NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS

SCHOOL OF HEALTH SCIENCES

DEPARTMENT OF DENTISTRY

POST-GRADUATE PROGRAM

SPECIALIZATION IN PROSTHODONTICS

CONVENTIONAL VS SIMPLIFIED COMPLETE DENTURES: A SYSTEMATIC REVIEW

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ATHENS 2021

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ΕΙΔΙΚΕΥΣΗ ΠΡΟΣΘΕΤΙΚΗ

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Επιβλέπουσα Καθηγήτρια για την εκπόνηση της Μεταπτυχιακής Διπλωματικής Εργασίας κα Ασπασία Σαραφιανού, *Επίκουρη Καθηγήτρια Ακίνητης Προσθετικής Οδοντιατρικής Σχολής ΕΚΠΑ*

Τριμελής Επιτροπή για την Αξιολόγηση της Μεταπτυχιακής Διπλωματικής Εργασίας:

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ΕΥΧΑΡΙΣΤΙΕΣ

Είμαστε το αποτέλεσμα των αλληλεπιδράσεών μας με όλους τους ανθρώπους που συναντάμε στη ζωή μας ανεξαρτήτως χρόνου και αποτελέσματος.

Ευχαριστώ θερμά τον Διευθυντή του εργαστηρίου Προσθετικής κ. Γρ. Πολυζώη για όλη την στήριξη και την εμπιστοσύνη που μου έδειξε όλα αυτά τα χρόνια.

Ευχαριστώ πολύ την κ. Ασπ. Σαραφιανού για τη συμβολή της στην εκπόνηση της διπλωματικής μου εργασίας.

Ευχαριστώ πολύ όλα τα μέλη ΔΕΠ του εργαστηρίου της Προσθετικής για την υποστήριξή τους και το ενδιαφέρον τους.

Θερμές ευχαριστίες σε όλους τους φοιτητές του εργαστηρίου της Προσθετικής με τους οποίους συμπορευθήκαμε, μοιραστήκαμε τις ανησυχίες μας αλλά και συνέβαλαν στην πρόοδό μου με την ελπίδα να αποτέλεσα κι εγώ ένα αντίστοιχο στήριγμα για εκείνους. Ασπασία, σε ευχαριστώ για όλη σου τη βοήθεια από την πρώτη ημέρα στις προπτυχιακές μας σπουδές μέχρι σήμερα. Η διαδρομή δεν ήταν πάντα εύκολη, αλλά σίγουρα ήταν πιο εύκολη και διασκεδαστική μαζί σου.

Οφείλω να ευχαριστήσω τους γονείς μου, τα αδέρφια μου Πηνελόπη και Γιώργο και τον σύζυγό μου Γιώργο αν και η ευγνωμοσύνη για όλη τους την στήριξη και σε αυτό το βήμα της ζωής μου δεν μπορεί να εκφραστεί ούτε να αποτυπωθεί σε μερικές γραμμές.

Κυρίως όμως θα ήθελα να ευχαριστήσω όλους εκείνους τους ανθρώπους που δεν ανήκουν στην οδοντιατρική οικογένεια κι ενδεχομένως δεν έχουν μία σαφή εικόνα των μεταπτυχιακών μας προγραμμάτων και παρ’ όλ’ αυτά μου συμπαραστάθηκαν και υποστήριξαν τις προσπάθειές μου αδιακρίτως.

ABSTRACT

Statement of problem: Complete dentures are usually fabricated with the use of a well-established conventional protocol. The conventional method requires six clinical sessions including the preliminary and the final impression, the recording of maxillomandibular relationships, the anterior and the posterior try-in, and finally the delivery of the denture. The final impression is a challenging and demanding session, requiring significant time. Due to its complexity, the conventional protocol has been challenged and simplified methods with the omission of the final impression stage have been proposed. Insufficient evidence exists on the necessity of the final impression in complete denture fabrication, as well as on its significance for the success of the restoration.

Purpose: The aim of this systematic review is to compare the conventional with the simplified method according to masticatory performance and ability, patient satisfaction, oral health related quality of life (OHRQoL), denture quality, time, and cost.

Material and Methods: An electronic search of the MEDLINE-PubMed, Scopus and Europe PMC databases was conducted by two independent researchers (P.E. and S.A.) for randomized clinical trials, cohort clinical studies and clinical studies of complete dentures fabricated either with the conventional or the simplified method. As simplified method was characterized every protocol of fabrication of complete dentures which did not include a final impression.

