Title: Success of endodontic management of compromised first permanent molars in children: a systematic review

Summary:

Background

Endodontic therapies may be required in the management of first permanent molar teeth, however, their success in children is unknown.

Aim

To determine the success of endodontic therapies used on first permanent molar teeth in children aged sixteen and under.

Design

MEDLINE, Embase, Cochrane library, CENTRAL, Clinicaltrials.gov and the ISRCTN registry as well as relevant paediatric, endodontic, and traumatology journal were searched using a detailed search strategy. References of included studies were hand-searched.

A PICOS question was formulated: (P): Children aged sixteen and under*;* (I): Endodontic therapies (not pulp-capping) on a first permanent molar tooth*;* (C): No treatment; (O): Success of endodontic therapy*;* (S): All study types included.

Bias was assessed using the Cochrane and Robins-I risk of bias tools. Quality of evidence was assessed using the GRADE approach. Significant heterogeneity precluded meta-analysis.

Results

4172 studies were retrieved with eleven included (three RCTs, five prospective and one retrospective cohort, one case series and one case report). Partial and coronal pulpotomies have high success rates in the short- and long-term. Limited evidence is available for conventional pulpectomy or regenerative techniques.

Conclusions

Partial and coronal pulpotomies are successful endodontic therapies for use in a compromised child's first permanent molar.

Keywords: endodontics; pulp biology; restorative dentistry/dental materials

Introduction

Compromised first permanent molars (cFPM) affect 25% of UK children[1] with the impact of these teeth being detrimental to the general health and social well-being of these children.[2-4] Dental caries and molar incisor hypomineralisation (MIH) are viewed as the most common aetiological factors that render a first permanent molar to be of compromised prognosis.[1, 5] The most recent UK child dental health survey in 2013 has shown that caries prevalence, in the first permanent molar tooth, increases with age as prevalence rises from 5% in 8 year olds to 25% by the time the child reaches age 15.[1] The mean number of molar teeth affected teeth per child diagnosed with MIH is reported as 1.6 to 3.16 (out of 4).[6]

The management of compromised first permanent molars in young children is under-researched. The key clinical question is whether restore the cFPM, which enters the tooth into the 'restorative cycle' at an early stage or to extract the cFPM and allow for spontaneous tooth closure by the second permanent molar.[7] Which approach to adopt is complicated and confusing for the dental profession with a recent UK study showing that general dental practitioners prefer to restore whilst specialists in paediatric dentistry prefer to extract cFPM.[8] Deciding which option to choose is complicated and will be influenced by several factors such as: patient and parental attitudes; diagnosis of cFPM; tooth restorability; pulpal and peri-radicular diagnoses; level of patient compliance; general dental health (including ability to maintain any advanced restorative work); current/future orthodontic need.

If a restorative approach is to be adopted, endodontic management could be required if a pulpal exposure is noted after tissue removal or if the patient presents with clinical and/or radiographic features of pulpal involvement. Perceived (yet not evidence-based factors) such as limited compliance, immature root development and lack of clinical benefit in retention are raised when considering endodontic treatment in children.[9] The American Academy of

Pediatric Dentistry (AAPD) guideline on pulp therapy for primary and young permanent teeth suggests several endodontic techniques (pulpotomy (partial & coronal), pulpectomy, axpefication and regenerative techniques) are available.[10] Despite these guidelines, their use for cFPM in amongst dental care professionals appears to remain limited.[8] Partial and coronal pulpotomies are endodontic techniques that have shown to be successful in immature anterior teeth in children and adults.[11] Coronal pulpotomies have good success rates in permanent posterior teeth with closed apices in adults.[12] Similarly, convectional pulpectomies, apexification and regenerative techniques have all been shown to be successful techniques in adults.[13, 14] However, there appears to be limited evidence for the use of these techniques specifically for cFPM in children. Therefore, the aim of this systematic review is to answer the following focused question: What is the clinical success of endodontic therapies used on first permanent molar teeth in a child aged 16 and under?

