a successful intervention works and how it can be optimised”.

The resulting initial programme theory/ies will reflect the macro, meso and micro features which we postulate can impact on the implementation of the intervention. At this stage, the initial programme theory will represent a range of context-mechanism-outcome configurations (CMOs), which postulate the relationship between contextual condition and mechanism, and how these are linked to outcomes. We will then follow a recognised approach to enable the testing and refining of the CMO configurations. Interview transcripts will be transcribed and analysed using a deductive coding framework based on the initial programme theory. The main approach to analysis will be the use of abductive reasoning to seek patterns (demi-regularities) from and within the CMO configurations.

**Missing outcome data and sensitivity analyses:** The aim is to minimise the amount of missing data however there is an expectation that some missing data may occur. Predictors of missingness will be investigated and will be considered for inclusion in the models. A maximum-likelihood multiple imputation approach will be used for the management of missing data with a sensitivity comparison to the complete cases dataset. Upon commencement of the procedure some participants randomised to receive Cp may require RCTx that could not be established prior to treatment starting. These participants will remain in the analysis set for the primary analysis but will be excluded for a subsequent sensitivity analysis.

**Frequency of analyses:** There are no planned interim analyses unless requested by independent committees and all analyses related to clinical effectiveness will be completed post data lock after the collection of the final primary end-point at 12 months.

**Data collection**

**Primary outcome data:**

The primary outcome will be assessed at 12 months by 1) Patient history taking and clinical examination for pain and clinical signs of infection such as swelling and sinus tract. Pain will be assessed using a numeric rating scale (NRS). NRS is an 11-point numeric scale with 0 representing “no pain” and 10 representing “pain as bad as you can imagine”. 2) Radiographic examination for periapical radiolucency and internal root resorption.

**Secondary outcome data:**

Secondary outcomes will be assessed as follows: 1) postoperative pain will be recorded at days 3 and 7. Patients will be instructed on how to use the NRS at home on days 3 and 7 after the procedure. Patients will return their responses at visit two. 2) Structural integrity of the tooth will be assessed by the general practitioner at the 12 month visit using the World Dental Federation (FDI) criteria. 3) Evidence of further interventions and adverse events will be obtained from patient records following the 12 month review visit. 4) Data for cost effective analysis and process evaluation will be collected as described earlier. 5) Concentration of inflammatory biomarkers will be determined by laboratory analysis of the pulpal tissue samples.

**Longer term follow- up**

Although the trial is designed for a primary outcome measure at 12 months post intervention, an opportunity exists to look at longer term consequences of the intervention. Participants will be asked to provide consent to allow the researchers access to any clinical and radiographic data held by the practice for three years post intervention. In addition, consent will be sought from participants to access data held by the Business Services Organisation covering all reimbursements for publicly funded dental care in NI. This data is at a sufficient level of granularity to identify any specific treatment provided to the intervention tooth. By doing this, we will be able to follow up outcomes data from the study population for up to ten years at a reasonable cost in future studies.

**Ethical Considerations**

Patients will be invited to enrol in the trial voluntarily and will be assured that should they chose not to participate then the standard treatment will be offered as normal with no prejudice.

Patients will be fully informed of the trial interventions, have the opportunity to ask questions and take additional time prior to their decision to participate. Dentists are familiar with obtaining informed consent as part of routine care. The nature of IP means that patients present to General Dental Practice in pain. Removal of the source of the infection is required to ease that pain so the patient needs to undergo treatment at the first visit to achieve this outcome. It would be explained to patients that the experimental treatment forms the first stage of the conventional treatment and that both treatments will provide symptom relief.

There is minimal risk for participating in the trial. Pulpotomy is a clinical procedure routinely carried out in children and also widely used as an emergency interim treatment for adults. Pulpotomy is the first stage of RCTx and is effective for managing the pain associated with an infected pulp. A number of studies have suggested that pulpotomy could serve as a definitive treatment for infected pulps rather than a simple emergency treatment. This alternative treatment is simpler, less costly and less destructive of tooth structure resulting in better long- term outcomes for patients and protecting teeth against future infections. Suspected Unexpected Serious Adverse Reactions (SUSARs) and other Serious Adverse Reactions (SARs) will be reported to the regulatory authority. The local investigator at each site will use the adjective MILD, MODERATE, or SEVERE to describe the intensity of any Adverse Event (AE):

1. MILD- does not interfere with participant’s usual function
2. MODERATE- interferes to some extent with participant’s usual function
3. SEVERE- interferes significantly with participant’s usual function

Each AE will be clinically assessed for causality based on the information available and reviewed as new information becomes available. Information on AEs must be evaluated by each participant’s dentist (local investigator) and recorded in the AE forms. The AE reporting period for this trial begins upon enrolment into the study and ends at the follow-up period for participants. All AEs will be reported during this period by the local investigator (dentist named on the signature list and delegation of responsibilities log who is responsible for the participant’s care). The Data Monitoring Committee will be presented with unblinded interim analyses of AEs. They will use this data to decide whether to stop the study.