The **PICO** question was formed as such: 'Does the simplified technique for fabrication of complete dentures provide equal or even better outcomes than the conventional technique in the treatment of edentulous patients?' Patients in need of a complete denture (**P**articipants/**P**opulation) were divided in two categories, named those who were treated with a complete denture fabricated by the simplified technique (**I**ntervention) and those who were treated with a complete denture fabricated by the conventional technique (**C**omparison). Between these two categories a variety of **O**utcomes were examined: masticatory performance and ability, patient satisfaction, Oral Health Related Quality of Life (OHRQoL), time, and cost.

The risk of bias for each study was assessed with ROBINS-I and ROBINS 2 tools. The risk of bias across the studies was assessed with the GRADE system.

Results: The electronic search of databases produced 19 articles which fulfilled the inclusion criteria. Moreover, two systematic reviews and one meta-analysis of the same topic were included. The studies examined different variables and therefore were compared in subgroups.

Conclusions: The null-hypothesis was confirmed in terms of cost and time but rejected in all the other factors. Cost and time differed significantly between the two methods favoring the simplified protocol, while masticatory performance and ability, patient

satisfaction, Oral Health Related Quality of Life (OHRQoL) and denture quality are not affected by the method of fabrication.

ΠΕΡΙΛΗΨΗ

Θέση: Οι ολικές οδοντοστοιχίες κατασκευάζονται συνήθως ακολουθώντας ένα καθιερωμένο συμβατικό πρωτόκολλο. Το πρωτόκολλο αυτό απαιτεί έξι κλινικά στάδια συμπεριλαμβανομένων του αρχικού και του τελικού αποτυπώματος, της καταγραφής των διαγναθικών σχέσων, της δοκιμής σύνταξης των προσθίων και των οπισθίων δοντιών, και τέλος της παράδοσης των οδοντοστοιχιών. Το στάδιο του τελικού αποτυπώματος είναι ιδιαιτέρως δύσκολο και απαιτητικό και απαιτεί σημαντικό χρόνο. Δεδομένης της δυσκολίας του, το συμβατικό πρωτόκολλο έχει αμφισβητηθεί και απλοποιημένες μέθοδοι με την παράλειψη του σταδίου του τελικού αποτυπώματος έχουν προταθεί. Δεν υπάρχουν επαρκείς αποδείξεις της αναγκαιότητας του τελικού αποτυπώματος στην κατασκευή των ολικών οδοντοστοιχιών, καθώς και της σημασίας του στην επιτυχία της αποκατάστασης.

Σκοπός: Ο σκοπός της συστηματικής ανασκόπησης είναι να συγκριθούν το συμβατικό με το απλοποιημένο πρωτόκολλο κατασκευής οδοντοστοιχιών αναφορικά με τη μασητική ικανότητα του ασθενούς, την ικανοποίησή του, την ποιότητα ζωής του σχετιζόμενη με την στοματική υγεία, την ποιότητα της οδοντοστοιχίας, τον χρόνο και το κόστος κατασκευής.

Μέθοδος και υλικά: Διεξήχθη ηλεκτρονική αναζήτηση στις βάσεις δεδομένων MEDLINE-PubMed, Scopus and Europe PMC από δύο ανεξάρτητες ερευνήτριες (Π.Ε. και Σ.Α.) αναζητώντας τυχαιοποιημένες κλινικές μελέτες, κλινικές μελέτες κοορτών και κλινικές μελέτες με οδοντοστοιχίες κατασκευασμένες με το συμβατικό ή το απλοποιημένο πρωτόκολλο. Ως απλοποιημένο πρωτόκολλο ορίζεται κάθε πρωτόκολλο κατασκευής ολικών οδοντοστοιχιών που δεν περιλαμβάνει το στάδιο του τελικού αποτυπώματος.

