The effectiveness of Atraumatic Restorative Treatment versus conventional restorative treatment for permanent molars and premolars

A critical assessment of existing systematic reviews and report of a new systematic review

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Abstract

Background: Atraumatic Restorative Treatment (ART) is the removal of caries using hand instruments and restoration of the resulting cavity using an adhesive restorative material. It was designed to restore teeth in communities without access to conventional dental clinics in poorer countries but has come to be used by dentists in the developed world too, as an alternative to conventional restorative treatment.

Objectives: 1) to assess the scope and the methodological and reporting quality of existing systematic reviews of the effectiveness of ART compared to conventional restorative treatment; 2) to evaluate the effectiveness of ART compared to conventional treatment in permanent teeth with class I and II cavities.

Methods:

Searches: 1) for the assessment of existing systematic reviews: Electronic searches were conducted of OVID Medline, OVID Embase, The Cochrane Database of Systematic Reviews (CDSR), the Centre for Reviews and Dissemination (CRD) databases (DARE, NHSEED and HTA), Google Scholar, and the CNKI and CAOD Chinese databases; 2) for the systematic reviews of ART in permanent teeth: the above searches were supplemented by searches of the Cochrane Central Register of Controlled Trials (CENTRAL), LILAC, BBO, IMEAR (WHO Index Medicus for South East Region), WPRIM (WHO Western Pacific Region Index Medicus) and IndMed, Current Controlled Trials, Clinical Trials, OpenSIGLE, IADR conference abstracts and NLM Gateway. Hand searches were conducted of six dental journals known to have reported ART studies. References from retrieved systematic reviews, trials and other related papers were searched for additional reports. Authors were contacted. There were no language restrictions.

Selection criteria: 1) for the assessment of existing systematic reviews: systematic reviews that compared ART to conventional treatment for the restoration of dental cavities; 2) for the systematic

reviews of ART in permanent teeth: randomised controlled trials that compared ART using any adhesive material to conventional treatment using amalgam or any adhesive material

Data collection: 1) for the assessment of existing systematic reviews: Reviews were selected and data was extracted by a single reviewer using a custom made data extraction sheet. Scope was assessed in terms of materials used, teeth and cavity type. Methodological quality was assessed using AMSTAR. Reporting quality was assessed using the PRISMA guidelines; 2) for the systematic reviews of ART in permanent teeth: reports of trials were screened and selected independently by two reviewers and data would have been extracted on a custom made data extraction sheet had there been eligible trials.

Results: 1) for the assessment of existing systematic reviews: three systematic reviews were identified. Two of these were restricted to comparing ART with glass-ionomer to conventional treatment with amalgam; two allowed for inclusion of all cavity types in both deciduous and permanent teeth. None was of high methodological quality and reporting quality was good in one of the reviews only; 2) for the systematic reviews of ART in permanent teeth: no eligible trials were identified.

Author's conclusions: 1) existing systematic reviews do not have sufficient scope to allow for the inclusion of potentially eligible trials that would assess ARTs effectiveness and they have been of high to medium risk of bias; 2) it is disappointing that there are no properly conducted randomised controlled trials comparing ART to conventional treatment in class I and II cavities in the permanent dentition.

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1. Introduction to the dissertation

1.1 What is Atraumatic Restorative Treatment (ART)?

In the mid-1980s a primary dental care project was developed at the Dental School in Dar es Salaam, Tanzania. Donors had sent out apparently-mobile iron dental chairs, suction devices and drills to deliver the service but it soon became clear that due to the cost of servicing this equipment and the difficulty of transporting it to, and using it in, rural communities the delivery of the project was severely hampered. So a means was developed to excavate dental caries and restore the cavities using instruments and materials available locally. This meant excavation using hand instruments and restoration, then, with zinc phosphate cement (1).

By using just hand instruments and a simply-mixed material, trained personnel could deliver restorative dental care in communities that may never otherwise have received it due to their remoteness from conventional clinics. This technique came to be known as Atraumatic Restorative Treatment (ART) and offered an alternative to leaving teeth with untreated dental caries. It should be noted, however, that until now the restoration of caries in primary teeth has not been demonstrated to be superior to no treatment for the outcomes of pain, sepsis and tooth loss in a randomised controlled trial. This is, however, now being tested in the FiCTION trial, which will recruit children with caries treated in primary care settings in the United Kingdom to either have conventional treatment, no restorative treatment or the so-called Hall technique (2).

By the early 1990s a trial was being conducted in Thailand using glass-ionomer cement (GIC) as the restorative material (3) compared to conventional treatment using amalgam. GICs have a number of physical and biological properties that made them potentially suitable materials for ART. These included their ability to stick to dentine and enamel without preparation of these surfaces and the release of fluoride that may arrest caries and make adjacent dentine and

enamel more resistant to recurring caries (4-6). A further development came as higher viscosity GICs were developed to be stronger and more resistant to occlusal wear than their less viscous predecessors (7), and to set quicker once placed (8).

A handbook on how to use ART was produced in 1997 (9) and it defined ART as "a procedure based on removing carious tooth tissues using hand instruments alone and restoring the cavity with an adhesive restorative material". Although GICs had been the material used in most clinical studies it was at least theoretically possible that other adhesive materials could be used. These include composite resins, resin-modified glass-ionomers (RMGICs) and compomers. These materials are made in light-activated forms, which are less suitable to the environment ART was intended to be used in but there are also chemically-cured forms, which are not dependent on light and, therefore electricity, and would be suitable for use in the non-clinical setting.

In 1998 ART was given a boost by the World Health Organisation (WHO) with the publication of a global initiative to promote ART through education, community demonstration programmes and research (10). Reports on the use of ART can be found from China (11, 12) , Brazil (13, 14), South Africa (15), Nepal(16), Tanzania(17, 18), Turkey (19, 20) and Syria(21) amongst others. ART appears to be a worldwide, if perhaps patchy, phenomenon.

Out of necessity ART was likely to be less destructive of sound tooth tissue than conventional treatment. The latter's use of high speed handpieces makes removal of healthy dentine and enamel probably. Thus by default rather than design, it is one of several different minimal intervention approaches that preserve tooth structure and, in theory, therefore minimise damage to the dental pulp (22). Partly for this reason ART has begun to be promoted as a means to manage caries in communities that are far removed from those it was originally conceived for, particularly in smaller, single surface, cavities (23). Indeed, it would appear that a number of UK dentists, for example, already use ART (24). There are other reasons apart

from the philosophy of minimal intervention that could account for its increasing use in the developed world. These include ART often not requiring local anaesthesia (25) and reportedly being less anxiety-causing (26, 27) due in part to the need not to give an injection and the lack of rotary instrument sounds and sensation.

Whilst often considered a means of restoring carious cavities ART also includes fissure-sealing adjacent surfaces with the GIC. Fissure sealants have been shown to reduce caries rates (28, 29) though retention of GIC sealants may be poor compared to other materials (30). Nonetheless, this concept of the preventive potential of ART has been present since its inception (31).

1.2 Aims of the dissertation

The main aim of this dissertation is to present an enquiry into the evidence supporting the use of ART in restoring single (class I) and two surface (class II) carious cavities in permanent posterior teeth.

Permanent posterior teeth include molars and premolars that erupt into the mouth from approximately 6 years of age (first molars) until 12.5 years (second premolars) (32) and are not exfoliated like the primary dentition. The focus was on understanding what the evidence is for using ART in the permanent dentition because maintaining the vitality and functionality of these teeth is of greater long term consequence than for deciduous teeth. Furthermore, loss of permanent teeth requires relatively complex interventions to restore to function the spaces left behind (33).

Initially this study had sought to establish whether ART was effective compared to the alternative for the populations it was developed for. For those populations the alternative is no restorative treatment or extraction. However, on scoping the medical databases for trials that compared ART to no treatment with outcomes focused on tooth loss, pain and sepsis, there appeared to be none. It may be that the FiCTION trial described above is able to shed

some light on this in due course. It is not a trial of ART versus no treatment but will at least compare no treatment to 'normal' treatment, which may include ART procedures as a subgroup.

As a consequence of the apparent lack of trials relating to the basic question of whether ART was needed in the first place, the study instead sought to understanding whether it is as effective as conventional means of restoring teeth. The definition of conventional used here is caries removal using drills rather than hand instruments and restoration with any material that could be used for ART, or amalgam. Scoping of PubMed suggested that this was how ART had been evaluated for the most part.

Thus this dissertation considers previously published systematic reviews addressing ART versus conventional treatment for their scope and quality, presents two systematic reviews conducted and discusses how research in this area could be enhanced so as to provide more robust evidence for or against the use of ART in future.

2. What is the current evidence regarding ART?

2.1 Introduction to the critical review of existing systematic reviews

Systematic reviews have the potential to aid clinicians, patients and healthcare planners in deciding the most effective interventions to address a particular health problem (34). Like any study, though, a systematic review is itself at risk of bias. In order to minimise this a systematic review should use explicit, systematic methods in collecting all available evidence to answer its question and is normally made up of clearly stated objectives, a systematic search that attempts to identify all relevant trials, an assessment of the validity of included trials, and a systematic presentation of the findings and conclusions of the included trials (35).

The QUORUM (Quality of Reporting of Meta-analyses) statement was developed in the late 1990s as a guide to assist authors in reporting their meta-analyses (36). The statement consists of a set of items to be checked against a prepared manuscript of a systematic review and a flow diagram showing the progress of the identification and selection of eligible trials. The list was generated by a group of 30 clinical epidemiologists, clinicians, statisticians, editors, and researchers who were asked to list the items they thought important in reporting a systematic review. Ideally there was research evidence that the absence of an item in a systematic review report could lead to bias but this was the case only for 8 of 18 items. Subsequently a modified Delphi method was used to choose the items that should form the QUORUM checklist.

The Delphi method is "...a method for structuring a group communication process so that the process is effective in allowing a group of individuals, as a whole, to deal with a complex problem" (37). It is used by committees to prioritise items, in this case the items that should be included in the QUOROM statement. This is done by encouraging individual contributions of information and knowledge, an assessment of the group's judgement or view, allowing for participants to revise their view and at the same time allow for individual anonymity. The idea

is that individuals should be able to be influenced by the views of their peers but only where those views truly alter theirs, rather than because of a feeling of being obliged to concede to an alternative view because of peer pressure.

QUOROM was superseded by the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement (38, 39). This was developed from the items in the QUOROM checklist and reflected conceptual and practical advances in the conduct of systematic reviews.

First of these was the recognition that because systematic reviews can be an iterative process reviewers should be required to report changes to a protocol and explain their reason for doing so without suggesting that this is inappropriate.

Secondly, there was recognition that whilst the conduct and reporting of a trial may be distinct in clinical trials, the nature of systematic reviews makes this distinction less clear.

Thirdly, the risk of bias of individual outcome reporting in trials, even within the same study, was seen as being as important as the risk of bias due to study conduct itself. Primary outcomes may be given more attention and collected more thoroughly than, say, adverse events that rely on self-reporting.

Finally, the outcome reporting bias within studies should be considered alongside other better known biases such as reporting bias. 62% of 102 trials in one empirical study had at least one primary outcome in the protocol that was changed, introduced or omitted in the published report of the trial (40). Thus PRISMA requires that systematic review authors consider this when appraising included studies.

Systematic reviewers have been encouraged to use these reporting guidelines to improve the transparency of their studies (41). The PRISMA guidelines, whilst being intended principally to assist authors, are also a useful means of critically appraising a systematic review as a reader.

Furthermore, they can be used to systematically assess the reporting quality of reviews in a particular field and so identify potential shortcomings that need addressing to improve the evidence available for decision-making (42, 43).

Despite the reporting guidelines and books to assist with conducting systematic reviews (44, 45) a number of studies have found that far from all systematic reviews have been conducted in a methodologically vigorous manner (46-50). It is, therefore, necessary to critically-assess systematic reviews as much as trials to ascertain their risk of bias, including those from the Cochrane Library (51).

The various studies that have looked at quality of reviews have identified areas the respective authors felt were important in conducting methodologically-sound reviews (46-50). Some have then assigned scores to reflect how well these appear to have been conducted in the review. Despite their consistency in finding that only a small number of reviews were conducted well, the direction of the resulting bias appears to be uncertain. One study, for example, found that reviews with high scores according to their criteria (i.e. being better quality) were more likely to report a positive effect for a new intervention (49) whilst another study found that lower quality reviews were more likely to report positive outcomes for the new intervention (50). Jüni found that there was a high degree of heterogeneity in the conclusions of 25 different numerical quality scales when used with the same set of 17 randomised controlled trials (52). In their analysis the effect size either increased or decreased with increasing trial quality despite the same trials being used for analysis. The Cochrane Handbook, for this reason, encourages review authors not to use scoring when assessing the methodological quality of trials but rather to use a risk of bias table (45). It is interesting to me that such caution has not been apparent in the generation of tools to assess systematic review quality as it would seem to be logical to assume that scoring could result in similar biases to those identified by Jüni for trials.

At least 24 instruments to assess the quality of systematic review reporting exist (53). A study that evaluated the quality of randomised control trials found that the average quality based on the published reports was 50% and that this rose only to 57% after the interview with the corresponding author (54). This has been taken to suggest that reports of trials (and by implication systematic reviews) are a reasonable reflection of the quality of the conduct of the research itself and this thinking is reflected in the development of QUOROM to PRISMA.

I chose to use a tool called AMSTAR (Assessment of Multiple Systematic Reviews) (55) to assess the quality of the systematic reviews I identified. The tool uses 11 items to assess the methods used by the reviewers in the conduct of their study. Scores of 1 have been assigned where an answer of 'Yes' is given and 0 when 'No' is given (i.e. the item is not covered)(56). However, because of the concerns over the use of scoring systems raised by Jüni in appraising clinical trials I decided to avoid the use of the AMSTAR scoring mechanism but to use the items themselves to qualitatively assess the reviews.

The AMSTAR tool combined elements of the 10 item Overview Quality Assessment Questionnaire (OQAQ) that was developed by Oxman et al (57) and the 24 item checklist created by Sacks for his assessment of the quality of systematic reviews (46). The authors also added another three items that have arisen since the development of these two instruments – language restriction, publication bias and publication status – resulting in 37 items. Factor analysis was used to identify 11 underlying components that were then assessed for validity by 11 experts in the fields of methodological quality assessment and systematic reviews using the nominal group technique.

Exploratory factor analysis is a statistical technique that looks to see if a number of variables (in this case the 37 checklist items) can be explained in large part by a smaller number of so-called latent variables or factors (in this case what the authors called components). A benefit

of this would appear to be to make the quality assessment shorter but maintain its validity to determine a high or low quality review.

Confirmatory factor analysis is sometimes used after exploratory factor analysis to see if the latent variables are able to explain the observed variables in a different sample (58). The sample used here for the exploratory analysis was a set of 99 paper-based systematic reviews and 52 Cochrane reviews. It is unclear why confirmatory factor analysis was not conducted as this would have provided an assessment of the construct validity of the 11 item AMSTAR checklist. This is similar to the concept of external validity when considering the results of trials or systematic reviews. Do they apply to populations other than those used in the studies?