Materials and Methods

Protocol and registration

The study protocol was registered at the Prospective Register of Systematic Reviews (PROSPERO - CRD42018089145), and it followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement for the report of this review.[15]

Search Strategy

The Medical Subject Headings (MeSH) terms and free keywords in the search strategy were defined based on the following PICOS question:

- Population (P): Children, aged 16 and under, undergoing endodontic therapies (not including pulp capping) on a first permanent molar tooth
- Intervention (I): Endodontic therapies on a first permanent molar tooth

- Comparison (C): No treatment
- Outcome (O): Success of endodontic therapies
- Study Design (S): All studies included

Clinical success, defined as the tooth being in-situ at the end of the study, was used as the outcome measure in this review. Given the variation in outcome measures this was a pragmatic broad measure likely to allow comparison across studies but this did involve an assumption that for the tooth to remain in-situ it was symptom free and showed no signs of new or progressive infection. Anticipating a scarcity of studies, it was agreed to avoid excluding potentially valid studies that reported clinical success but not radiographic success. Similarly, the expected paucity of data provided the rationale for including all study designs, including case reports and case series.

To identify articles to be included in this review, an electronic search was developed for the following databases: MEDLINE via PubMed and Embase. The search strategies were defined appropriately for each database and are shown in **Table 1.** A search was run on 6th November 2019, and all studies up to this date were included in this review. A minimum follow-up of 6 months was required for evaluation. A hand search was performed, using keywords *'children'* and *'molar'*, in the Cochrane library, the Cochrane Central Register of Controlled Trials (CENTRAL), Clinicaltrials.gov and the ISRCTN registry as well relevant journals: Journal of Endodontics, Australian Dental Journal, Australian Endodontic Journal, Dental Traumatology, International Endodontic Journal, and International Journal of Paediatric Dentistry. The reference lists of included articles were examined to verify whether there were additional relevant studies that were not found during the database searches.

Eligibility Criteria

In this review, any study that assessed the overall success of endodontic therapies (partial pulpotomy/coronal pulpotomy, pulpectomy, apexification, regenerative techniques) in a first permanent molar of a child under the age of sixteen were included. Any studies (including editorial letters and in-vitro studies) that had a follow-up period of less than 6 months and were not written in English were excluded.

Study Selection and Data Extraction

The search strategies were executed by one reviewer (GT), to identify eligible studies. Duplicates were removed, and two reviewers (GT and BA) screened the titles and abstracts to identify eligible studies. Full-text versions of all eligible studies were obtained and two reviewers (GT & BA) extracted the data and carried out an assessment of bias. Any disagreements between reviewers during study selection and bias assessment were discussed until an agreement was met. If necessary, any unresolved differences were resolved by a third reviewer (CRV).

A data-extraction spreadsheet was designed and two reviewers (GT, BA) collected data independently. The quality of the evidence was assessed using the GRADE approach. For each selected article, the following information was collected: author; year; type of study; operator; number of children in study; age range of children; pre-operative clinical and radiographic diagnosis; number of teeth; maturity of apex; type of endodontic therapy used; rubber dam use; material used; follow up period; comparator treatment; overall success of treatment (tooth still in-situ after the follow-up period). Where there was a lack of data in the articles, the authors were contacted to request the missing information.

Risk of bias assessment

The quality assessment was conducted according to Cochrane Collaboration for randomised clinical trials for bias[16] and ROBINS-I tool for non-randomised clinical trials[17], independently by two reviewers (GT and BA), with any disagreements being resolved by discussion or seeking the opinion of a third reviewer (CRV).

The Cochrane collaboration's risk of bias for randomised control trial included assessment of the random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting.[16] Studies were considered to be at 'low risk' of bias if all the key domains were judged as adequate.[16] A study was considered as 'high risk' if one or more of the domains were deemed inadequate.[16] In all studies assessed using this method, some domains were of 'unclear' bias, however, authors were not contacted for more information as each had at least one domain judged as 'high risk' of bias, so overall these were judged as 'high risk'.

For non-randomised control trials, the following domains were evaluated for bias using the ROBINS-I tool[17]: confounding; selection of participants into the study; classification of interventions; deviations from intended interventions; missing data; measurement of outcomes; selection of the reported results. Each domain was recorded as low, moderate, serious, critical, or no information available for risk of bias. An overall risk of bias judgement was determined through combining the levels bias in each domain

Case reports and case-series were not assessed for risk of bias.