Η θέση της συστηματικής ανασκόπησης διατυπώθηκε μέσω της ερώτησης: «Προσφέρει το απλοποιημένο πρωτόκολλο κατασκευής οδοντοστοιχιών ισάξια ή και ανώτερα αποτελέσματα από το συμβατικό ως τρόπος θεραπείας του νωδού ασθενή;» Ασθενείς που χρειάζονταν την κατασκευή μιας ολικής οδοντοστοιχίας (Συμμετέχοντες/Πληθυσμός) διαχωρίστηκαν σε δύο κατηγορίες, σε αυτούς που αποκαταστάθηκαν με μία ολική οδοντοστοιχία κατασκευασμένη με την απλοποιημένη τεχνική (Παρέμβαση) και αυτούς που αποκαταστάθηκαν με μία ολική οδοντοστοιχία κατασκευασμένη με τη συμβατική τεχνική (Σύγκριση). Μεταξύ των δύο αυτών κατηγοριών, εξετάστηκε πλήθος Αποτελεσμάτων: η μασητική ικανότητα του ασθενούς, η ικανοποίησή του, η ποιότητα ζωής του σχετιζόμενη με την στοματική υγεία, η ποιότητα της οδοντοστοιχίας, ο χρόνος και το κόστος κατασκευής.

Το ρίσκο του βεβιασμένου λάθους (risk of bias) σε κάθε μελέτη αξιολογήθηκε με τα εργαλεία ROBINS-I και ROBINS 2. Το ρίσκο του βεβιασμένου λάθους (risk of bias) μεταξύ των μελετών αξιολογήθηκε με το σύστημα GRADE.

Αποτελέσματα: Η ηλεκτρονική αναζήτηση απέδωσε 19 άρθρα που πληρούσαν τα κριτήρια επιλογής. Επιπλέον συμπεριελήφθησαν δύο συστηματικές ανασκοπήσεις και μία μετα-ανάλυση επί του ιδίου θέματος. Οι μελέτες εξέταζαν διαφορετικές παραμέτρους και για αυτόν τον λόγο η σύγκρισή τους έγινε σε υποομάδες.

Συμπέρασμα: Η μηδενική υπόθεση επιβεβαιώθηκε όσον αφορά το κόστος και τον χρόνο κατασκευής αλλά απορρίφθηκε για όλους τους υπόλοιπους παράγοντες. Το κόστος και ο χρόνος κατασκευής διέφεραν σημαντικά μεταξύ των δύο μεθόδων ευνοώντας το απλοποιημένο πρωτόκολλο, ενώ η μασητική ικανότητα του ασθενούς, η ικανοποίησή του, η ποιότητα ζωής του σχετιζόμενη με την στοματική υγεία και η ποιότητα της οδοντοστοιχίας δεν επηρεάστηκαν από τη μέθοδο κατασκευής.

INTRODUCTION

Edentulism is the state of having lost all of the natural teeth and increases following the ageing of the population. Life expectancy has increased significantly following the medical advances including the vaccinations, the decline in infant mortality and the better living conditions. Following a healthier lifestyle without smoking or alcohol consumption combined with a better nutrition, increases the probability of a healthy ageing.[1] According to World Health Organization (WHO), healthy ageing is the process of developing and maintaining well-being in older age. The definition does not refer to the presence of diseases or disabilities which are related to ageing. This means that the occurrence of a disease or a disability does not exclude the well-being and therefore the healthy ageing.[2] This is extremely important if we take into consideration that the number of people aged over 65 years is constantly increasing in the last decades. More specifically, according to the World Population Prospects 2019, the population of people over 65 years is estimated to increase from 9 to 12 million in the next 10 years.[3] This will slowly change the ratio of people aged over to people aged under 65 years.

With an increasing older adult-population the probability of compromised oral health increases as well. The World Dental Federation defines oral health as the ability to speak, smile, smell, taste, touch, chew, swallow and express emotions through the whole face without pain, discomfort or disease. According to this broad definition, oral health does not only refer to the ability to eat or the absence of oral pathology, but it involves a wide range of different aspects of social life.[4] Oral health depends on oral and general diseases, harmful habits such as alcohol consumption, smoking or an unhealthy diet and socioeconomic conditions.[1]