The nominal group technique mentioned above is a structured method to help groups make decisions with the intention of generating many ideas, allowing all to participate equally and rank-ordering a set of decisions using a method of voting (59). Used here it will in itself not validate that the 11 items when ticked do indeed reflect the absolute truth about the bias of a review, but instead reflects experts' opinions on the quality or bias of the review. For this reason the AMSTAR checklist was judged to have good face validity – it looked like it *would be* able to assess the quality of systematic reviews.

I sought to identify systematic reviews that compared ART to conventional treatment for the restoration of dental cavities and then to assess each of the included reviews for 1) the scope of trials they could potentially have included according to their inclusion criteria, 2) their methodological quality and 3) the reporting standard of the review.

2.2 Materials and Methods

An electronic search of OVID Medline, OVID Embase, The Cochrane Database of Systematic Reviews (CDSR), the Centre for Reviews and Dissemination (CRD) databases (DARE, NHSEED and HTA), Google Scholar, and the CNKI and CAOD Chinese databases were made (last search

on August 31st 2011). For Medline, Embase and CENTRAL a detailed search strategy was developed that included both free text and MeSH terms (see appendix 1). 'MeSH' refers to a database in which all papers have been categorised under certain headings, and if a search matches one of the headings in the MeSH database all those associated papers will be included in the search results. The keyword search retrieves all papers which contain the search term(s) in the reference. I combined both types of search to increase the sensitivity of the search. Keywords and MeSH terms relating to all permanent dental restorations, ART and the materials used for this were combined using 'OR'. Keywords and MeSH terms relating to amalgam and caries were combined with 'OR'. The two sets of results were combined using 'AND' (see appendix 1). This search strategy was also used for the systematic review conducted subsequently.

For the other sources the term 'Atraumatic Restorative Treatment' was used. In addition, the references of retrieved systematic reviews were searched for relevant references. All potential studies were merged in Endnote and a filter applied. This was: systematic OR review OR meta-analysis OR metaanalysis. The remaining reports were screened for potential inclusion.

In order to be eligible reports had to identify themselves as a systematic review or meta-analysis, compare ART to conventional treatment for the restoration of dental cavities and have been published. ART was defined as the removal of caries using hand instruments only and restoration of the cavity with any adhesive material. Conventional treatment was defined as caries removal in part or whole using mechanical means and restoration with amalgam or any adhesive material. No language restriction was placed on reports.

For each review identified the following review characteristics were extracted using a specially designed data extraction sheet (see appendix 2): primary author, language of publication, review title, year published, sources searched, whether the search strategy included free text and subject heading terms, last search date for review, references of included trials and

duration of eligible trials (minimum, maximum or both). In addition, the following were recorded: whether there was any restriction on the tooth type (permanent, deciduous) or class of cavity that could potentially have been included (classes I through to V), if the materials for ART were limited to one or more adhesive materials (GIC, RM-GIC, composite) and if the conventional treatment was limited to one or more restorative materials (amalgam, GIC, RM-GIC, composite). A consensus approach was used where there was disagreement and this was successful in all cases.

The AMSTAR and PRISMA checklists were used to assess methodological and reporting quality respectively.

2.3 Results

9,109 reports were screened for papers relating to ART or GIC. Of these 1,105 were potentially eligible. To these the filter for systematic reviews in Endnote was applied and 131 reports retained. Further screening of these resulted in 14 potential reviews. Of these 3 systematic reviews that compared ART to conventional treatment were eligible (60-62). There was one Cochrane protocol for a systematic review into ART (63).

Table 1 shows that the two systematic reviews in English have been limited to glass-ionomer as the ART material and amalgam as the conventional material. The Chinese review appears not to have applied any restriction on the material used for either ART or conventional treatment though this was not made explicit.

Primary author	**Frencken, J.E.** (60)	**Mickenautsch, S** (61)	**Pettar, M** (62)
Title	Effectiveness of single surface ART restorations for restorations in the permanent dentition: a meta-analysis	Atraumatic restorative treatment versus amalgam restoration longevity: a systematic review	Atraumatic restorative treatment versus conventional treatment for childhood caries: a systematic review
Language	English	English	Chinese
Year published	2004	2010	2011
Last search date	01/09/2003	16/03/2009	April 2010
Sources searched	PubMed and MEDLINE [these both access the same biomedical index]	Biomed Central, Cochrane Library, Directory of Open Access Journals, PubMed, and ScienceDirect	CENTRAL, Medline, Embase, Chinese biomedical literature database, WHO and Chinese clinical trial databases
Search strategy	Free text	Free text	Free text
Duration of eligible trials	1-3 years	Minimum of 1 year	None stated
Classes of cavity eligible	I	Not explicit but includes studies with classes I, II and V	All
Tooth type	Permanent	Permanent & deciduous	Permanent & deciduous (in children aged 4-16 years)
ART material(s) eligible	GIC	GIC	Not defined
Conventional material(s) eligible	Amalgam	Amalgam	Not defined but could include adhesive
Included trials	Phantumvanit (64), Mandari (65), Rahimtoola (66), Kalf-Scholte (67), Taifour (68)	Yip (69), Taifour (70), Honkala (71), Gao (72), Yu (73), Yu (73), Frencken (74), Frencken (21)	Rahimtoola (75) Taifour (70) Schriks (26) Eden (76) Frencken (74) Van de Hoef (77) De Menesea Abreu (78) (this is cited as a 2010 article in the review)

Table 1 Characteristics of included systematic reviews

The Mickenautsch review had the potential to include cavities of class I, II and V in permanent and deciduous teeth based on the included cavities in the results, but this was not made explicit in their inclusion criteria. The Frencken review included only class I cavities in permanent teeth. Again, the Pettar review appears not to have restricted the restoration class at all but this was not stated explicitly. Also, whilst both deciduous and permanent teeth could potentially be included, the Pettar review restricted trials to those that included patients aged 4-16 years. It is unclear how they would have dealt with trials that included participants that spanned both ends of this range for which patient level data was not available.

Both English reviews had one year as a minimum follow-up whilst the Chinese review appears not to have placed any restriction on the length of follow-up perhaps because they also considered short term outcomes such as anxiety. The Frencken review restricted the maximum follow-up to three years. This seems to be an odd choice given that it would exclude trials that could give useful data on longevity beyond this time. ART is not proposed as a temporary or short term restoration in this review but as a permanent one. By restricting the outcome data in time this would appear to put the review at risk of outcome reporting bias. It is possible that trials with longer term results would reveal higher failure rates.

There was no limit for the Mickenautsch review.

Whilst the Frencken and Mickenautsch reviews looked solely at the survival of the restorations, the Pettar review gave equal weight to different outcomes: longevity as well as anxiety and pain associated with the different restorative techniques.

The Mickenautsch review explicitly rejected all of the reports included in the earlier Frencken review based on their eligibility criteria. The Pettar review included just two studies of the seven that the Mickenautsch review included (70, 74) and none of the five included in the Frencken review. Because the Pettar review does not list the papers it rejected, nor the

reasons why, I cannot say why this is the case. The additional five trials included in the Pettar review would appear not to have been eligible for the Mickenautsch review based on the latter's eligibility criteria.

Table 2 shows the assessment of the quality of each review using the AMSTAR tool. Whilst the Mickenautsch and Pettar reviews appear to have followed a more structured approach to the review process than the earlier, Frencken review, all three reviews are at risk very early on of missing relevant studies. This is because they all use only free text terms for their database searches and do not include subject heading (MeSH) terms. Furthermore, the Mickenautsch and Frencken reviews were limited to reports written in English and only searched English-language databases. The Pettar review placed no such restriction on language and did additional searches of a number of Chinese sources. None of the reviews searched the BBO or LILAC databases that index journals from Brazil, Latin America and the Caribbean (79). The LILACS database has been shown to identify randomised controlled trials not identified by other databases (80) though it may be difficult to use (81).

AMSTAR item	**Frencken, J.E.** (60)	**Mickenautsch, S** (61)	**Pettar, M** (62)
Was an 'a priori' design provided?	No	Yes	Unsure
Was there duplicate study selection and data extraction?	Can't answer	Yes	Yes
Was a comprehensive literature search performed?	No	No	Yes
Was the status of publication used as inclusion criteria?	No	No	No
Was a list of studies provided?	Yes	Yes	No
Were the characteristics of the included studies provided?	Yes	No	Yes
Was the scientific quality of the included studies assessed and documented?	Can't answer	Yes	Yes
Was the scientific quality of the included studies used appropriately in formulating conclusions?	Can't answer	Yes	Yes
Were the methods used to combine the findings of studies appropriate?	Can't answer	Yes	N/A
Was the likelihood of publication bias assessed?	No	No	No
Was a conflict of interest stated?	Yes	No	No

Table 2 AMSTAR checklist for included systematic reviews

Whilst references from included reports were scanned for further studies in the Mickenautsch review, neither the Frencken nor the Pettar reviews report doing this. None of the reviews report hand searching journals, contacting experts in the field or checking the grey literature.

The Frencken review combined the results of studies using low and high viscosity GIC independently. The Mickenautsch review was only able to combine results for 2 subgroups: class I cavities in primary teeth at 12 and 24 months. The Pettar review stated that the studies were too clinically heterogeneous to combine in a meta-analysis.

The Frencken review did not attempt to assess the quality of the included trials and was not able, therefore, to bring this to bear on the interpretation of the results. Mickenautsch assessed the included studies to be particularly at risk of allocation bias and, therefore, urged caution in interpreting the conclusions from the trials. The Pettar review did assess bias in all 6 domains recommended by the Cochrane Handbook and concluded that all included studies were of low quality. Thus, while all reviews included trials that found there to be no significant difference in the longevity of ART compared to conventional treatment, the two reviews that assessed the risk of bias concluded that all the included trials were compromised.

Table 3 shows the reporting of the PRISMA checklist items for each of the studies. For each I have noted whether the item was reported in full (=yes), in part (=part) or not at all (=no).

It can be seen that the reporting of the Mickenautsch review was more comprehensive and closer to current guidelines than was the Frencken review. The Pettar review was consistent with some aspects of the PRISMA guidelines but not to the same degree as the Mickenautsch review.

Of the 27 items Frencken reported fully just 11 of them, Mickenautsch 17 and Pettar 8.

Item	Frencken, J.E. (60)	Mickenautsch, S (61)	Pettar, M (62)
TITLE			
Title	☺	☺	☺
ABSTRACT			
Structured summary	☹	☺	☺
INTRODUCTION			
Rationale	☺	☺	☺
Objectives	😐	☺	☹
METHODS			
Protocol & registration	☹	☹	☹
Eligibility criteria	☺	☺	😐
Information sources	😐	☺	☺
Search	☺	☺	😐
Study selection	☹	😐	😐
Data collection process	😐	😐	☹
Data items	😐	😐	☹
Risk of bias of individual studies	☹	☺	😐
Summary measures	☺	☺	☹
Synthesis of results	😐	☺	☹
Risk of bias across studies	☹	☹	☹
Additional analysis	☹	☺	☹
RESULTS			
Study selection	☺	☺	☺
Study characteristics	☺	☺	😐
Risk of bias within studies	☹	😐	☺
Results of individual studies	😐	😐	☹
Synthesis of results	☺	☺	☹
Risk of bias across studies	☹	☹	☺
Additional analysis	☹	☺	☹
DISCUSSION			
Summary of evidence	☺	☺	😐
Limitations	☹	😐	😐
Conclusions	☺	☺	☺
FUNDING			
Funding	☺	☹	☹

Table 3 PRISMA Checklist for included systematic reviews (☺=Yes, 😐=Part, ☹=No)

2.4 Discussion

I was able to identify three systematic reviews that compare ART to conventional restorative treatment. Whilst the two later reviews appear to be more methodologically sound, all three are at risk of missing relevant publications either through a limited search strategy, a restriction on the sources searched or the language that eligible trials could be reported in.

Hand searching has been demonstrated to improve the yield of searches for randomised controlled trials: 92-100% of trials compared to 55% in Medline (82). Non-English publications were particularly susceptible to being missed by not hand searching: only 39% of trials were identified when published in a language other than English. By not conducting hand searches all of the reviews risked missing potentially eligible trials.

The MeSH term "Dental Atraumatic Restorative Treatment" was introduced in Medline in 2010 and ART was previously categorised under "Dental Restoration, Permanent". These and other ART-related MeSH terms were not used in any of the reviews' searches. A search in PubMed using "Atraumatic restorative treatment" (as per the Mickenautsch review) included all 74 results from the Dental Atraumatic Restorative Treatment MeSH search (personal search 13/04/2012). This may be because over the years the phrase "Atraumatic restorative treatment" has become synonymous with the treatment worldwide, or because those who categorise trial reports do not categorise anything without ART in the title or abstract as ART. Since ART was previously categorised under "Dental Restoration, Permanent", from 1995, it seems possible that early reports on minimal caries excavation and restoration with GIC did not include the term ART or Atraumatic Restorative Treatment. By not searching with the earlier MeSH either, and not including terms related to GIC, such trials seem unlikely to be retrieved.

Frencken searched PubMed and Medline, which are essentially accessing the same database. Mickenautsch searched in PubMed and the Cochrane Library, though it is not stated which of

the Cochrane databases were searched. Interestingly, these authors also searched Biomed Central, Directory of Open Access Journals and ScienceDirect. It is not conventional practice to search these and so I examined the consequence of searching them.

ScienceDirect (83) is a full-text scientific database of 2,500 journals and other publications from the Elsevier publishing company only (84). It can be searched without a subscription, though one is needed to access the full text of articles. Its sister service, Scopus, is a database of journal articles, trade journals, books, web pages and conference proceedings that include all Medline and OldMedline entries. It works in a similar way to Web of Knowledge and as such the service covers many more journal articles than ScienceDirect and includes the possibility of identifying grey literature through the database of conference abstracts (85). However, a subscription is necessary to search the database. Perhaps for this reason, Mickenautsch only searched ScienceDirect, using the term "Atraumatic Restorative Dentistry" (including the parentheses). When I did this on 15/04/2012 just 86 articles were retrieved. Repeating this simple search string in Scopus (to which I have institutional access) and limiting to title, abstract and keywords identified 270 documents. This included 258 articles in English, six in Portuguese, two each in Chinese, Spanish and Dutch, and one each in Croatian and German. The same string, "Atraumatic Restorative Treatment", in PubMed limiting to title or abstract resulted in 197 hits.

The Directory of Open Access Journals (86) is maintained by Lund Universities and listed 7622 open access journals on 15/04/2012. The search facility for articles here is very limited, providing two search boxes, which could be combined using AND, OR or NOT. Searching using the "Atraumatic Restorative Dentistry" string in one box identified just 6 articles.