Quality of evidence

The quality of evidence was assessed using a GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.[16] A level of quality ('High',

'Moderate', 'Low', or 'Very Low') was assigned to each study by assessing the follow domains: within-study risk of bias; directness of evidence; heterogeneity; precision of effect estimates and risk of publication bias.[16]

Results

The search resulted in 4177 articles and after the removal of duplicates, 3786 articles were identified for title and abstract screening. Fifty-four papers were included for review of the full text. Hand searching and reference linkage did not result in any additional papers. Forty-three were excluded because they did not meet the inclusion criteria. Eleven articles were included for further analysis to inform this review. A summary of article selection is presented as a flowchart, based on PRISMA guidelines (**Figure 1**). The characteristics of the eleven included studies are shown in **Table 2,** which has been separated into four sections reflecting the clinical status of patients at the beginning of the study**.** Three studies were of high quality, six of low quality and two of very low quality.

Risk of Bias

The risk of bias of the included studies has been tabulated (**Figure 2 and 3**). The risk of bias was high in all randomised control trials for blinding of participants and personnel because these details were not mentioned. Similarly, the six non-randomised control studies were all classified to be of 'critical' bias as no information was provided on measurement of outcomes. Two studies, a case-series and a case report were not assessed for bias. The overall risk of bias was considered high.

There was significant heterogeneity in the methodological variables, and hence, a quantitative synthesis could not be performed. A qualitative synthesis of the eleven papers was performed.

Endodontic Therapies used

Five studies undertook a partial pulpotomy[18-22], four studies a coronal pulpotomy[23-26], one a conventional pulpectomy[27] and one a regenerative technique.[28]

Success of endodontic therapies

Pulpotomies have an overall success rate of 91.1% (range 70% to 100%), with partial and coronal pulpotomies having overall success rates reported at 91.3% (range 78.5% to 100%) and 90.5% (range 70% to 100%) respectively. For both pulpotomy treatments alone, rubber dam use, material of choice (MTA vs $Ca(OH)_2$) and pre-operative apical status (mature vs immature) did not influence the success rates of either techniques. Pulpectomies had a success rate of 36%, with success deemed as the tooth having clinical or radiographic pathological features of endodontic failure, although it is unknown whether the presence of known radiographic pathology influenced the success rate. There was only one case report, covering regenerative techniques, which reported success in one tooth [28].

Rubber Dam Use

Six studies provided information on rubber dam use during the endodontic technique.[18, 23-26, 28] In these studies, which included the range of endodontic techniques being reviewed, rubber dam was found to have a mean influence on success rates of 10.9%.

Materials used

Mineral trioxide aggregate (MTA) was used alone in four studies [20, 24-26], calcium hydroxide ($Ca(OH)_2$) alone in two studies[18, 29], and a comparison of both MTA and $Ca(OH)_2$ was undertaken in three studies.[21-23] One study used a recognised regime of triple antibiotic paste

(containing ciprofloxacin (250 mg), metronidazole (500 mg), and minocycline (50 mg)) & MTA, for regenerative techniques.[28] One study did not provide any details.[27]

Assessor/Operator identification

Only seven of the studies provided the number of operators who carried out the chosen therapy.[18, 20, 21, 23, 25, 26, 28] Five studies provided specific details on who examined the patients at the clinical and radiographic reviews.[20-23, 28]

Discussion

This review aimed to ascertain the success of endodontic therapies on a first permanent molar tooth in a child under the age of 16. In summary, there appears to be very limited evidence to support conventional and regenerative endodontics techniques for managing first permanent molar teeth in children, however, there is some evidence to suggest that partial and coronal pulpotomies can be useful techniques. Although some studies were of high quality, the sample size and high and critical level of bias amongst several of the studies suggest the findings must be interpreted with some degree of caution.