According to the systematic review and meta-analysis of Roberto et al[5], the prevalence of edentulism increases with age and in elderly people this is influenced by demographic and socioeconomic factors.[5] As mentioned before, the population is ageing but this does not occur globally at the same percentage. The region plays an important role in longevity and well-being and the oral health is affected likewise. Not all people in all regions have an easy access to dental care. The access to dental care is not only associated with demographic factors, but also with socioeconomic factors. Lower income may be the strongest factor not to visit a dental office, as the majority is private and not covered by insurance. The education level, which often implies little oral health literacy, makes oral health a minor priority.[1] Taking all this into consideration, the conclusion of Roberto et al[5], that lower income and education level are associated with higher prevalence of edentulism may be justified. All this indicate the multifactorial etiology of edentulism.[5]

Implant therapy is well documented and can provide a long term and efficient treatment for tooth loss. However, it is not always possible to proceed with implant rehabilitation for the edentulous patients. With ageing increases not only the probability of losing teeth but also the prevalence of diverse and multiple systemic

diseases, accompanied with the appropriate medication which can complicate implant therapy. There are medical prescriptions that have to be altered or stopped in order to place implants, which can cause fear to the patients. Additionally, older patients are not willing to sustain extended treatment plans that include several surgical procedures, which sometimes are essential in order to assure an adequate bone substrate. In fact, a lot of cases need extended surgical procedures such as sinus or bone augmentation prior to implant placement. This was shown in a study of Walton and MacEntee[6]. The researchers asked the participants if they would consider a treatment plan with implants if it was free of charge. However, a significant high number of the participants (more than one third) still rejected the implant therapy, although the cost was not a compounding factor. The complexity of the surgical procedures and the concerns about surgical risks were the reasons of the participants declining the implant therapy.[6] The cost, the risks and the time needed for these therapies is a deterrent factor. In such cases patients are looking for an alternative, simpler solution, which includes complete dentures.

Complete dentures provide a solid rehabilitation for edentulism. They reconstruct all the missing hard and soft tissues. The standard protocol for fabricating a complete denture requires six clinical sessions followed by five laboratory stages. The clinical sessions include preliminary and final impression, maxillomandibular records, try-in of the dentures with the anterior teeth, try-in with all the teeth, and finally delivery of the complete denture. The preliminary impression is made with alginate on a stock tray or with compound on a metal tray. The purpose of this impression is to create a cast which will be used to fabricate a custom tray. This custom tray combined with a variety of materials will reassure the most detailed impression. This clinical session (final impression) is of highest importance, as the stability of a complete denture relies on the supporting tissues. The more detailed the form of supporting tissues on the final cast, the better the stability of the complete denture. The final impression is performed in two stages on the same clinical session. First, the borders are impressed with either compound or heavy body silicone and then a light body material is used to impress the intaglio surface. On the final casts, base plates are fabricated with occlusal rims to proceed with the maxillomandibular records, in order to transfer the final casts to the articulator. The try-in of the complete dentures is also a two-stage approach: during the first session, only the anterior teeth are placed on the base plates and tried-in. In a second clinical session the base plates are tried-in with all the teeth. After the approval of both clinician and patient, the complete dentures are processed and delivered to the patient.[7] This is the conventional technique, which is the most widely taught technique for complete dentures worldwide. However, there is a lack of evidence that this strict protocol is necessary for a functional and esthetic complete denture outcome. This raised the dilemma of whether the procedure could be simplified by reducing the clinical appointments. There is insufficient evidence for the necessity of the clinical step of the final impression. Are two impressions -a preliminary and a final one- a prerequisite for the success of a complete denture? This

question was the initiative for fabricating complete dentures with a simplified technique.