Finally, Biomed Central is the portal for the open access publisher of the same name. Once registered, users can search using a sophisticated search facility rather than the simple search box facility on the homepage. Using the search string here resulted in 10 articles being

identified. BMC Oral Health, in which I would expect research articles on ART to be published, is indexed in PubMed (87) so I would expect these to be identified there.

Searching these three sources, I would suggest, probably helped little in widening the authors' access to relevant trials. In neither the Mickenautsch nor the Frencken reviews were attempts made to search the grey literature or the various databases for registered clinical trials or to contact subject specialists who may be able to point them towards other trials.

The Chinese review by Pettar *et al* searched a set of databases that one would expect to increase the chance of identification of all relevant trials. They included CENTRAL, Medline, Embase, three Chinese biomedical literature databases (Chinese Biomedical Literature Database – CBM, China National Knowledge Infrastructure Database – CNKI and VIP information / Chinese Scientific Journals database), WHO and Chinese clinical trial databases.

Of particular interest to me here were the Chinese databases as I had come across these in my original search, before I found the Chinese systematic review and was uncertain of their coverage and functionality. A paper by Jun Xia of the Cochrane Schizophrenia Group identified five large Chinese databases and compared them for access, journals indexed and cross-over with the Medline index (88). The three databases searched in the Pettar review were included in this paper, plus Chinese Medical Current Content database (CMCC) and the Wanfang Chinese Medicine Premier database.

I had used the CNKI and Wanfang databases because these were easy to search and gave abstracts in English of the retrieved papers. There is a difficulty in retrieving identified articles as a local credit card is required. However, when I came to do the systematic review, it was easy for a Chinese colleague to download the full articles for a small fee using a Chinese credit card.

The Xia paper found that all the databases except for CBM allowed open search and an abstract-viewing facility in English. All of the databases, though, produced significantly fewer hits when the author searched for 'schizophrenia' in English compared to when the simplified Chinese term was used. The Chinese authors of this review could potentially, therefore, have an advantage over non-Chinese speakers when searching these databases. This I have to bear in mind in interpreting my own search results from the Chinese databases as I only searched in English.

The Frencken and Mickenautsch reviews both restricted publications to English-only. Non-English trials made up 20% of 600 published trials included in a study of 159 meta-analyses (89). The range of non-English trials was between 4.3% and 72.7% depending on the systematic review and accounted for an average of 17.5% of the weight of the meta-analyses. Whilst overall the authors concluded that there was little effect on the outcome in the reviews they examined it is unclear for an individual review whether this would be the case.

An earlier study found that of 36 systematic reviews 28 had language restrictions that resulted in 19 eligible trials being excluded. One of the 36 reviews' conclusions would have been reversed had a non-English language paper been included (90).

A balance needs to be struck when doing a systematic review between minimising risk of language bias and the time and cost it can take to search, collate and translate non-English articles. Given that ART is known to be used in large, research-active countries such as China and Brazil, such a restriction on non-English publications could put a review at higher risk of missing potentially eligible trials. There is the potential in such a case for the review's conclusions to be over optimistic about the test intervention (91) as positive results are more likely to be published in English than negative results.

This analysis has shown that two of the three systematic reviews were not designed to be able to answer questions of efficacy relating to ART using a material other than GIC or a conventional treatment using a material other than amalgam. This is not a quality issue but a legitimate restriction on eligibility imposed by the authors, perhaps for practical reasons or to answer their own limited research question. The Pettar review would appear to have allowed for other combinations and, indeed, included a review that compared ART using composite with conventional treatment using amalgam. The reason why this is of significance is that the ART method includes adhesive materials of any kind, even if GIC has been the predominant material used. Also, whilst amalgam may be a regular material used in conventional treatment, it is not the only one. Thus for a review to be relevant to a clinician trying to decide between using conventional caries removal in combination with composite or ART caries removal in combination with composite he or she would seek a review that allows for this combination.

I have attempted to follow a rigorous methodology informed by those designed for systematic reviews including: framing a clear question; pre-specifying eligibility criteria; designing and following a protocol; conducting a systematic and exhaustive search; data extracting using custom forms; assessing included reviews for bias; and reporting in a transparent manner following applicable components of the PRISMA guideline. However, the limitations are that I did not publish my protocol and I recognise that whilst the AMSTAR tool can assist in assessing quality, a degree of judgement is required in using it. For example, one person may say that a search of PubMed, Embase and CENTRAL is a comprehensive search, whilst another insists that this is the case only if non-English databases are also searched.

To set this study in the context of quality of systematic review reporting more generally in dentistry, a review of the reporting quality and scope of 38 systematic reviews into topical fluoride efficacy found reporting quality in most reviews was well below accepted standards

and that the inclusion criteria of the reviews meant that some topical agents had not been considered (42). However, whilst methodological quality is not optimal, the quality has improved over time.

A study that assessed the methodological quality of systematic reviews into interventions for temperomandibular joint disorders (TMJD) used three quality assessment methods in appraising their retrieved studies and combined summary scores from these to arrive at a single quality score for each review (92). The authors also used the GRADE criteria to assess the quality of the included studies (93). The GRADE approach has been adopted by, amongst others, the Cochrane collaboration as a guide to the strength of recommendations that can be drawn from a study and has recently been described in relation to dentistry (94).

I have chosen not to use quality scores for reasons described above but attempts have been described to validate a scoring system for AMSTAR (95). I chose not to apply the GRADE criteria to this study. My reasoning was that if a systematic review was of high methodological quality then an assessment of the included trials would already have been conducted and reported. In order for me to use GRADE I would need to conduct the review of the primary research myself, which was not the objective of this study.

I am mindful that a single review may not accomplish a broad scope on its own. I am also aware that I have already limited this study by, for example, not allowing for the inclusion of alternatives to restoration in the management of dental cavities (e.g. no treatment or extraction), the combination of techniques to prepare a cavity (including so-called 'modified ART') or the ability to identify trials that compare ART using different materials (e.g. GIC versus RMGIC or composite). Once systematic reviews of the efficacy of ART compared to conventional treatment have been conducted that are more comprehensive these other comparisons should be attended to so that our understanding of ART becomes more whole.

At present, however, I conclude that the systematic reviews available to us are unable to allow an unbiased assessment of the effectiveness or otherwise of ART using any material compared to conventional restorative treatment using any material in the management of dental cavities.

Based on this conclusion I proceeded to conduct a systematic review of the use of ART in permanent teeth.

3. Two systematic reviews of ART compared to conventional treatment for the treatment of class I and class II cavities in permanent posterior teeth

3.1 Introduction to the systematic reviews

The systematic appraisal of current reviews discussed above identified a need for more comprehensive systematic reviews comparing ART to conventional treatment as all three published reviews had shortcomings in their methodology and the scope of the reviews were narrow.

Two systematic reviews were conducted independently but the methodology was the same with the exception of the inclusion of class I or class II cavities respectively. I have combined the two reviews here to prevent unnecessary duplication.

3.2 Protocol development

3.2.1 Reasoning behind the choice of population

Two systematic reviews were conducted. In each the population was any patient – adult or child – with a cavity in a permanent molar or premolar. Only the type of cavity differed – class I or class II. Class cavities are those that occur in the biting (occlusal) surface of the tooth only. Class II cavities involve the biting surface and one or other of the surfaces contacting the neighbouring tooth (proximal surface).

The reason for making the reviews homogenous from the outset was to avoid confusion when presenting the results relating to the particular class of cavity in a permanent tooth and to be pragmatic. I had anticipated identifying a number of relevant trials for both deciduous and permanent teeth and felt that it would be unworkable to conduct a review and meta-analysis including all of these.

In Frencken's systematic review only class I cavities in deciduous teeth are included. Although this review suffered from poor methodology it was clear what his conclusions related to.

In the Mickenautsch review class I, class II, class III and V cavities were eligible in both deciduous and permanent teeth. There were many more studies involving deciduous teeth than permanent and with so many cavity-types being considered the presentation of conclusions was complex. It was difficult, for example, to be clear what was being said in relation to ART in deciduous and permanent teeth, and it would be easy to imagine a strong conclusion, say, regarding ART in deciduous teeth to be interpreted as relating to permanent teeth too, even if evidence of this effect was not forthcoming.

The Cochrane systematic review protocol (63) casts a very wide net. It does not limit at all on the cavity types, teeth or material comparisons in included trials. In contrast, on the topic of replacing missing teeth with implants 11 separate Cochrane titles were published looking at different aspects of the intervention (96-106). The latter means that if one wishes to know about, say bone augmentation, it is clear which review to read. This approach may be more pragmatic too as it would be quicker for authors to complete the review and to update it. The ART review protocol was registered in October 2009 and personal contacts suggest that it is not near completion. Might this have been different if it had taken a narrower approach?

A benefit of a single review is that all the evidence relating to the topic can be kept together. However, a review of reviews (or "overview") could achieve this once individual reviews had been done. In some ways this offers the best of both worlds – accessible individual reviews on a narrow topic along with a summary of all the evidence relating to the broader topic in the overview. There are a growing number of such reviews (107-109).

3.2.2 Reasoning behind the choice of interventions

In designing the protocol it became clear that there were two different components to ART that could contribute to its effectiveness, or otherwise. The first is the way in which the caries

is removed. Whereas ART uses hand instruments only, "conventional treatment" uses a drill. At least in theory, the removal of caries by hand could result in less trauma to the pulp because the accidental removal of healthy dentine is less likely and the caries removal procedure probably generates less heat. Thus hand excavation could result in less pulpal death and tooth loss than mechanical caries removal.

However, there is also a difference in materials that could affect the outcome. ART requires that adhesive materials be used to restore the cavities. Minimal intervention dentistry and, in particular, approaches such as the step-wise technique, suggest that using an adhesive material could allow one to leave caries behind that then remineralises, or is removed at a later stage once the pulp has receded (110). Thus we could expect a cavity restored with GIC, say, to behave very differently from one restored with amalgam, which has no adhesive properties. On the flip side, amalgam is a strong material and has been used for over a century to restore teeth (111), whereas GIC is a softer material and may be more prone to mechanical failure.

Thus if one was to restrict the eligibility of trials to ART with GIC and conventional treatment with amalgam there are two variables – the caries-removal process and the restoration material – that could account for any difference in the outcomes. One could allow for one of two possibilities: studies using the same caries removal process (ART or conventional) but with different restorative materials (adhesive versus amalgam) or studies that use different caries removal methods (ART versus conventional) but restoration with one material only (i.e. an adhesive material or amalgam).

Because the caries-removal process is critical to defining ART as a minimum intervention technique, it was logical to allow for a comparison of the two different caries-removal methods. In order to allow for the inclusion of a study that could compare the caries-removal process alone, I allowed for conventional treatments to include restoration with any of the

adhesive materials that could be used in ART in addition to amalgam. Therefore, a study that compared hand-excavation to mechanical excavation and restoration with GIC in both cases would be eligible.

This logic could have been taken further if one were to pursue an experimental rather than pragmatic approach. The inclusion criteria could have been that the restorative material had to be the same but the caries removal should be different in any one study but when I scoped during the protocol design stage for ART trials none of them did this. All included amalgam in their conventional restoration group. I reluctantly concluded that to restrict the inclusion criteria to remove this heterogeneity would probably result in me excluding all studies.

In the discussion section of the systematic review I have drawn attention to this problem and suggested that in order to better understand the roles of the caries removal method and restorative material respectively future randomised control trials restrict the variables to one.

3.2.3 Reasoning behind the choice of outcomes

The primary outcome of interest in this review was failure of the restoration. If ART is to be a reasonable alternative to conventional treatment in permanent teeth then we need to understand what proportion of teeth restored with it are still functioning years after it has been placed.

A restoration could fail because it wears down so much or fractures so that it is no longer functional. One that has minor damage to it or minor wear such that function is not affected seems hardly to have failed in practical terms. Furthermore, there are several different indices for monitoring these more minor alterations to restorations over time (112, 113), none of which – as far as I have been able to ascertain – have been validated in terms of predicting failure of the restoration. For example, if a restoration scores a given mark on an index short of being non-functional the clinical implications of this are unclear. It is unclear if there is an increased probability that the restoration will fail.

A restoration may be classed a failure if it needs replacing for other reasons. The most likely of these in this context is the presence of caries around the restoration. One of the claims of glass-ionomers is that they are able to leach fluoride and so inhibit caries (114). Logically, then, we might expect amalgams to be relatively inferior in this regard. So caries around a restoration was also a reason for failure in this review. I do accept, however, that this clinical decision can be very subjective and that the decision to replace a restoration for this reason could be open to bias based on the material of the restoration used. It would be impossible to blind an assessor if the comparison materials were GIC and amalgam, but not if they were both GIC.

A tooth may develop signs and symptoms of irreversible pulpal damage, pulpal necrosis and sepsis following restoration (115). This could lead to extraction of the tooth or root-canal treatment. I decided to include these as reasons for restoration failure because, in theory, if the ART is less traumatic to the pulp then we would expect fewer teeth to need root canal treatment or extraction. These outcomes were classified as secondary rather than primary at the time of writing the protocol because I felt that my primary concern was how the GIC restorations performed. However, with hindsight I feel that it would be more logical to include root canal treatment or extraction as reasons to classify a restoration as failed because ART is, in theory, supposed to be less likely to cause pulpal damage.

Teeth that needed to be extracted for other reasons, such as orthodontics, would not be included here because the reason for extraction would not be expected to reflect the success or otherwise of the intervention.

3.3 Protocol submission

The protocols for each of the reviews were submitted to the PROSPERO database (116). The intention of this database is to increase the transparency of the systematic review process and to help avoid unplanned duplication of reviews.

Class II cavities:

http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42011001411

Class I cavities:

http://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42011001624

Despite conducting these reviews and submitting them for publication separately, because the methodology was the same for each, I present below an amalgamation of the two reviews.

3.4 Method

3.4.1 Criteria for considering studies for this review

Types of studies

Eligible studies were randomised controlled trials that compared ART using any adhesive material to conventional treatment using amalgam or any adhesive material. Trials could be parallel group (where each patient is randomised to one type of restoration), split mouth (where one of each restoration is randomised for placement in one of two teeth in the same patient) or cluster randomised trials (where each patient is in one intervention group, which is randomised to one or other intervention).

Quasi-randomised trials, where patients are allocated using non-random allocation methods (e.g. hospital number, alternation), were eligible for inclusion but would be subjected to sensitivity analysis owing to their higher risk of allocation bias.

Studies had to report the longevity of the restorations and follow up had to be at least 2 years. The decision over follow-up is to some degree arbitrary. For a restoration to last one year only seems hardly to make it permanent. We would certainly hope that permanent dental restorations last well beyond two years. A number of other systematic reviews in restorative dentistry have taken this as a minimum (117).

Types of participants

Trials had to involve adults or children with a class I or class II cavity in a permanent molar or premolar that requires restoration. The trials had to either concern this cavity type alone or include an identifiable subset that did.