The 90.5% (range 70% to 100%) success rate over a mean follow-up of 28.4 months (range 6 months to 73.6 months) shown for coronal pulpotomies in this review is consistent with those studies carried out in the adult population. A review by Alqaderi *et al*[12] suggested that coronal pulpotomies carried out in closed-apex adult permanent teeth have a 94% (95% confidence interval (CI): [90,99]) and 92% (CI: [84,100]) over one and two years respectively.[12]

A similar success rate of 91.3% (range 78.5% to 100%) is observed for a partial pulpotomy review over a mean review period of 34.4 months (range 12 months to 140 months). This is

slightly less when compared to previous literature in adults which has suggested a 97.6% rate >2–3 years.[30] This suggests that pulpotomies are attractive techniques for use in all ages of children given they are less technique-sensitive and time consuming when compared to conventional pulpectomies and regenerative techniques. They may provide an alternative to an elective extraction. Furthermore, equivocal success is noted in this review for immature and mature first permanent molars, providing the operator with a higher degree confidence when using these techniques. A recent prospective study[31] reported 100% clinical success (n=20) and 95% radiographic success (n=19) at 12 months which twenty cariously affected permanent molars, in fourteen children aged 9-17 years, where managed a biodentine coronal pulpotomy.[31] As they included children both within and out with the age range pre-determined for this review it could not be included. Unfortunately, baseline characteristics of study participants did not identify the ages of individual children to identify success for children under 16 alone, but where the teeth managed had immature roots (n=3), they all showed signs of continued root development.[31]

It appears from this review that conventional pulpectomies appear to be rarely employed by practitioners in children as only one study was included. The success rate of 36% (although in a small number of cases (n=10)) noted from this review contrasts markedly with a pooled survival rate of 87% (95% CI: 82%, 92%) noted at 10 years for a conventional pulpectomies in permanent teeth in adults [32]. This is unsurprising, as molar teeth are often harder to treat in children with cooperation often being a limiting factor. In these cases, extraction is likely to be favoured by practitioners and the findings of this review would support this approach until further evidence is available.

In terms of case-selection, it appears that for partial and coronal pulpotomies, pre-operative clinical diagnoses did not influence the overall success of either of these techniques. This

suggests that using these techniques should be based on the clinical assessment of the pulpal tissues solely rather than being led by pre-operative clinical signs or symptoms. A number of studies included in this review undertook either a partial pulpotomy[18, 21, 22] or a coronal pulpotomy[25] for children who were diagnosed with a reversible pulpitis. It could be argued that for these teeth, adopting minimally invasive approaches[33] or placing an indirect pulp cap may be more appropriate than electively removing pulpal tissues.[34]

In contrast, for conventional pulpectomies, the extent of the pathology will influence overall success and so this should be carefully considered. In some situations, such as for patients with congenital absence of teeth, when only one molar is compromised or retention is required to prevent worsening a class II malocclusion, retention of molars is desirable and as such, endodontic techniques are more likely to be carried out. However, which technique to undertake will be determined by the pre-operative clinical and radiographic signs and symptoms of the tooth, which are essential prognostic variables for overall success.

There were no studies included in this review that reported on apexification in first permanent molar teeth in children. This could suggest that it is a technique that is not used, due to being technically demanding, or the evidence base is yet to establish for its' use in these teeth. Further research is clearly required before a conclusion about this technique for these teeth can be reached.

Success was shown in one case report that used regenerative techniques for an isolated immature first permanent molar[28]. Regenerative techniques have shown some initial success in anterior teeth[35], however their use in immature first permanent molar teeth requires further evidence before its use can be formalised.

Although rubber dam is mandatory for patient safety, it does appear from our review that rubber dam use was found to have improved success rates by on average 10.9% across the six

studies. Ahmad[36] suggested due to a lack of direct evidence, using rubber dam does not improve the outcome of endodontic treatment.[36] Our review appears to contradict these findings, although, it is recognised that the applicability of this comparison may not be of great worth as Ahmad's[36] review is now 10 years old and it is likely that significantly more studies will have reported on this issue during this time period. For children where co-operation is often regarded as the main barrier to endodontic treatment[9], rubber dam placement acceptance may be a good indicator for compliance.

Strengths and Limitations

To our knowledge, this is the first systematic review that includes a thorough and quantitative synthesis on the success of endodontic therapies in compromised first permanent molars in children. This is a potential strength of the article as it follows a robust and detailed methodology and reporting scheme whilst includes an assessment of the quality and level of evidence overall for each study. An extensive and comprehensive literature search was employed in relevant databases in addition to hand searching relevant paediatric, endodontic and traumatology journals, however, the authors note that the grey literature was not fully explored.