Whilst patients will be connected to the trial for 26months following enrolment and randomisation, all data will be collected at routine monitoring appointments as part of routine care and will not involve any extra visits or additional investigations being conducted. Personal data will not be retained any longer than is required for the purpose for which they have been collected and will be stored in compliance with the sponsor’s standard operating procedures. Documents will be reviewed by the chief investigator (CI) before being destroyed. A radiograph has been included in the protocol as despite it being a recommendation of both the European Society of Endodontists and the Faculty of General Dental Practitioners that all teeth post pulpal treatment have radiographic follow-up at 12 months, this practice is not adopted by all general dental practitioners. Willingness to undergo this investigation will be a pre-requisite for trial participation. This radiograph will demonstrate healing and assure patients of the success of treatment. Any failure identified would enable future intervention to minimise long term risk to survival of the tooth as not all failure will present with clinical symptoms.

Patients are required to report on their experience of pain on days 3 and 7 post-treatment. This places additional burden on the patient as this data is not normally collected. To off-set this, the advantage is better supervision of the post-operative period for patients. Treatment of the dental pulp either by partial or complete removal is typically accompanied by some level of post-operative discomfort or pain prior to resolution of symptoms. This is often overlooked by dentists with patients receiving little explanation or strategies to overcome symptoms. Participants in the trial will receive explanations about the nature of any anticipated pain or discomfort, the likely duration of such and methods to relieve any symptoms.

As a result of randomisation, half of the patients will be allocated to the pulpotomy arm. There is currently no accurate diagnostic measure of the extent of inflammation within the pulp and so it is possible that because of the extent of the inflammatory process already present in a pulp, pulpotomy may not be sufficient to fully resolve the symptoms in a small number of patients allocated to this arm. A systematic review showed pulpotomy to have a pooled success rate of 95% in patients with a diagnosis of IP so this group is likely to be small. Having partially removed the infected pulp will however lead to a reduction in symptoms and pain experienced. To minimise the risk of incorrect diagnosis, pulpal bleeding will be used as a proxy measure of inflammation. Inflamed pulps bleed but it should be possible to achieve haemostasis within five minutes. If it is not possible to achieve haemostasis within five minutes and the patient has been allocated to the pulpotomy arm, they will automatically be moved into the RCTx arm and this has been included in the intervention protocol.

There may remain dental pulps that whilst haemostasis can be achieved within five minutes still have undiagnosed more advanced inflammatory changes not capable of repair. This small group of patients may continue to experience some low- grade pain post intervention. These patients will be able to access emergency care to address their symptoms including escalation to root canal treatment if appropriate. The process of RCTx will have been simplified by the commencement of pulpotomy in these patients.

All data sharing and storage will be managed in line with good practice and current data protection regulations.

Dental practitioners participating in the trial will receive Good Clinical Practice training and training in the intervention.

**Trial management**

The trial will be subject to monitoring, audits, ethics committee review and regulatory inspections. Consent from patients for direct access to data will be obtained. A trial management group (TMG) which includes Prof Mike Clarke the director for the NI Clinical Trials Unit will be supported by a UK expert in translational and applied health research and chaired by an independent. The trial will also be overseen by a trial steering group (TSG) who will oversee the running of the trial and ensure that it is conducted in accordance with the principles of Good Clinical Practice and all relevant regulations.