Types of interventions

Experimental group:

This must include the removal of caries using hand instruments only. The chemo-mechanical removal of caries was not included because this would introduce an additional layer of heterogeneity, though I feel there is scope to do another review that compares so-called 'pure ART' to this modified version of ART in due course to establish whether there is a benefit to using chemical gels or liquids as adjuncts in the caries-removal process.

The cavities had to be restored with one of GIC, RMGIC, compomer or composite. These are all adhesive materials and would, therefore, conform to the original ART protocols.

Control group:

Caries had to be removed - in part or whole - by the use of mechanical means (i.e. a handpiece with a bur). This includes gaining access through enamel with subsequent caries removal using hand instruments. The cavity will be restored with one of GIC, RMGIC, compomer, composite or amalgam.

Types of outcome measures

Suitable outcome measures will include:

- for dichotomous data (e.g. failure or not of the restoration, loss or not of the tooth) the risk ratio or odds ratio, with confidence intervals

- For continuous data the standard mean difference with standard error. (At the time of writing the protocol I mistakenly included this. However, as I intended to dichotomise any continuous data there would be no need to use the standard mean difference.)
- for time to event data the hazard ratio with confidence intervals

Continuous data would have been dichotomised where possible when combining data. This would allow straight-forward synthesis of trial outcomes in the form of relative risks at fixed time points - 2, 3, 4, 5 and 10 years.

Primary outcome

The primary outcome was the failure of the restoration. This included: loss of filling and replaced filling (or filling needing to be replaced) due to significant material loss, tooth fracture or caries.

Secondary outcomes

Outcomes that are not long term outcomes (e.g. they occurred during or shortly after treatment) would be reported but not synthesized. These include:

- Extracted teeth
- Irreversible pulpal damage (e.g. signs and symptoms of irreversible pulpitis, abscess, catastrophic tooth fracture)
- Post-operative pain and sensitivity
- Cost-effectiveness of treatment
- Time needed to complete treatment
- Adverse effects

I chose not to include other short term outcomes. This is because the review was to consider only studies that have a minimum follow up of two years. As such I would exclude short term trials that may have considered such outcomes as anxiety, patient comfort and clinician satisfaction. Short follow-up would have been reasonable in these cases and though this information is of relevance to the use and acceptability of ART, if I collected this data only from studies lasting longer than 2 years then this would not be comprehensive and, I believe, it would, therefore, be at risk of introducing a publication bias. The best way to deal with this would be to conduct a separate systematic review to look at these outcomes in which there is no follow-up restriction.

3.4.2 Search methods for identification of studies

I attempted to identify all relevant studies regardless of language or publication status (published, unpublished, in press, and in progress).

Electronic searches

The following databases and trials registers were searched:

- OVID Medline, OVID Embase and the Cochrane Central Register of Controlled Trials (CENTRAL)
- Regional bibliographic databases LILAC, BBO, CNK (Chinese), CAOD (Chinese), IMEAR (WHO Index Medicus for South East Region), WPRIM (WHO Western Pacific Region Index Medicus) and IndMed.
- Current Controlled Trials (http://www.controlled-trials.com/) and Clinical Trials (http://clinicaltrials.gov/) to identify on-going trials that may have unpublished data
- Google Scholar and OpenSIGLE (http://opensigle.inist.fr/ up to 2005) to identify related grey literature

- IADR conference abstracts 2001-2011 (http://iadr.confex.com/iadr/search.epl) and NLM Gateway (http://gateway.nlm.nih.gov/gw/Cmd) for conference abstracts

The search strategies for the Medline, Embase and CENTRAL searches include both keywords and MeSH terms as described earlier (full search in appendix 1).

Searching other resources

Hand searching

A methodology review reported in the Cochrane Library found that hand searching identified 92-100% of randomised controlled trials in 34 studies (82). When electronic searches were combined (e.g. Medline, Embase and Psych Info) a maximum of 80% of trials were identified using a highly-sensitive search strategy, dropping to 42% when a simple search strategy was used. Thus hand searching is still a necessary component of a comprehensive search.

I identified the journals below to hand search. These were journals in which ART studies of one sort or another had been reported previously or could be expected to publish articles on ART given their scope.

ART was developed in the mid-1980s. I therefore searched from 1985 onwards. However, a number of years for these have already been searched by the Cochrane Oral Health Group – OHG – (years covered are in square brackets – available at http://us.cochrane.org/master-list) and so clinical trials from these years should be included in the CENTRAL database search. As a consequence I only searched years not already covered by the OHG.

- International Dental Journal [OHG 1970-2001 complete, 2002-3 incomplete]
- Journal of Dental Research [OHG 1980-7, 1990-8, 2001-3 complete, remainder incomplete]
- Journal of Dentistry [OHG 1970-2001 complete, 2002-3 incomplete]

- Caries Research [OHG 1967-2003]
- Community Dentistry & Oral Epidemiology [OHG 1971-2001 complete, 2002-3 incomplete]
- Journal of Clinical Pediatric Dentistry [OHG 1996-2003 complete]

Reference lists

I examined the reference lists of relevant trials, reviews and articles in an attempt to identify any other studies or those not identified in previous searches.

Correspondence

I attempted to contact a number of authors who had written on ART via email (see appendix 2). I received replies from Jo Frencken, Steffan Mickenautsch, Roger Smales and Martin Tyas. (None were able to identify additional trials to those I had already identified through the electronic search.)

3.4. 3 Data collection and analysis

Selection of studies

1. Reports retrieved from the various searches were merged in Endnote and duplicates removed using automated and manual means.
2. The articles left were screened by me and a colleague for reports that could possibly be related to ART.
3. A subsequent screening was conducted of these for clinical trials that could potential meet my inclusion criteria using the titles and abstracts.
4. Full copies of these reports were obtained and, using the predefined eligibility criteria and a custom sheet (see appendix 4), my colleague and I looked for studies that

should be included for data extraction and further analysis. Where there was disagreement this was resolved through discussion.

I created a flow diagram to assist the other review team members in understanding what was required at each stage. This is reproduced below. I could have avoided this step if I had used search filters (see discussion in 'results').

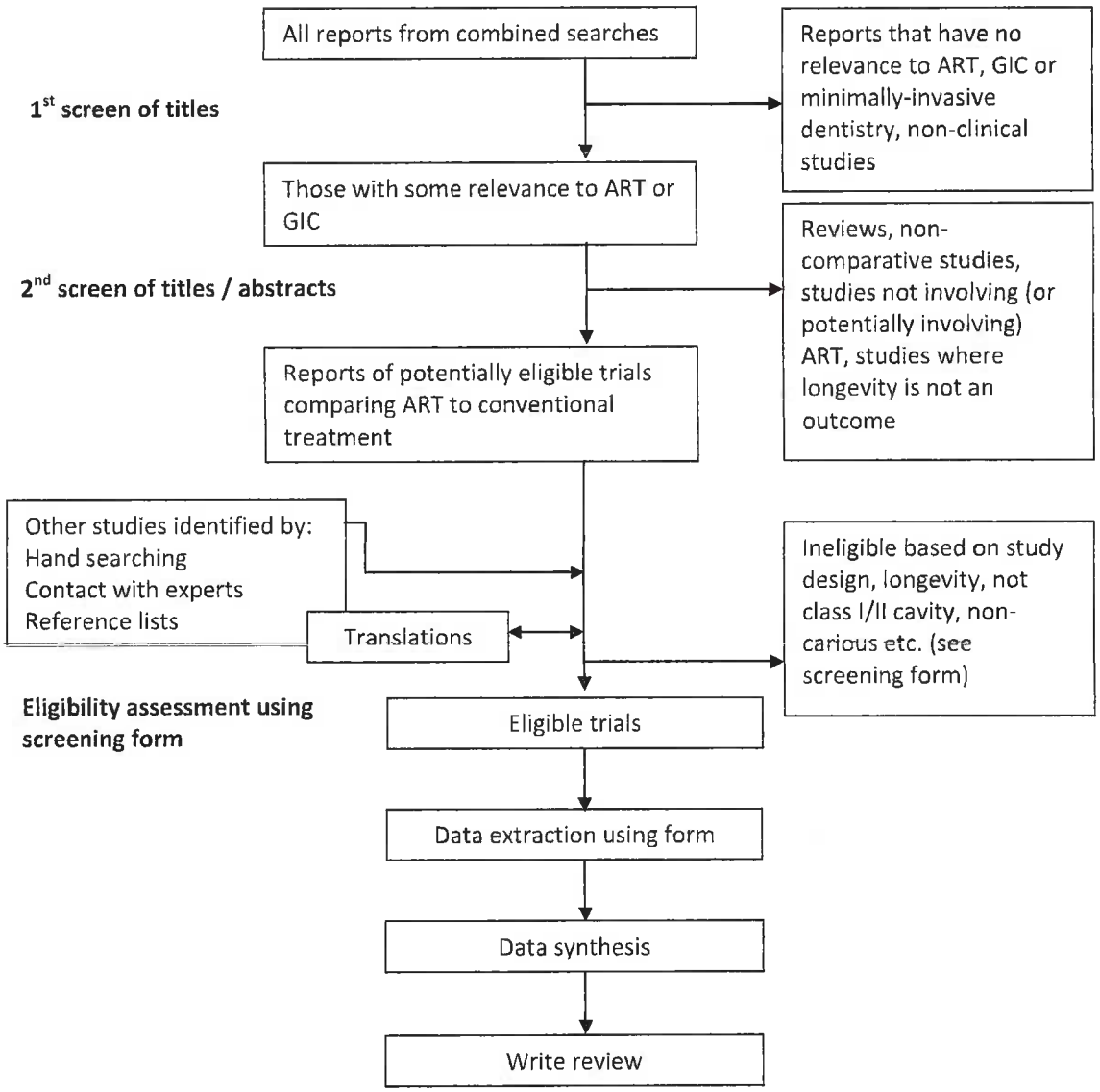

Figure 1 Flow diagram of review process

Data extraction and management

Data from eligible trials was to be extracted using a data extraction form designed by myself (Appendix 5). The form was created using various resources including a sample data extraction form from the Cochrane Cystic Fibrosis and Genetic Disorders Group (118), another from the Services Group of the HIV Group on HIV Infection/AIDS (119) and the Cochrane Handbook

(120). This was to be piloted with an eligible trial to check it was clear and collected the right information.

I tried to contact two trial authors for clarification of methodology in their respective trials – Kalf-Scholte (67) and Frencken(74). Frencken replied with answers that were critical to the exclusion of his trial from the review. Kalf-Scholte did not reply.

I was fortunate that in our department there were speakers of multiple languages, though in the end there were only Chinese papers that required translation. This was conducted by a Chinese Masters student (Xiaoli Cheng) on my behalf.

Studies with duplicate publications were to be treated as a single source of data as systematic reviews are of trials not of reports of trials.

Data extractors were not to be blinded to the names of the authors, institutions, journal of publication or results of the studies. A methodology review comparing blinded to un-blinded assessment of the risk of bias within studies did not find clear evidence that un-blinding resulted in a different result from blinding (121).

Items that were to be extracted were:

- Study 1st author and year of publication
- The reference for the article
- The language it was written in
- Contact details for the relevant author
- Study design:
    - Randomised controlled trial (RCT) or Quasi-RCT

- Parallel, split mouth or cluster randomisation design

- Risk of Bias assessment
  - Sequence generation method
  - Blinding
  - Outcome data
  - Allocation concealment
  - Other concerns regarding bias
  - Overall risk of bias

- Participants
  - Total participants in the study
  - Total with class I and II cavities (respectively) in permanent teeth
  - Diagnostic criteria used by study authors for caries
  - Mean age and standard deviation (SD)
  - Per cent that were male
  - Per cent that were female
  - Country(ies) in which study was conducted
  - Sociodemographic details
  - The clinician type (dentist, other dental care professional (DCP), dentist or DCP student, other healthcare worker)

- Average Decayed Missing of Filled Teeth (DMFT) score

- Interventions
  - ART:
    - material used – High, Medium or Low density GIC, Resin-modified GIC, Compomer, Carbomer, or composite
    - Whether local anaesthetic (LA) was used (I realised after designing the protocol, however, that this was redundant as I was not collecting short term patient outcomes such as pain or anxiety)
  - Conventional
    - Material used – amalgam, High, Medium or Low density GIC, RMGIC, Compomer, Carbomer, or composite
    - Whether LA was used

- Outcomes
  - Time point:
    - When data was collected
    - Whether this time point was the same as that pre-specified in the protocol
    - Whether the protocol time points are reported
  - Definition of outcome with criteria (e.g. failure of restoration: criteria = anything that meant dentist felt need to replace)
  - Unit of measurement (e.g. failed / not failed)

- If a scale was used, then the upper and lower limits of this should be recorded

- Results
  - For dichotomous data
    - Data was to be entered into a 2 x 2 table (e.g. failure +/- as rows, ART / conventional as columns)
  - Continuous and ordinal data
    - Mean and standard deviation for ART and conventional treatment were to be entered into a table, and the total number of participants for each entered.
    - I did not expect that data would be presented in this way for the primary outcome, but may have been for some of the secondary outcomes.

- Miscellaneous
  - Funding sources
    - A systematic review of methodological studies looking at the effect of funding source on reporting of adverse effects concluded there may be little threat of bias from industry funding in the reporting but that industry sponsorship may make authors more inclined to interpret and conclude a drug is safe even when there is a statistically-significant increase in adverse events associated with the test drug (122). A review of gastro-intestinal trials found no apparent bias in the industry-funded trials compared to non-industry-funded but did find

the former were of a higher methodological quality (123). However, the CONSORT statement (124) requires that trials report on funding sources. This is because another systematic review found the odds of reporting a favourable outcome for the test drug in pharmaceutical trials was 4 times greater in industry-sponsored trials than non-industry-sponsored trials (125). So as to be able to interpret the results of included trials in the light of their funding source, I planned to collect this data.

- Key conclusions of study authors
- Miscellaneous comments from study authors
- References to other relevant studies for follow-up
- Miscellaneous comments by review authors

Individual patient data were not to be used.

3.4.4 Assessment of risk of bias in included studies

Bias is a systematic error that means the results of a study deviate from the true result and would do so each time the study was repeated. This is different from a random error, which is usually due to sampling issues and occurs more in small studies where it is reflected in wide confidence intervals (45).

Bias means that should the study be repeated the error would always be in the same direction – either over or underestimating the true effect of the intervention. Indeed, if different studies all have the same bias, this would result in the same effect. Where there is random error the results of multiple studies would be in both directions and thus the mean may actually be close to the truth.

Since it is impossible to know whether a given study does in fact have a bias it is usual to discuss the risk of bias instead. The evidence for bias from various aspects of study design has been established using meta-epidemiology. This takes a number of meta-analyses and breaks them down to the characteristic(s) of interest to see how these affect the outcome by comparing the odds ratios of treatment effects.