The review was based on a range of study types rather than just randomised control trials. This meant the studies included were of variable quality (three studies were of high quality, six of low quality and two of very low quality according to GRADE), however, given the perceived anecdotal scarcity of evidence, having such variation in quality was acceptable. Each study had a relatively small sample size, which does question the reliability of the findings. Despite small numbers, coronal and partial pulpotomies have shown to be successful options for managing immature and mature compromised first permanent molar teeth in children. These options should be given due consideration, irrespective of the pre-

operative clinical state as this did not appear to influence the success rates of these modalities. We cannot however draw definite conclusions regarding conventional pulpectomy, apexification and regenerative techniques, in first permanent molars in children, due to the paucity of available evidence. This is not say that these techniques cannot be used.[10] Further well-designed studies, with larger sample sizes, should be undertaken with the range of techniques available to provide a more definitive answer.

Reviewers (GT & BA) involved in the screening process, specifically study identification and data extraction, were not blinded to either author's names and/ or study origin. This could introduce bias; however, it should be negligible as each reviewer worked independently and consulted with a third reviewer when disagreement was noted. Adopting this approach conforms to the Cochrane Collaboration for Systematic Reviews of Interventions, which suggests that at least two reviewers should carry out these processes, and that blinding is not essential, as it is time consuming and does not result in benefit or protection against bias.[16]

Why this is important to paediatric dentists:

- Managing compromised first permanent molars is essential as these teeth are routinely encountered in clinical practice
- Coronal and partial pulpotomies appear to be successful techniques that can be used in children
- Conventional pulpectomies have limited success when carried out in children, and until further evidence is available, it could be suggested that these teeth could be extracted.

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Table 1

Electronic Database	Search Strategy
MEDLINE via Pubmed	1. immature teeth.mp. 2. immature tooth.mp. 3. first permanent molar*.mp. 4. FPM*.mp. 5. dentition, mixed/ or dentition, permanent/ (MESH) 6. 1 or 2 or 3 or 4 or 5 7. exp Dental Caries/ (MESH) 8. exp Dental Enamel Hypoplasia/ (MESH) 9. molar incisor hypoplasia.mp. 10. molar incisor hypomineralisation.mp. 11. MIH.mp. 12. Dentinogenesis Imperfecta/ (MESH) 13. AI.mp. 14. DI.mp. 15. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 16. 6 and 15
Embase	1. immature tooth.mp. 2. immature teeth.mp. 3. first permanent molar*.mp. 4. FPM*.mp. 5. mixed dentition/ 6. secondary dentition/ 7. 1 or 2 or 3 or 4 or 5 or 6 8. exp dental caries/ 9. exp enamel hypoplasia/ 10. molar incisor hypoplasia.mp. 11. molar incisor hypomineralisation.mp. 12. MIH.mp. 13. tooth malformation/ or amelogenesis imperfecta/ 14. dentinogenesis imperfecta.mp. 15. AI.mp. 16. DI.mp. 17. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 18. 7 and 17

Table 1: Electronic Database and Search Strategy

Table 2

Author/Year	Study Design	GRADE	Number of Operators	Age Range (years)	Pre-Operative Status	Number of teeth	Maturity of the Apex	Type of Pulp Therapy	Comparator Treatment	Rubber Dam/ Material(s)	Follow-Up Period (months)	Success	Conclusion
Studies of patients with a reversible pulpitis diagnosis													
Chailertvanitkul et al. / 2014	RCT	High	2	7-10	Reversible Pulpitis with no peri-radicular changes	76	*	Partial Pulpotomy	No Comparator	*/ MTA & $Ca(OH)_2$	24hrs 3, 6, 12, 24	MTA: 39/41 $Ca(OH)_2$: 34/35	Partial Pulpotomy favourable treatment No difference between MTA and CaOH
Alqaderi et al./2014	Prospective Cohort	Low	4	10-15.4	Deep caries & reversible pulpitis; absence of peri-radicular changes	24	24M	Coronal Pulpotomy	No Comparator	Yes/ MTA	Range: 6-47 Mean: 27.5	24/27	Coronal pulpotomy successful alternative to Root Canal Treatment for cariously exposed molar teeth
Mejàre et al. / 1993	Prospective Cohort	Low	16	6-15	Group 1: No clinical or radiographic signs Group 2: Clinical and/or radiographic signs	Group1 (n=31) Group2 (n= 6)	Group1 14 IM: 17M Group2 1 IM: 5M	Partial Pulpotomy	No Comparator	Yes/ $Ca(OH)_2$	Range: 24 – 140 Mean: 56	Group 1: 29/31 Group 2: 4/6	Partial Pulpotomy is successful treatment