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| **Study Summary**  |
| Title | Tradit**i**onal or minimal intervention endodontics for managing carious teeth with symptomatic pulpitis (REFORM): A pragmatic randomised trial in general dental practice in Northern Ireland  |
| Aims | The aim of the trial is to compare the clinical and radiographic outcomes and cost-effectiveness of two management techniques for the treatment of IP in an NHS general dental practice over a 12month period. The trial is set to answer the question: Is the minimally invasive treatment complete pulpotomy (Cp) **(I)** as clinically effective and cost effective **(O)** as conventional root canal treatment (RCTx) **(C)** for managing infected tooth pulps when carried out in general practice **(P)** and can objective measures of inflammation be utilised to determine pulpal diagnosis and subsequent treatment need? |
| Methodology | Single blinded, pragmatic randomized controlled trial |
| Study Duration | Estimated duration for the main trial (2 years 10 months=14 months post follow-up of last patient enrolled) September 2021-July 2024 |
| Study Centre | Multi-centre (General Dental Practices across NI) |
| Objectives | 1. Undertake a pragmatic individually randomised controlled trial in general dental practice to determine the clinical effectiveness of Cp in the management of IP in symptomatic adult teeth. The primary outcome will be a composite measure which requires absence of pain, absence of apical periodontitis and absence of internal root resorption to be confirmed by clinical and radiographic assessment. Secondary outcome measures include short-term post-operative pain relief (3-7 days); structural integrity of teeth and no evidence of adverse events or need for further interventions at 12month follow-up. Secondary outcomes also include health economic, process evaluation and laboratory analysis of inflammatory proteins.
2. Undertake a parallel cost-effectiveness analysis from an NHS perspective to examine the potential long-term costs and benefits of the intervention. This will be an incremental cost-effectiveness analysis undertaken from the perspective of a publicly funded third party payer. Incremental costs will be related to the composite outcome measure in a primary analysis.
3. Undertake a process evaluation to assess the acceptability of the intervention to both patients and general dental practitioners, while exploring the barriers and enablers to implementation. A realist informed process evaluation will be undertaken alongside the trial to study acceptability for patients and dentists and treatment fidelity. It will also capture the contextual factors that shape the intervention, mechanisms that sustain or potentiate effects and unexpected pathways and consequences.
4. Undertake laboratory analysis of inflammatory proteins to test the feasibility of using biomarkers for pulpal diagnosis and subsequent treatment need.
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| Number of Subjects | 164 patients  |
| Inclusion Criteria | 1. Patients 18 years or older with symptoms of IP affecting a permanent posterior tooth. Symptomatic IP may include sharp pain upon thermal stimulus, lingering pain, spontaneity (unprovoked pain) and referred pain (AAE 2017)
2. Tooth should be responsive to sensibility tests
3. Tooth should be restorable and can be adequately isolated during treatment.

**Exclusion criteria:** 1. Teeth with active periodontal disease (pocket depth >5 mm)
2. Participants with complex medical histories that may affect their caries experience and healing ability
3. Inability to provide consent
4. History of trauma to tooth
5. Presence of apical radiolucency or ligament enlargement on radiograph
6. Pregnant or breast-feeding patient
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| Study Regime | Control group: will receive current standard of care- Root canal treatment (RCTx)Intervention group: will receive complete pulpotomy (Cp) |
| Primary outcome | Primary outcome is a composite measure:1) Absence of pain at 12 months 2) Absence of swelling or sinus around the tooth indicative of acute or chronic periapical infection 3) No radiographic evidence of periapical radiolucency or internal resorptionPrimary end point analysis will be success or failure of the composite outcome measure at 12 months. This will be defined by achieving all 3 criteria. Failure of any single criteria within the composite will indicate a treatment failure |
| Secondary outcome | The secondary outcome measures will be:1. Absence of pain 3-7 days post-operatively
2. Structurally integral tooth with an intact, non-defective restoration at 12 months
3. No further interventions during the 12month follow-up period or adverse events
4. Health economic evaluation to include incremental cost effectiveness analysis
5. Process evaluation (patients’ and practitioners’ satisfaction with the procedure) and identification of facilitators and barriers
6. Concentration of inflammatory biomarkers collected from pulpal tissue samples
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| Statistical Methodology | A sample size calculation has been carried out. Based on a 17% difference between success rates of pulpotomy and RCTx (92% V 75%) respectively, a sample size of 142 participants will have 80% power at the 5% significance level. We have inflated this to 164 participants to account for a 12% attrition rate at 12mth follow-up and allocation on a 1:1 basis. Numbers of patients screened, eligible randomised, consented and withdrawn from the trial will be reported by treatment group. Baseline demographic and clinical data will be summarised for each of the treatment groups. Analysis will be on an intention- to-treat basis and p value of 0.05 will be considered significant. The analysis will be logistic regression adjusting for variables including age, method of tooth isolation, tooth type, location of caries. A regression model will aid interpretation of results establishing if effect is being driven by any particular element. Treatment effect estimates will be presented with 95% confidence intervals. Exploratory analysis using marginal models with generalised estimating equations may be used to consider the possibility of within or across practice correlation. Quantitative biomarkers data will be categorised and correlated with success outcomes following complete pulpotomy or root canal treatment. This will also be tested with a regression model.  |



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