An early study of this type was conducted to examine the influence of allocation concealment, exclusions after randomisation and lack of double-blinding on the summary measures in a series of meta-analyses from the Cochrane Pregnancy and Childbirth Database (126). Where allocation concealment was judged to be inadequate the odds ratios for the treatment effects were 41% greater than in adequately concealed studies and 31% higher where it was unclear what the allocation concealment was. Exclusion after randomisation (see attrition below) was found to have little effect but the lack of double-blinding resulted in a 17% increase in the odds ratios of treatment effects to those where double-blinding was adequate. The bias that may result from lack of blinding of participants and clinical personnel is known as a performance bias. Where the assessor of the outcome is un-blinded this is thought to increase the risk of so-called detection bias.

In contrast to the study quoted above, a more recent study found that whilst allocation concealment was important in trials with subjective outcomes, there seemed to be little effect from the lack of allocation concealment or blinding where the outcome was objective (127). In the present systematic review, the failure of a restoration due to its loss, or to the loss of the tooth, would seem to be fairly objective. Where one uses more subjective criteria such as the decision that caries is present or not, or an index of the quality of the restoration, one would expect there to be a greater risk of bias. It is often the case in restorative dentistry, as probably in other surgical disciplines, that the allocation cannot be concealed, nor a blind

assessment made of the outcome. So long as we try to keep the outcome as objective as possible the risk of this causing bias should be insignificant.

Selection bias – or the way in which participants are allocated to one intervention or another – can result from inadequate randomisation. This has been demonstrated in a systematic review of studies comparing the treatment effects of randomised versus non-randomised trials (128). It was found that on average non-randomisation over-estimated the effect of the test intervention, though in some cases it under-estimated the effect. Unfortunately this review was unable to quantify what the range in over and underestimate was.

A baseline imbalance resulting in a selection bias would be unlikely in a large and properly randomised trial, but a small study or one in which participants were in fact withdrawn after randomisation (though perhaps not reported as such) could result in such imbalance. In the context of trials involving ART I would be particularly concerned about baseline differences in caries experience often recorded as Decayed Missing of Filled Teeth / Surfaces (dmft/s for deciduous teeth or DMFT/S for permanent teeth) as a higher dmft/DMFT in one of the groups would be expected to result in a higher failure rate due to recurrent caries.

Attrition and exclusions in trials result in missing data for the primary outcome. Data can be missing because a participant withdraws from the trial, refuses to be examined, is excluded by the researchers or is lost to follow-up. Data could also be missing because it has been lost or not recorded correctly in the first place. The concern is that the missing data may not be random but in some way associated with one or other of the interventions. The baseline characteristics of the subgroup within each of the trial arms, therefore, changes. For example, patients in one intervention group may experience greater side-effects than those in the other and, therefore, withdraw from the trial. If this is not reported and not taken into account when calculating the relative outcomes of the two interventions, a bias could be introduced, though empirical studies have not demonstrated this (126, 129)

Loss of outcome data can make intention-to-treat analysis impossible without some form of imputation. Intention-to-treat analysis (ITT) has been advocated as a means to preserve the reduction in risk of bias that randomisation produces. ITT says that the results of the different arms of the trial should be analysed as per the original random allocation regardless of whether that intervention was what they received (130). For ITT to work properly all participants should be followed-up to the end. In reality this is unlikely, particularly where studies are large, for the reasons described above. The inevitable loss of data means that assumptions are made in calculating the ITT outcomes and, whilst this is accepted, the assumptions should always be stated (131).

Publication bias is a well-recognised problem resulting in a systematic over-representation of significant or positive results at the expense of those reporting a non-significant or negative result. Publication bias is also known as between-study selective reporting bias i.e. a paper is published or not because of its results. However, a related bias is that of within-study selective outcome reporting. This is when the reported outcomes for a published study are chosen based on the results (132). Three types of selective outcome reporting were described in a recent paper (133): selective reporting of only a subset of the outcomes collected; selective reporting of a given outcome e.g. at specific time points but not all; and incomplete reporting of a given outcome e.g. by reporting the mean but not the standard error. There is the potential also for being selective in reporting the outcomes for certain subgroups within the participant population too (134). I identified this in one of the largest ART trials conducted and deal with it in more detail in the discussion.

Between 40 and 62% of studies were found to have at least one primary outcome changed, introduced or omitted suggesting that selective outcome reporting is common and outcomes that were statistically significant had higher odds of being fully reported (132). Some degree of outcome reporting bias was suspected in at least one trial in a third of Cochrane reviews

analysed (133). 19% of the reviews with significant effects became non-significant after taking into account the selective reporting bias and 26% had overestimated the treatment effect by 20% or more. The consequence for systematic reviews of ignoring this source of bias is that the validity of the meta-analysis is open to question and even where meta-analysis is not conducted the conclusions of a systematic review may be compromised.

The risk of outcome reporting bias can be assessed by comparing protocol versions of the trial with the reported version(s) to identify those outcomes that should have been collected and reported but which were not. The methods section should also give an indication of the outcomes planned for collection, though this may in itself be doctored already by the time the authors write the report. Finally, authors may be conducted to identify data that was collected but not reported. As I will report later, I did this for one trial where data had not been reported for a particular class of cavity, though the data sent to me was poor.

Where data is missing sensitivity analysis has been proposed as a method of testing the robustness of the summary statistic (134). If I had been in a position to do this I would have engaged a statistician due to the complexity of doing this.

The Cochrane risk of bias tool includes a catch-all section for 'Other sources of bias'. These include: design specific risks such as those incurred in non-randomised trials, cross-over trials and cluster randomisation; blocked randomisation of a fixed size in un-blinded trials leading to interventions being predictable; and differential diagnostic activity whereby one arm of the trial is more likely to have more tests that detect unwanted effects not detected in the other group.

Selection, performance, detection, attrition, reporting and other biases would be assessed using the Cochrane 'risk of bias' tool. This involves making a judgement of 'yes / no / unclear' for each of 6 questions:

- Was sequence generation adequate?
- Was allocation concealment adequate?
- Was blinding of personnel and patients adequate?
    - I did not anticipate this being possible in most studies due to the use of mechanical means of caries removal being so different in feeling from the hand removal, and of the difference in colour of amalgam and the adhesive materials.
- Was blinding of the assessor(s) adequate?
    - As above but where the same material is used the assessor could be blinded.
- Was incomplete outcome data dealt with adequately?
- Was selective outcome reporting dealt with adequately?
- Was the trial free of other sources of bias?

The data would be summarised in a 'risk of bias' summary figure. An example of such a figure taken from a Cochrane review (135) is shown below.

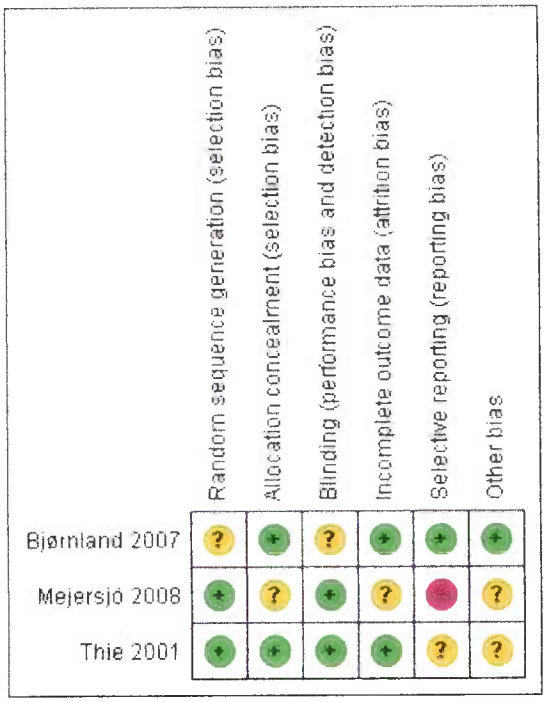

Figure 2 Example of risk of bias summary

Visual figures such as these allow a very quick judgement to be made about the risk of bias in the included studies. The decision about whether to include a green plus, yellow question mark or a red minus lies with the authors.

3.4.5 Measures of treatment effect

The effect measure of choice for dichotomous data would be risk ratio (RR) plus 95% confidence interval. I did not anticipate using continuous data as the primary outcome was failure / success.

The risk ratio (or relative risk) is the ratio of the risk of the event in the intervention group to the risk of the event in the control group. An alternative relative statistic for dichotomous data would be the odds ratio – the ratio of the odds of an event in the intervention group to the odds of the event in the control group. However, it is argued that since odds is a concept less well comprehended by clinicians than risk it would not be a useful way of communicating the

summary of the effect of the intervention to them (136, 137). Relative risk can, in a straightforward manner, be combined with local prevalence rates to give an indication of the *clinical* significance of the difference in outcomes (i.e. absolute risk reduction) between interventions in that group of patients.

Relative statistics allow for the effect of an intervention to be estimated in populations with different control event rates as it is relatively constant even at different control event rates (138). Trials could report on the *absolute* difference in event rate in their population and, whilst this is useful in getting a sense of the magnitude of the effect, it cannot be easily transferred to a population with a larger or smaller control event rate. The risk difference or absolute risk reduction is thus the risk of the event in the intervention minus the risk of the event in the control group. Whilst this complimentary information should be expressed in reports of trials, it would probably be unsuitable to combine in a meta-analysis.

Where odds ratio is reported this can be converted to the risk ratio using the formula:

$$RR = \frac{OR}{1 - Pc\,(1 - OR)}$$

where *Pc* is the typical event rate with the control.

Where the risk ratio is not provided it can be calculated from a 2x2 table of event frequencies (139):

	ART	Conventional	
Success	A	B	a+b
Failure	C	D	c+d
Total	a+c	b+d	*n*=a+b+c+d

$$RR = \frac{a/a+c}{b/b+d}$$

3.4.6 Unit of analysis issues

In parallel group studies the unit of analysis was to be the patient. In split mouth studies, it was to be the tooth. For cluster randomised trials the unit of analysis was to be the group, which could mean a school or a village, for example.

3.4.7 Dealing with missing data

Where data was missing I attempted to contact the authors. If I had identified more eligible trials and there was missing data that I could not get from the authors I would have conducted sensitivity analysis to see the effect on the meta-analysis conclusion using three scenarios: 1) assume the worst case and that all missing data are due to failure of the restoration 2) assume the best case and that all missing data are intact restorations 3) assume that proportionally the same number of restorations failed / survived as in the non-missing data.

3.4.7 Assessment of heterogeneity

Differences in trial outcomes can be due to different sources of heterogeneity: clinical heterogeneity (where the participants or the interventions they receive are different); methodological heterogeneity (due to differences in the design of the trials e.g. in outcome measures or times); and statistical heterogeneity (when there really is a difference in the way different populations respond to an intervention) (140).

By conducting the reviews as I did I was hoping to limit the clinical heterogeneity. That is, the tooth types and the class of the restorations (both of which I believed to affect the longevity of dental restorations) were restricted to permanent teeth and then for one review class I cavities and the other class II cavities.

Other potential clinical heterogeneity might have arisen out of the age of patients since older patients would be more prone to periodontal disease that results in the exposure of soft and

less caries-resistant root dentine. Thus recurrent caries might be more likely in these patients and so, if there really was to be an anticariogenic component to the ART procedure, the results might have been affected by this potential increased risk of caries.

Another potential and very significant source of clinical heterogeneity was the material used in the intervention. Not only are there different brands and formulations of GIC but if some studies were to compare, say, ART with GIC to conventional treatment with amalgam and others ART with composite to conventional treatment with composite, this would be likely to introduce more heterogeneity.

Methodological heterogeneity could have arisen due to different follow-up times, different measures of success and failure, different study designs (split mouth versus parallel group versus cluster), and various study features that contribute to the quality of the study e.g. means of allocation (pseudo- versus true randomisation) and completeness of follow up.

The Forrest Plot of included trials can give a visual indication of statistical heterogeneity by demonstrating the degree of overlap of confidence intervals. Where overlap is not present, heterogeneity is greater than where overlap is significant (141).

Statistical heterogeneity would have been assessed formally using the Chi^2 test using P=0.10 as the upper limit for statistical heterogeneity due to the lower power of these tests (142). The Chi^2 test quantifies the difference between actual and expected frequency counts of categorical data in two or more studies (139). The expected frequency is that there is no difference between the study results. This is the null hypothesis and in this case the result of the Chi^2 test would be χ^2 value=0 (χ^2 value is the value of the Chi^2 test). In theory the χ^2 value could run to infinity but the actual size of the χ^2 value is of less importance than the p value associated with it. If the p value is below a level of significance then the test is taken to demonstrate heterogeneity.

The test is dependent on the number of studies included in the review (143). Therefore, it would be unlikely to detect heterogeneity in a review with few studies but in a review with many studies would be likely to detect heterogeneity even where the clinical difference between the trials is insignificant (143, 144). Another feature of the Chi^2 test is that it can at best only indicate whether heterogeneity exists or not, not how great that heterogeneity might be.

The Cochrane Q test is based on the Chi^2 test and appears to be afflicted by the same problems as the Chi^2 test itself when testing for heterogeneity including only being suitable where the reported outcomes are the same (e.g. categorical data) (145). The I^2 test was developed in response to overcome the problem of the number of studies included in the review and to allow comparison of meta-analyses with different outcome measures such as categorical and continuous data (145). This should allow for a quantification of the degree of heterogeneity (or inconsistency) between studies and in my protocol I followed convention in describing these values:

- 0-40% - inconsistency might not be important
- 30-60% - may represent moderate heterogeneity
- 50-90% - may represent substantial heterogeneity
- 75-100% - considerable heterogeneity.

However, there are concerns that this test may itself be a weak one and may also have low statistical power with small samples (146).

As with other metrics the I^2 test carries with it uncertainty (147). This can be calculated and expressed as confidence intervals around the point estimate of heterogeneity. In a study of 1011 Cochrane meta-analyses Ionnadis *et al* found that where the reported I^2 estimate was

less than 25% (so would be judged to be low heterogeneity) the upper 95% confidence interval crossed 50% (substantial heterogeneity) in 83% of the reviews (147). Of those meta-analyses with I^2 greater than 50%, two thirds had a lower 95% confidence interval below 25%. There were 373 Cochrane reviews that reported an I^2 estimate of 0% and therefore judged the included studies to have no heterogeneity. However, in all of these the upper 95% confidence interval was greater than 33%, and in 81% of them the upper limit was greater than 50%. These authors called for confidence intervals to be reported with I^2 estimates to give a sense of the uncertainty around the heterogeneity estimate.

It was unlikely that I would have identified more than a handful of trials at best in this review. Due to the small number I doubt now if there would be any benefit in conducting the I^2 test or the Chi^2 test given the abovementioned issues relating to them.

3.4.8 Assessment of reporting biases

A funnel plot will be used to assess the risk of publication bias on included trials. The plot is a scatter plot of the effect size of the study on the horizontal axis and the standard error of the intervention effect (a measure of the size of the study) on the vertical axis. Asymmetry of the plot, particularly the absence of smaller studies on one side of the plot or the other would suggest publication bias.