Barrieshi-Nusair et al. /2006	Prospective Cohort	Low	1	7.2-13.1	Reversible pulpitis and no periradicular changes	28	7IM: 21M	Partial Pulpotomy	No Comparator	*/ MTA	3,6,12,24	22/28	MTA partial pulpotomy suitable for young permanent molar teeth
Studies of patients with an irreversible pulpitis diagnosis													
Qudeimat et al./ 2017	Prospective Cohort	Low	1	7.6-13.6yrs	Irreversible Pulpitis No radiographic internal or external resorption or furcation radiolucency	23	10 IM:13 M	Coronal Pulptomy	No Comparator	Yes/ White MTA (n= 14) Grey MTA (n=9)	3,6,12, annually Range: 18.9 - 73.6 Mean: 57.5	23/23	MTA complete pulpotomy good success rate for young permanent molars
Witherspoon et al./2006	Case Series	Very Low	*	7.5-10	Irreversible Pulpitis & carious exposure; no radiographic changes	10	*	Coronal Pulpotomy	No Comparator	Yes/ MTA	Range: 17-53 Mean: 27.2	7/10	Good success rate for MTA pulpotomy
Schmoeckel et al/2017	Case Report	Very Low	1	8	Irreversible Pulpitis No radiographic internal or external resorption or furcation radiolucency,	1	Immature	RET	No Comparator	Yes/ Triple Antibiotic Paste (containing ciprofloxacin (250 mg), metronidazole (500 mg), and minocycline (50 mg)) & MTA	3,9,16,24	1/1	Management of an immature partially necrotic permanent molar is feasible in vivo

Studies of patients with no pulpitis diagnosis													
Qudeimat et al./2007	RCT	High	*	6.8-13.8	Asymptomatic carious exposures with no radiographic changes	51	$Ca(OH)_2$ Group: 8IM: 15M MTA Group: 6IM: 22M	Partial Pulpotomy	No Comparator	$Ca(OH)_2$ Group: 10/28 MTA Group: 18/23 / MTA & $Ca(OH)_2$	3, 6, 12, annually Range: 25.4-45.6 Mean: 34.8	MTA: 26/28 $Ca(OH)_2$: 21/23	MTA and CaOH show comparable success rates for partial pulpotomy in permanent molars
El-Meligy et al./2006	RCT	High	1	6-12	No clinical or radiographic signs	24	MTA Group: 11IM $Ca(OH)_2$ Group: 13IM	Coronal Pulpotomy	No Comparator	Yes/ MTA & $Ca(OH)_2$	3,6,12	MTA: 11/11 $Ca(OH)_2$: 11/13	MTA Pulpotomy suitable alternative to Calcium Hydroxide
Studies of patients with undefined diagnosis													
Nosrat et al. / 1998	Prospective Cohort	Low	*	10 - 15	*	4	*	Partial Pulpotomy	No Comparator	N=2/ $Ca(OH)_2$	1, 3, 6, 12 Final Review range: 24-33	4/4	Partial Pulpotomy useful technique
Peretz et al./1997	Retrospective Cohort	Low	*	8-16	16/28 pathology pre-treatment; no clinical status given to teeth before	28	*	Root Canal Treatment	No Treatment	*/*	Range: 24-77 Mean: 45.1	10/28	Relative success of root canal treatments in first permanent molars

Table 2: Summary of the included studies (RCT: Randomised Control Trial; MTA: Mineral Trioxide Aggregate; $Ca(OH)_2$: Calcium Hydroxide; RET: Regenerative Endodontic Technique; * - denotes no information is provided

Figure Legends

Figure 1: PRISMA Flow Diagram

Figure 2: Bias Assessment: Randomised Control Trials

Figure 3: Bias Assessment: Non-Randomised Control Trials