3.4.9 Data synthesis

In my protocol I wrote: "Where statistical heterogeneity is low, the summary results from the studies will be combined using the fixed-effects method. Where there is moderate heterogeneity it will be combined with the random-effects method. Where the Chi^2 and I^2 tests suggest moderate to high heterogeneity, or where the studies are considered too clinically or methodologically heterogeneous, the results will not be combined."

In view of what I have learnt about the uncertainty around the heterogeneity estimate, I think now that if the trials were sufficiently clinically and methodological homogenous I would

probably combine the results using the random-effects method because I would assume that there was a reasonable degree of statistical heterogeneity. The random effects model assumes that there is a true mean effect of the intervention and it is around this true mean that individual studies' effects vary. Because it assumes greater variance to exist between studies than the fixed-effects model the standard error of the estimate is greater. This means that there is less likely to be statistical significance between the interventions than if the fixed-effects method was used.

3.4.10 Subgroup analysis and investigation of heterogeneity

If a much larger number of studies were identified and if there were several trials comparing similar interventions (e.g. all using GIC in ART and amalgam in conventional treatment and all true randomised controlled trials) it may have been plausible to conduct subgroup analyses based on an assumption of low heterogeneity and thus conducted the analysis using the fixed-effects method. However, it was not anticipated that a sufficient number of trials would be identified to be able to do this.

3.4.11 Sensitivity analysis

Sensitivity analysis was to be conducted where:

- different materials were used for either of the interventions
- randomisation and quasi-randomisation have been used in different studies
- different clinical operators have been used between studies
- where baseline measures of caries experience were very high or very low
- studies were judged to be at moderate or high risk of bias

Sensitivity analysis allows us to test the assumptions that underlie the analysis in order to see how robust the outcome is. There are many different ways of conducting sensitivity analysis

and depends on the initial analysis. For the purposes of this review I planned sensitivity analysis that would compare the meta-analytic results of the studies combined with the results after removing studies identified above one by one. This would allow us to assess the effect that each trial has on the combined treatment effect.

The corresponding assumptions tested would therefore be:

- that different materials used in ART or conventional treatment have no effect on the outcome
- that quasi-randomisation has no effect compared to true randomisation on the outcome
- that different clinical operators (dentists versus therapists versus other healthcare professionals) are equally effective
- that baseline caries has no effect on the outcome
- that trials at moderate or high risk of bias do not affect the outcome

In a systematic review into the effectiveness of guided tissue regeneration sensitivity analysis was used to assess the effect of removing trials with maintenance visits occurring less than 3 monthly. This was because the authors felt it was unlikely this frequency of maintenance would occur in practice and so wanted to see if the results held up under the more realistic scenario of maintenance visits occurring less frequently. They also conducted sensitivity analysis by excluding poorer quality studies (148) as did a review into the regenerative effect of Emdogain(149).

I discussed the intention to treat principle earlier in the dissertation. Whilst it would be ideal if all trials reported their results in this way it seemed probable that this would not be the case. Participants may not be included in the analysis because they were not treated as per their initial allocation or because they were lost to follow up. Egger recommends that one use

sensitivity analysis to test three different assumptions in this case: a worst case scenario, best case scenario and most likely case scenario for each trial that does not report all its outcome data (150). Thus if we assumed an intervention group with a large drop-out rate were all treatment failures then we would test the result of this conclusion against the assumption that all were successful and the third assumption that the failure rate was similar to that of the outcomes reported for the rest of the participants in that group.

3.4.12 Reporting

The review was to be reported as per the PRISMA guidelines. The PRISMA checklist is included and a flow diagram shows the number of reports identified and the reasons for exclusion.

3.5 Results

15,929 reports were identified and after removal of duplicates this reduced to 9,169. At this stage of the review process I had thought, mistakenly, that the use of a filter for randomised controlled trials would be detrimental to the retrieval of trials despite their suggested use in the Cochrane Handbook. Perhaps this was due to having read that one such filter had only 87% sensitivity (151). As a consequence one colleague and I screened the entire 9,169 trials at great waste of time and resource. I later discovered that in a comparison of 38 filters a number were in fact 99% sensitive (152). This made me realise that in future the small sacrifice of sensitivity was worth the gain in time.

After the 1st screening that was based mainly on the title, there remained 1,138 reports. A subsequent screening using the titles and abstracts reduced the number to 99. A third screening still using the titles and abstracts excluded 87 of these as it was clear they did not meet one or more of the inclusion criteria. With hindsight this third screening could have been avoided if we had been more exclusive in the second screening.

The remaining 12 required assessment of the full text in order to decide whether to include or not.

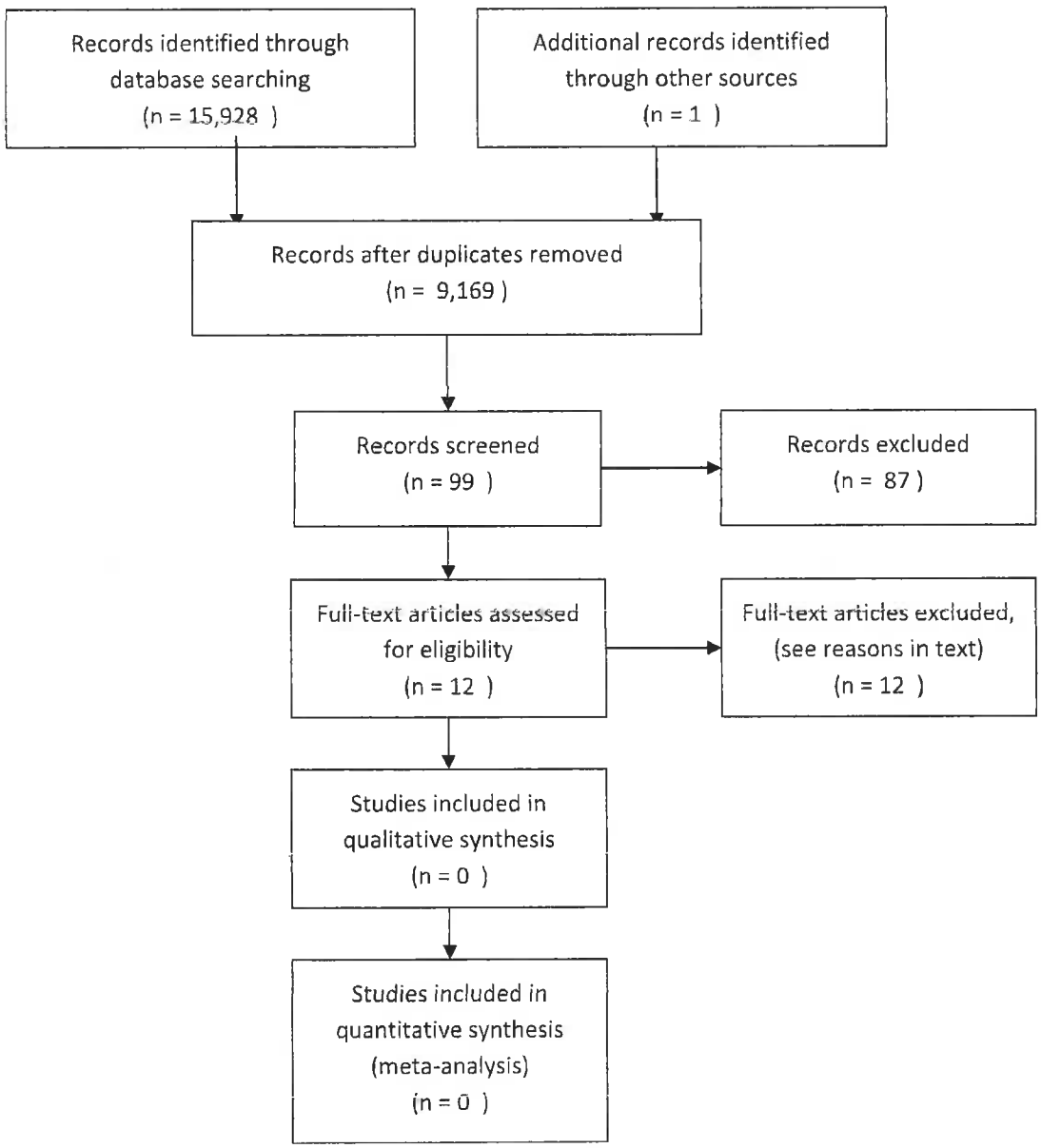

Figure 3 Flow diagram of review

The reasons for exclusion of these trials are summarised below.

Study	Reason for exclusion
Chen, Bao-xing 2006(153) (translated from Chinese)	Not reported as an RCT; unclear whether permanent, deciduous or both
Ling, L 2003(154) (translated from Chinese)	Primary teeth
Mandari 2003 (155)	'Modified' ART and therefore not 'true' ART
Phantumvanit 1996 (64)	Not a randomised controlled trial – villages assigned to either ART or conventional but not a randomised cluster trial
Yip 2002 (156)	12 months' duration
Huang 2009 (157)(translated from Chinese)	Unable to identify either tooth or cavity type
Smith 1990(158)	Not ART
Kalf-Scholte 2003(67)	Not randomised to ART or conventional; randomisation to one or other GIC used for the ART arm
Li, Hui-min 2005 (159)	Both arms had caries removed by hand instruments i.e. ART caries removal but with restoration using GIC or amalgam
Taifour 2003 (68) Frencken 2006 (74) Frencken 2007 (21)	All reports on the same study. Not a randomised controlled trial as 8.7% of participants allocated to ART *without* randomisation or quasi-randomisation

Table 4 Reasons for excluding studies

The Mandari study was excluded because the ART arm used a caries-removal solution called Caridex. This rendered it ineligible for this review. It actually had 3 different caries-removal arms each of which was then divided into restoration with amalgam or GIC. Participants were children with at least 2 permanent molars with a class I cavity requiring restoration. They were randomised to one of the caries-removal methods: conventional in a clinic, 'modified' conventional using a battery-operated drill in the field, and 'modified' ART in the field.

Permuted blocks were used to randomise the participants to the caries-removal group and the material to be used in each cavity was allocated based on the flip of a coin.

If I had included modified ART as a means to remove caries, this trial could have been eligible as it followed up the participants for 6 years and there was a conventional caries removal

comparison arm. However, there would have been some difficulty over the material used because although this was apparently split mouth there could be more than two cavities treated in any individual participant and, therefore, the number of GIC and amalgam restorations placed in an individual could be uneven. The number of GICs or amalgams placed for each cavity preparation type was not reported.

The Phantumvanit 1996 (64) study, conducted in Thailand, was excluded because it compared the use of ART in the population of one village to conventional treatment in the population of another village. This trial was included in the systematic review conducted by Frencken that I reviewed initially (60). The Mickenautsch 2010 review did exclude it because the participants were not randomised (61).

The Kalf-Scholte trial was a three-year comparison of ART to conventional treatment in Malawi. 14 – 20 year-old students were recruited and I assume, therefore, that all the molars treated were permanent. This should be the case because deciduous molars have normally exfoliated by this stage but deciduous molars can be retained into adulthood. It is perhaps a pedantic point but it would have been useful if they had clarified it was permanent teeth that were eligible.

More of a problem – and the reason for excluding this trial from the review – was that they used a split-mouth design but do not appear to have randomised which tooth of the pair received ART and which conventional treatment. Instead they randomised (it is not stated how) students into two groups: "The pairs of class I cavities were divided randomly into two groups, since two different GIC filling materials were used." Thus it would appear that only the ART restorative material used in each participant was randomised.

I sent an email to Dr Kalf-Scholte checking that it was in fact the case that the teeth had not been randomised to ART and conventional treatment, but received no reply. It is a shame that randomisation was not done as 89 pairs of teeth were involved in the trial.

The Li trial from China recruited 204 participants ranging from 60 to 78 years of age. In total there were 119 class I cavities and 167 class II cavities. It has been unusual to find studies with class II cavities in permanent teeth. Unfortunately for the purposes of this review, though, the caries removal process was atraumatic in both arms, with the material – GIC or amalgam – being randomised and so I had to exclude it. However, I think it is actually much more experimentally sound in that there is only one variable – the restoration material. Teeth were evaluated after 2 years and whilst they found no statistical difference between the number of 'successful' class I restorations, amalgam was retained in 46 of 78 class II cavities compared to 35 of 72 in the GIC group. This was statistically significant at $p<0.01$.

The relative risk, absolute risk reduction and number needed to treat can be calculated for the amalgam group:

	Failure	Success	Total
Amalgam	32	46	78
GIC	37	35	72
Total	69	81	150

Risk (of failure) for amalgam is 32/78=0.41

Risk (of failure) for GIC is 37/72=0.51

The relative risk (of failure with amalgam) is 0.41/0.51=0.80

The absolute risk reduction is 0.51-0.41=0.10 which means the number needed to treat with amalgam instead of GIC to prevent one failure is 1/0.10 =10.

I have explored this here to get a sense of the size of the impact of the material on the outcome rather than the caries removal process, as it was the latter that I chose for this review. Another review concentrating on the material used with the ART caries removal could result in some interesting conclusions if this study were to be representative as it has been assumed in ART that the adhesive restoration is critical to its success.

The last trial that I had to exclude was one that was reported in three reports (Taifour 2003 (68), Frencken 2006 (74), Frencken 2007 (21)). This trial was conducted in Syria and involved 681 children aged 6-9 years with caries in a permanent tooth (i.e. not limited to molars or premolars). 1117 restorations were placed in total, an average of 1.64 restorations per child. The children were bussed in to the dental clinic where they were 'randomly' allocated to either ART or conventional treatment. In the reports it is not reported how they were randomised. Tucked away, though, in the discussion section (rather the results or method) of one of the papers is that the clinic had problems with electricity supply: "On those days, the principal investigator decided that all of the children, who had been transported to the WHO Centre for treatment, would be treated by the ART approach. We do not think that this decision biased the outcome of the study."

I wrote to Dr Frencken with a list of questions regarding the study in anticipation that it may be eligible (see appendix 6). Crucial to the decision whether or not this should be included in the review was whether the children had been randomised to the intervention groups at the outset of the study or whether this happened as they arrived.

In response to my questions it emerged from Dr Frencken that the students had been randomised by flipping a coin for the allocation of the first child in the class list and then alternating the intervention thereafter. Thus this was quasi-randomisation, which I had allowed in my eligibility criteria. However, the children were randomised on the day they arrived, not at the outset of the trial. Therefore, on the days when there was no electricity

there was no randomisation – all patients received ART. If the children had been randomised at the beginning of the trial then their outcomes could have been assessed using the intention to treat principle. Thus those assigned to conventional treatment but who received ART (half the students on the affected days) would have had their outcomes assessed as if they had been treated with conventional treatment. The breach of protocol would have been noted in the assessment of risk of allocation bias and due consideration given to how this could affect the conclusions of the study.

However, the case was that a significant proportion of children were not randomised in this trial. Dr Frencken, in his response to my question of how many this was, provided an estimate. He assumed that if randomisation had been effective half of the 681 children would have been allocated to each group. That is 341 to ART and 340 to amalgam. In the end 370 were treated in the ART group and 311 in the amalgam group. The difference in number allocated to each intervention is 59. Frencken calculates that this means an extra 30 participants (half of the 59) out of a total of 681 were treated with ART than should have been. However, in order for those *extra* 30 children to be treated with ART none of the 59 children would have been randomised. That is, 59 out of 681 children or 8.7%.

I had been of the mind that if the proportion of children not randomised had been very small – say, less than 1% - that as long as this was made explicit in the analysis of the results it would be worth including the trial even though in fact it was no longer even a truly quasi-randomised trial. I would have felt that the potential useful evidence gained from such a large trial could outweigh the small number not randomised. But with approximately 8.7% of the participants being non-randomised the potential impact of this on the results was too great to ignore. For this reason this trial was excluded on the grounds that it was not a randomised controlled trial after all.

Furthermore, we are unable to say how many restorations were placed in these 59 children, as the calculations are based on Frencken's assumptions. Data for the children treated in this way is not available and so he is unable to say how many ART restorations were placed on the days without electricity. It is possible that significantly more or less than the average of 1.64 were placed. Since the calculations made of ART effectiveness in the study are based on the number of restorations placed, this large uncertainty would be troublesome.

Given the large number of children involved the problems identified here could have been avoided by suspending recruitment to the trial on the days when there was no electricity, so preserving the quasi-random allocation. It seems to me that even if the electricity had been suspended half way through the day and that, therefore, a random allocation to interventions had been achieved that the participants that followed the electricity outage could have been excluded from the trial. Unfortunately this was not the case.

It is of interest to note that this trial was considered eligible in all three of the previously conducted systematic reviews without a comment on the risk of bias attributable to the break in random allocation. It is perhaps not surprising that it was included in the first review by Frencken given that he conducted the trial, but it would appear that none of the other authors followed up on the clue to this allocation bias in the discussion part of the reports of the trial. This experience reinforces the need to contact authors not only as part of the search for reports but also to clarify the methodology of their trials.

I had hoped after reading the previous systematic reviews and after scoping PubMed before beginning this review that there would be at least four or five trials that could have been included. It was therefore disappointing to discover that there were none that would meet my inclusion criteria.

The result, therefore, of this review was that there were no identifiable randomised controlled trials that compared ART using any adhesive material to conventional treatment with any material in class I or II cavities in the permanent dentition.

3.6 Discussion

This review was unable to identify any randomised controlled trials to answer the review question, which was how ART with any adhesive material compared to conventional treatment with any adhesive material or amalgam.

With hindsight it would seem that this review was too narrow and that by broadening some of the eligibility criteria I could have allowed for more trials to be included. One obvious area would have been to allow for the use of so-called modified ART involving the use of chemical agents to assist in the removal of caries. I am aware, having screened so many trials, that a number of trials using this method exist, though I have not looked in sufficient detail to know whether they would meet the other eligibility criteria (i.e. tooth type, length of follow up, randomised / pseudo-randomised controlled trial, intervention comparisons).

The other limitations on eligibility were explained in the methods section, particularly around focussing the review on permanent teeth. I had anticipated enough trials to be available for the limited question of how effective ART is in permanent teeth and, despite the absence of trials, think that this limitation assists in clarifying that using ART in permanent teeth is not evidenced by high quality research. Such a message could be lost within a review with broader eligibility that includes deciduous teeth.

Much of the ART literature seems to be concerned with GIC and amalgam as ART and conventional restorative materials respectively. This review shows that not only is there an absence of properly conducted trials comparing these two materials but that there is a need to assess both ART and conventional treatment in relation to other materials too.

This review does not assess whether ART is better than no treatment or other, non-restorative, treatment modalities. In the countries in which ART was developed there was perceived to be a need for ART because conventional treatment was not possible or too expensive. I think now that a wider review into whether there is RCT evidence to support the use of ART rather than do nothing would help identify if there was a knowledge gap here. This review cannot help in this regard but when scoping before beginning the review I was unable to identify research that considered this question.

I attempted to identify all trials with a thorough search of the literature but I suspect that this could have been improved by having a Chinese speaker help in searching the Chinese databases. It could be that this becomes more and more important as the Chinese expand and improve upon their research in the coming years. Before beginning another review I plan on contacting Chinese researchers in the field in order to collaborate and, therefore, hopefully improve upon the search for trials.

The need for ART to be researched properly for the restoration of permanent teeth is pressing. Interestingly, given that ART was developed in Tanzania, this region of the world actually had one of the lowest DMFT (Decayed Missing or Filled permanent Teeth) scores amongst 12-year-olds in the world in 2004(160) with an average of <1.2 (i.e. on average children had 1.2 decayed, missing or filled teeth). Much of Africa and southern Asia, areas often associated with lower incomes and fewer dental services, did in fact record low DMFT scores in this age group. Indeed, the DMFT scores for 12-year-olds in developed and developing countries were similar in 2004 at just above 2. However, South America and parts of Eastern Europe had DMFT scores above 2.7 and a more recent report from the Philippines found that 55.7% (95% CI; 53.5%-57.9%) of 12-year-olds had experienced odontogenic infections because of caries(161).

The ratio of dentists to population is about 1:2000 in the developed world compared to 1:150,000 (160) in the developing world. It may well be, therefore, that a higher proportion of the DMFT is due to the Filled component in western countries and the Decayed or Missing component in the developing countries.

Health inequality exists within countries as well as between them (162, 163). This takes the form of a social gradient rather than a dichotomous distribution of high and low disease between the low socio-economic classes and the higher classes respectively. The need for cost-effective treatment to help reduce these inequalities may therefore be just as pressing as delivering effective caries management in the developing world.

The ART philosophy, which fits into a programme of preventive measures too, appeals because of its simplicity, allowing non-dentists to deliver care. It fits well within the concepts aired by the Global Oral Health community (164, 165) though it would seem unable to have any influence on the so-called 'causes of the causes' – the reasons why individuals consume more cariogenic foods, don't have access to fluoride or oral hygiene aids. But however well the concept fits, it must be demonstrated in robust clinical trials to be effective – or at least cost-effective. Assertions from those in influential places that ART is suitable for the restoration of permanent teeth with class I cavities (166) does not change the fact that high quality clinical trials have not been conducted to demonstrate this.

3.7 Conclusion

3.7.1 Implications for practice

Since this review is empty it is unable to positively recommend that clinicians change their behaviour in any way. It does, though, inform policy makers and clinicians of the very large gap in knowledge relating to the use of ART in permanent teeth. Given the enthusiasm for ART amongst, for example, the WHO and the Pan American Health Organisation (PAHO) (167) in deciduous teeth it would seem sensible to hold back on endorsing its use in permanent teeth

if conventional alternatives are already being used. A large randomised controlled trial with deciduous teeth across 3 countries conducted by PAHO concluded that ART could cost half what conventional treatment with amalgam does. The follow-up of participants was three years, though, and did not involve permanent teeth. It could be tempting to extrapolate these short term clinical results and conclude that ART should be used in permanent teeth given the potentially large financial savings. This has yet to be demonstrated.

3.7.2 Implications for research

This review is really concerned with those patients with permanent posterior teeth who could in fact receive conventional treatment instead of ART should the evidence suggest this was more effective. Thus my recommendations for future primary research are that randomised controlled trials with methodological rigour be conducted that compare ART using a given material to conventional treatment using the *same* material. Given the findings of the Chinese study that found ART with amalgam to be more effective than ART with GIC, I would also advocate conducting ART with amalgam even though this goes against the original definitions of ART that required the restorative material to be adhesive.

It may well be that even if ART were not to be demonstrated to be effective compared to conventional treatment in the wider population, in certain groups (such as those unable to sustain anaesthesia) it could, none-the-less, be more effective than conventional treatment simply because it could be conducted. We should be careful in my view, in looking at the effectiveness of treatments in the general population, not to ignore the large number of clinical encounters that are not 'normal'.

Regarding future systematic reviews I have alluded already to the need to assess the need for restorative treatment *per se*. It may well be that given the consensus on the need to restore teeth trials designed to answer that question may be judged unethical.

There is also a need to establish whether different materials affect the success rate of ART and would, therefore, propose a systematic review that compares the effectiveness of ART using one material with ART using another material. From an experimental point of view, trials that explore this would contribute to our understanding of the role of the material in ART and perhaps move the research forward by finding more robust materials that do not fit the GIC-ART mould but which improve patient outcomes. And as a minimal intervention technique it would be helpful to conduct a systematic review of the effectiveness of ART compared to other minimal intervention techniques for use in clinics where these are possible.

Finally, I was conscious in conducting this review that I had excluded studies that dealt with shorter-term outcomes like anxiety and pain associated with different treatments. A review of these would help inform us of the acceptability of different interventions to adults, children and those with special needs that could potentially benefit from the relative simplicity of carrying out ART.

3.8 Support

Internal organisation funding paid for the time of a colleague to data extract with me and to pay for translation of the Chinese papers into English. There were no other sources of funding.

Appendix 1: Search strategies

~~OVID Medline search strategy~~

#	Search
1	Dental Restoration, Permanent/
2	Dental Atraumatic Restorative Treatment/
3	Dental Cavity Preparation/
4	Dental Restoration, Temporary/
5	Glass Ionomer Cements/
6	exp Dental Cements/
7	limit 6 to yr="1972 - 1992"
8	"Pit and Fissure Sealants"/tu [Therapeutic Use]
9	Glass ionomer.ti,ab.
10	GIC.ti,ab.
11	Resin modified glass ionomer.ti,ab.
12	RMGIC.ti,ab.
13	RM-GIC.ti,ab.
14	ART.ti,ab.
15	(atraumatic adj6 restorative).ti,ab.
16	(atraumatic adj6 treatment$).ti,ab.
17	(atraumatic adj6 technique$).ti,ab.
18	(atraumatic adj6 restoration$).ti,ab.
19	(atraumatic adj6 therap$).ti,ab.
20	(atraumatic adj6 filling$).ti,ab.

21 exp Dental Caries/

22 caries {Including Related Terms}

23 carious {Including Related Terms}

24 dental cavity {Including Related Terms}

25 or/21-24

26 1 or 2 or 3 or 4 or 5 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20

27 amalgam.ti,ab.

28 25 or 27

29 26 and 28

30 limit 29 to yr="1972 -Current"

31 limit 30 to animals

32 limit 31 to humans

33 31 not 32

34 30 not 33

OVID Embase search strategy

#	Search
1	dental surgery/
2	Dental Atraumatic Restorative Treatment/
3	Glass Ionomer Cements/
4	exp Dental Cements/
5	limit 4 to yr="1972 - 1992"
6	Glass ionomer.ti,ab.
7	GIC.ti,ab.

8 Resin modified glass ionomer.ti,ab.

9 RMGIC.ti,ab.

10 RM-GIC.ti,ab.

11 ART.ti,ab.

12 (atraumatic adj6 restorative).ti,ab.

13 (atraumatic adj6 treatment$).ti,ab.

14 (atraumatic adj6 technique$).ti,ab.

15 (atraumatic adj6 restoration$).ti,ab.

16 (atraumatic adj6 therap$).ti,ab.

17 (atraumatic adj6 filling$).ti,ab.

18 exp Dental Caries/

19 caries {Including Related Terms}

20 carious {Including Related Terms}

21 dental cavity {Including Related Terms}

22 or/18-21

23 1 or 2 or 3 or 5 or 6 OR 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

24 amalgam.ti,ab.

25 22 or 24

26 23 and 25

27 limit 26 to yr="1972 -Current"

28 limit 27 to (animals and animal studies)

29 limit 28 to human

30 28 not 29

31 27 not 30

CENTRAL search strategy

Search

1 MeSH descriptor Dental Restoration, Permanent explode all trees

2 MeSH descriptor Dental Atraumatic Restorative Treatment explode all trees

3 MeSH descriptor Dental Cavity Preparation explode all trees

4 MeSH descriptor Dental Restoration, Temporary explode all trees

5 MeSH descriptor Glass Ionomer Cements explode all trees

6 MeSH descriptor Dental Cements explode all trees

7 (#6), from 1972 to 1992

8 (Glass ionomer):ti,ab,kw or (GIC):ti,ab,kw or (Resin modified glass ionomer):ti,ab,kw or (RMGIC):ti,ab,kw or (RM-GIC):ti,ab,kw

9 (ART):ti,ab,kw

10 (atraumatic restorative):ti,ab,kw or (atraumatic treatment*):ti,ab,kw or (atraumatic technique*):ti,ab,kw or (atraumatic restoration*):ti,ab,kw or (atraumatic therap*):ti,ab,kw OR (atraumatic filling*):ti,ab,kw

11 MeSH descriptor Dental Caries explode all trees

12 (caries) or (carious)

13 (dental cavity) or (tooth decay) or (tooth decayed) or (teeth decayed) or (saprodontia)

14 (amalgam):ti,ab,kw

15 (#1 OR #2 OR #3 OR #4 OR #5 OR #8 OR #9 OR #10)

16 (#11 OR #12 OR #13 OR #14)

17 (#15 AND #16)

Appendix 2: Data extraction sheets for existing systematic reviews

A systematic review of current systematic reviews of the atraumatic restorative technique (ART)

Cover sheet

Primary author		Language			
Review title					
Reference			Year of Review		
References of included trials:			Follow up		

Key: **AMSTAR** - Y / N / Can't answer / N/A = Yes / No / Can't Answer / Not applicable

Table 1: potential scope of review based on the eligibility criteria

ART material	Control material	Yes	No	Unsure
GIC	GIC			
	RMGIC			
	Composite			
	Amalgam			
RMGIC	GIC			
	RMGIC			
	Composite			
	Amalgam			
Composite	GIC			
	RMGIC			
	Composite			
	Amalgam			

Tooth	Cavity	Yes	No	Unsure
Permanent	Class I			
	Class II			
	Class V			
Deciduous	Class I			
	Class II			

Table 2: assessment of methodological quality of systematic reviews using the AMSTAR tool

1. Was an 'a priori' design provided? Summary: Yes / No / Can't Answer / Not applicable	Research question clear?	Y / N / Can't answer / N/A	
	Inclusion criteria stated?	Y / N / Can't answer / N/A	
2. Was there duplicate study selection and data extraction? Summary: Yes / No / Can't Answer / Not applicable	At least two independent data extractors?	Y / N / Can't answer / N/A	
	Consensus procedure for disagreements in place?	Y / N / Can't answer / N/A	
	[Was it used if there was disagreement?]	Y / N / Can't answer / N/A	
3. Was a comprehensive literature search performed? Summary: Yes / No / Can't Answer / Not applicable	At least two electronic sources searched?	Y / N / Can't answer / N/A	
	Databases used reported?	Y / N / Can't answer / N/A	
	Years used reported?	Y / N / Can't answer / N/A	
	Key words and/or MESH terms stated?	Y / N / Can't answer / N/A	
	Search strategy provided?	Y / N / Can't answer / N/A	
	Searches supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found?	Y / N / Can't answer / N/A	
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? Summary: Yes / No / Can't Answer / Not applicable	Authors state that they searched for reports regardless of their publication type?	Y / N / Can't answer / N/A	
	Authors state whether or not they excluded any reports based on their publication status, language etc.?	Y / N / Can't answer / N/A	

5. Was a list of studies (included and excluded) provided? Summary: Yes / No / Can't Answer / Not applicable	A list of included studies provided?	Y / N / Can't answer / N/A	
	A list of excluded studies provided?	Y / N / Can't answer / N/A	
6. Were the characteristics of the included studies provided? Summary: Yes / No / Can't Answer / Not applicable	Were data from the original studies provided on the participants, interventions and outcomes in an aggregated form such as a table?	Y / N / Can't answer / N/A	
	Were the ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases reported?	Y / N / Can't answer / N/A	
7. Was the scientific quality of the included studies assessed and documented? Summary: Yes / No / Can't Answer / Not applicable	Was an 'A priori' method of assessment provided (e.g., for effectiveness studies if the author(s) chose to include only randomised, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria)?	Y / N / Can't answer / N/A	
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? Summary: Yes / No / Can't Answer / Not applicable	Were the results of the methodological rigor and scientific quality of included studies considered in the analysis and the conclusions of the review?	Y / N / Can't answer / N/A	
	Were they explicitly stated in formulating recommendations?	Y / N / Can't answer / N/A	
9. Were the methods used to combine the findings of studies appropriate? Summary: Yes / No / Can't Answer / Not applicable	If results were pooled was a test done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2)?	Y / N / Can't answer / N/A	
	If heterogeneity exists was a random effects model used and/or the clinical appropriateness of combining taken into consideration (i.e. is it sensible to combine?)?	Y / N / Can't answer / N/A	
10. Was the likelihood of publication bias	Was there an assessment of publication bias?	Y / N / Can't answer / N/A	

assessed? Summary: Yes / No / Can't Answer / Not applicable	Did this include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test)?	Y / N / Can't answer / N/A	
11. Was conflict of interest stated? Summary: Yes / No / Can't Answer / Not applicable	Were potential sources of support clearly acknowledged in the systematic review?	Y / N / Can't answer / N/A	
	Were potential sources of support clearly acknowledged in the included studies?	Y / N / Can't answer / N/A	

Table 3: Assessment of reporting quality using the PRISMA checklist

Mark either "yes", "partly" or "no" for each item.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	

Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	

Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

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Appendix 3: Email request to authors

25/08/2011

Dear ,

I trust you will excuse this unsolicited email.

I am currently undertaking a systematic review into the use of ART compared to conventional treatment in class I and II cavities in permanent posterior teeth. The protocol is available on PROSPERO at:

http://www.crd.york.ac.uk/prospero/full_doc.asp?ID=CRD42011001411

One of the requirements of a systematic review is to use all possible means to identify trials that could answer the review question, including contacting experts in the field.

I am therefore writing to you because of your history in the development of the ART technique to see if you are aware of randomised controlled trials that compare ART with any adhesive material to conventional treatment with any material in permanent teeth with class I or II cavities.

If you are aware of any on-going trials, the details of these and contact information would be helpful.

I would be most grateful for any assistance you can provide.

Yours sincerely,

Dominic Hurst

Appendix 4: Screening form for systematic reviews

ART Systematic Review: Permanent teeth with Class I or II cavity – Incl / Excl Scan Form

Study ID (Au1,pub year)	Design/allocation	Participants	Interventions – "true" ART (hand instruments only, no LA): Low GIC, High GIC, RM-GIC, Composite, Compomer, +/- fissures, +/- conditioner, +/- finger / instrument Comparisons – conventional (any mechanical): Low GIC, High GIC, RM-GIC, Composite, Compomer, Amalgam, +/- fissures, +/- conditioner, +/- LA **IN** – "true" ART v. Comparison; **EXCLUDE** - data not comparing like cavities in the two groups; intervention is "modified" ART, ART v. ART	Outcomes **IN** – failure of restoration (caries, fracture, loss, cuspal #), loss of tooth due to carious process (abscess, fracture, pulpitis); recurrent caries; **EXCLUDE** – loss of teeth due to trauma, periodontitis / gingivitis, only patient behaviour (anxiety levels, attendance), post-op sensitivity / pain; time for tx; cost-benefit analysis (only)	Length of follow-up **IN** – all periods of follow up ≥2yrs **EXCLUDE** – follow-up not recorded or <2 years	Notes other potential reasons for exclusion OR other potential actions following first scan e.g. translate, contact author	Inc/excl/in based on Title, Title +Abstract, Full Text

Appendix 5: Data collection form for systematic reviews

ART Systematic Review: Permanent teeth with Class I or II cavity – Data Collection Form for Included Studies Only

Source:	Study ID (Author1, year)								Language:				
	Citation(s)												
	Contact details												
Methods:	Study design:	RCT / Q-RCT	Parallel / split mouth / cluster				Total study duration:		Years			Months	
*summary from risk of bias assessment on following pages	Sequence generation Method*	Adequate / Inadequate / Unsure					Allocation concealment*		Adequate / Inadequate / Unsure / N/A				
	Blinding*	Adequate / Inadequate / Unsure / N/A					Other concerns re: bias						
	Outcome data*	Complete / Incomplete / Unsure					Overall risk of bias:		Low / High / Unknown				
Participants:	Total participants in the study		Setting:						Diagnostic criteria:				
	Age – mean (range)						% Female			% Male			
	Country						Socio-demographics:						
	Clinician type	Dentist / DCP / Student / Other					Average DMFT score						
	Total participants with permanent teeth with a class II cavity		Loss to follow up:	ART: Conv:			% Female			% Male			
Interventions:	Number of intervention groups: 2 / 3												N=
Permanent	Specific intervention:	ART*	H GIC	M GIC	L GIC	RMGIC	Composite	Compomer	Carbomer				
		Conv1*	H	M	L GIC	RMGIC	Composite	Compomer	Carbomer	Amalgam			

teeth with class II cavity only	*Insert name of product	Conv2*	GIC H GIC	GIC M GIC	L GIC	RMGIC	Composite	Compomer	Carbomer	Amalgam	

Notes:

Outcomes: *Were the pre-specified outcomes (i) collected at the pre-specified time points and (ii) were they reported?	Outcome 1		Time points		Collected*	Yes / No / Unsure	Reported*	Yes / No / Unsure
	Definition (+/- diagnostic criteria)							
	Unit of measurement							
	For scales – upper and lower limits						Validated scale?	Yes / No / Unsure
	Outcome 2		Time points		Collected	Yes / No / Unsure	Reported	Yes / No / Unsure
	Definition (+/- diagnostic criteria)							Dichotomous / Continuous
	Unit of measurement							
	For scales – upper and lower limits						Validated scale?	Yes / No / Unsure
	Outcome 3		Time points		Collected	Yes / No / Unsure	Reported	Yes / No / Unsure
	Definition (+/- diagnostic criteria)							Dichotomous / Continuous
	Unit of measurement							
	For scales – upper and lower limits						Validated scale?	Yes / No / Unsure
	Outcome 4		Time points		Collected	Yes / No / Unsure	Reported	Yes / No / Unsure
	Definition (+/- diagnostic criteria)							Dichotomous / Continuous
	Unit of measurement							
	For scales – upper and lower limits						Validated scale?	Yes / No / Unsure
	Outcome 5		Time points		Collected	Yes / No / Unsure	Reported	Yes / No / Unsure
	Definition (+/- diagnostic criteria)							Dichotomous / Continuous
	Unit of measurement							
	For scales – upper and lower limits						Validated scale?	Yes / No / Unsure
	Outcome 6		Time points		Collected	Yes / No / Unsure	Reported	Yes / No / Unsure
	Definition (+/- diagnostic criteria)							Dichotomous / Continuous
	Unit of measurement							
	For scales – upper and lower limits						Validated scale?	Yes / No / Unsure

Notes:

Risk of bias assessment: Domain			Description	Review author's judgement
Adequate sequence generation?				Yes / No / Unclear
Allocation concealment?				Yes / No / Unclear
Outcome1	**Blinding?**	Participants		Yes / No / Unclear
		Operator		Yes / No / Unclear
		Assessor		Yes / No / Unclear
	Incomplete outcome data addressed?			Yes / No / Unclear
Outcome2	**Blinding?**	Participants		Yes / No / Unclear
		Operator		Yes / No / Unclear
		Assessor		Yes / No / Unclear
	Incomplete outcome data addressed?			Yes / No / Unclear
Outcome3	**Blinding?**	Participants		Yes / No / Unclear
		Operator		Yes / No / Unclear
		Assessor		Yes / No / Unclear
	Incomplete outcome data addressed?			Yes / No / Unclear
Outcome4	**Blinding?**	Participants		Yes / No / Unclear
		Operator		Yes / No / Unclear

		Assessor		Yes / No / Unclear
	Incomplete outcome data addressed?			Yes / No / Unclear
Outcome5	**Blinding?**	Participants		Yes / No / Unclear
		Operator		Yes / No / Unclear
		Assessor		Yes / No / Unclear
	Incomplete outcome data addressed?			Yes / No / Unclear
Outcome6	**Blinding?**	Participants		Yes / No / Unclear
		Operator		Yes / No / Unclear
		Assessor		Yes / No / Unclear
	Incomplete outcome data addressed?			Yes / No / Unclear
Free of selective outcome reporting?				Yes / No / Unclear
Free of other bias?				Yes / No / Unclear

Notes:

Results: Dichotomous Data Only include data for permanent teeth with class II cavities	Intervention group:		ART	Conv1	Conv2	
	Outcome:	+				
		-				
			N=	N=	N=	All=
			ART	Conv1	Conv2	
	Outcome:	+				
		-				
			N=	N=	N=	All=
			ART	Conv1	Conv2	
	Outcome:	+				
		-				
			N=	N=	N=	All=
			ART	Conv1	Conv2	
	Outcome:	+				
		-				
			N=	N=	N=	All=
			ART	Conv1	Conv2	
	Outcome:	+				
		-				
			N=	N=	N=	All=
			ART	Conv1	Conv2	
	Outcome:	+				
		-				
			N=	N=	N=	All=
			ART	Conv1	Conv2	
	Outcome:	+				
		-				
			N=	N=	N=	All=

Results: Continuous and ordinal data Only include data for permanent teeth with class II cavities	Intervention group:	ART		Conv1		Conv2	
	Outcome:	M	SD	M	SD	M	SD
		N=		N=		N=	
		ART		Conv1		Conv2	
	Outcome:	M	SD	M	SD	M	SD
		N=		N=		N=	
		ART		Conv1		Conv2	
	Outcome:	M	SD	M	SD	M	SD
		N=		N=		N=	
		ART		Conv1		Conv2	
	Outcome:	M	SD	M	SD	M	SD
		N=		N=		N=	
		ART		Conv1		Conv2	
	Outcome:	M	SD	M	SD	M	SD
		N=		N=		N=	
		ART		Conv1		Conv2	
	Outcome:	M	SD	M	SD	M	SD
		N=		N=		N=	
		ART		Conv1		Conv2	
	Outcome:	M	SD	M	SD	M	SD
		N=		N=		N=	

Results: **Other data** e.g. adverse events, cost-effectiveness Only include data for permanent teeth with class II cavities		
Miscellaneous:	Funding Sources	
	Key Conclusions of study authors	
	Misc. comments from study authors	
	References to other relevant studies	
	Misc. comments by review authors	
~~**Further action:**~~	~~Correspondence with author~~ (note what is needed)	

Notes:

Appendix 6: Email to Professor Jo Frencken

17/10/2011

Dear Professor Frencken,

I wrote previously to say that I am conducting a systematic review of ART versus conventional treatment for class [I and] II cavities in permanent teeth.
http://www.crd.york.ac.uk/prospero/full_doc.asp?ID=CRD42011001411
http://www.crd.york.ac.uk/prospero/full_doc.asp?ID=CRD42011001624

If [I am] not mistaken, you have reported on a study in Syria at a number of time points reported in these three papers:

Taifour D, Frencken JE, Beiruti N, van't Hof MA, Truin GJ, Helderman WHV: Comparison between restorations in the permanent dentition produced by hand and rotary instrumentation - survival after 3 years. Community Dentistry and Oral Epidemiology 2003;31:122-128.

Frencken JE, Taifour D, van 't Hof MA: Survival of art and amalgam restorations in permanent teeth of children after 6.3 years. Journal of Dental Research 2006;85:622-626.

Frencken JE, van't Hof MA, Taifour D, Al-Zaher I: Effectiveness of art and traditional amalgam approach in restoring single-surface cavities in posterior teeth of permanent dentitions in school children after 6.3 years. Community Dent Oral Epidemiol 2007;35:207-214.

I would be very grateful if you could answer a few questions regarding these studies to help us with our analysis. Each of these items is essential to completion of the review. If the answers to any
of these questions are within the papers I do apologise for not having identified them after several re-readings.

1. You report that participants were randomised to either ART or amalgam restorations "All eligible pupils were randomly allocated to one of the treatments using the class list". Can you say when the
randomisation occurred (e.g. at the outset or as they attended clinics)?

2. Can you say how the participants were randomised (e.g. random number tables, computer randomisation, flip of coin)?

3. In the discussion sections you report that on a number of days the electricity supply failed and the principal investigator decided that all children would receive ART restorations on these days. Can you say why you came to the conclusion that "We do not think that
this decision has biased the outcome of the study"? Can you also say whether the participants

who were treated with ART because of the electricity shortages had already been randomised before the decision
was made to place ART in all of them?

4. Can you say how many children were treated during the days when there was no electricity, how many ART restorations were placed and how many conventional restorations would have been placed (i.e. how many ART restorations were placed in those assigned to conventional treatment on those days)? Can you also say how many of the ART and amalgam restorations were class I and class II?

5. We understand that 97 multiple surface restorations were placed but you do not report the results for these in the 2003 paper. Can you say (i) how many of these were class II cavities, (ii) how many were restored using ART and how many with amalgam, and (iii) what the failure rate was for each at the time points you recorded?

6. Were the time points used pre-specified at the protocol stage?

7. To enable us to determine the relative risks for failure at each time point, for each of them could you provide (i) the number of ART and amalgam restorations in class I and class II cavities (ii) the
number of failures for each and the loss to follow-up for each?

8. Do you have additional baseline data for each of the intervention groups that would allow us to see how well balanced they were? e.g. average age, average DMFS and DMFT, indicators of socio-economic status.

We understand that it may take time to collate this information. If you could provide an estimate of how long you think it might take this would help us in planning the remainder of the review. As an indicator of our time scale, we would need this data before we begin data analysis, which we plan to start at the beginning of December.

I look forward to your response.

Yours Sincerely,

Dominic Hurst

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