There are protocols in the literature which suggest the fabrication of dentures with five, four, three or even two clinical visits. It is worth mentioning, that combining the two sessions of try-in into one, converts the conventional technique into a five-step procedure. However, this is still considered conventional. It is, therefore, important to clarify which steps are omitted in the simplified technique. As implied before, a simplified protocol does not include a final impression. Thus, a five-session protocol with only one impression is called simplified while a five-session protocol with two impressions but one try-in is still considered conventional. The five-session simplified protocol is described by Lira-Oetiker et al.[8] In their trial they performed two separate clinical sessions of try-in, but only one impression. In more details, for Lira-Oetiker et al[8] the conventional protocol consisted of six clinical sessions: a) preliminary impression with a stock tray and alginate, b) final impression with custom tray, compound and zinc oxide impression paste, c) maxillomandibular records, d) selection of teeth/try-in e) final try-in/patient's and clinician's approval of the denture, and f) delivery of the denture. The test group of this trial received complete dentures fabricated by the simplified protocol. This was described as a five-session protocol as following: a) impression with stock tray and alginate, b) maxillomandibular records, c) selection of teeth/try-in, d) final try-in/patient's and clinician's approval of the denture, and e) delivery of the denture. The only difference between the two protocols used in this trial is the omittance of the final impression. However, Lira-Oetiker et al[8] was the only research group who used a five-session simplified protocol. Reviewing the literature, the most common simplified protocol used is the four-session one, which includes a preliminary impression, maxillomandibular records, a try-in, and the complete denture delivery. The majority of the researchers omit besides the final impression also the second try-in session in the simplified protocol. That converts the simplified protocol into a four-session one. The four-session simplified protocol is thoroughly described by Duncan and Taylor.[9] In the first session the clinician apart from the medical and dental history and the examination of the patient, makes an impression of alginate using a stock tray, either metallic or plastic. This is the only impression required for the fabrication of the complete denture. The prerequisite for this simplified technique to be successful is, according to the writers, the knowledge of the oral anatomy. It is crucial to know which anatomical landmarks are necessary to be recorded. An interesting suggestion for this abbreviated method is that alginate should be syringed not only on the tray but also directly in the oral cavity on which the tray will be seated. The cast produced from this impression is the final cast on which the record bases with the occlusal rims are fabricated. In the next session is the recording of the maxillomandibular relationship. In the try-in session the clinician and the patient evaluate the aesthetics of the denture and test the phonetics by the pronunciation of specific words and sounds. This session is of high importance because it is the last chance to make changes. Minor changes can be made chairside, while major ones have to be tested in another session. Therefore, in order to continue

with the delivery of the denture, both the patient and the clinician have to accept the denture at this session.[9] Owen and MacEntee[10] described a three-session simplified protocol defined as 'abbreviated complete denture technique' or 'minimum acceptable protocol (MAP) for complete dentures'. According to this, the anterior teeth are arranged by the clinician in the second session simultaneously with the maxillomandibular records. In other words, in the first clinical session the impression is made. With the assistance of a preformed anterior tooth arrangement guide (ANTAG) the position of the maxillary anterior teeth is defined. Then, there is a second session for the maxillomandibular records. Apart from this, the clinician rearranges if needed the anterior teeth on the occlusal rim which are positioned from the technician according to the information of ANTAG and performs their try-in. The rest of the teeth will be placed in the laboratory by the technician who continues with the setting of the denture. In the following clinical session, the denture is delivered to the patient. Compared to the four-session protocol, the three-session one, as described from Owen and MacEntee[10], combines two clinical steps (maxillomandibular records, try-in) into one. Interestingly, in this protocol the patient never tries the dentures with all the teeth before the delivery.[10] Ceruti et al[11] used another version of a simplified protocol. This version consists of only two clinical sessions and is defined as 'simplified edentulous treatment (SET)'. The impression, the maxillomandibular records, the selection of the teeth and the try-in of the anterior teeth are performed in the first clinical session. After that, the technician completes the arrangement of the teeth and finalizes the denture. Therefore, in the next and last clinical session the denture is delivered. This protocol is possible only by using a specific material fabricated for this purpose. It is called the multilayer impression tray (MIT), consists of light-polymerizing composite resin, and can be adapted to each patient chairside. When adapted, it is polymerized and used as a baseplate. An occlusal rim is placed and adapted on the baseplate with which the maxillomandibular records will be made. The selection of the teeth occurs with adhesive paper teeth. The baseplate will be relined with a polysulfide impression material in order to make an accurate impression of the intaglio surface. This protocol is only possible because multiple clinical steps are performed in one session.[11,12] As we can conclude from all the different protocols, there are clinical steps which cannot be omitted. So, the steps of at least one impression, the maxillomandibular records, a try-in with all or some of the teeth selected and the delivery cannot be omitted. Some of them may be combined in one session, but they definitely have to be performed. Apart from all the differences, none of the simplified protocols includes a second impression session. The clarification of these protocols and their stages are shown in Table 1. The stages of the conventional and the most used four-session simplified protocols are shown in Figure 1 (Fig. 1) The simplified protocol aims to a shorter procedure of fabrication of the complete denture. Therefore, the use of a facebow and the remount of the denture in order to perform selected grinding before delivery, are usually omitted.

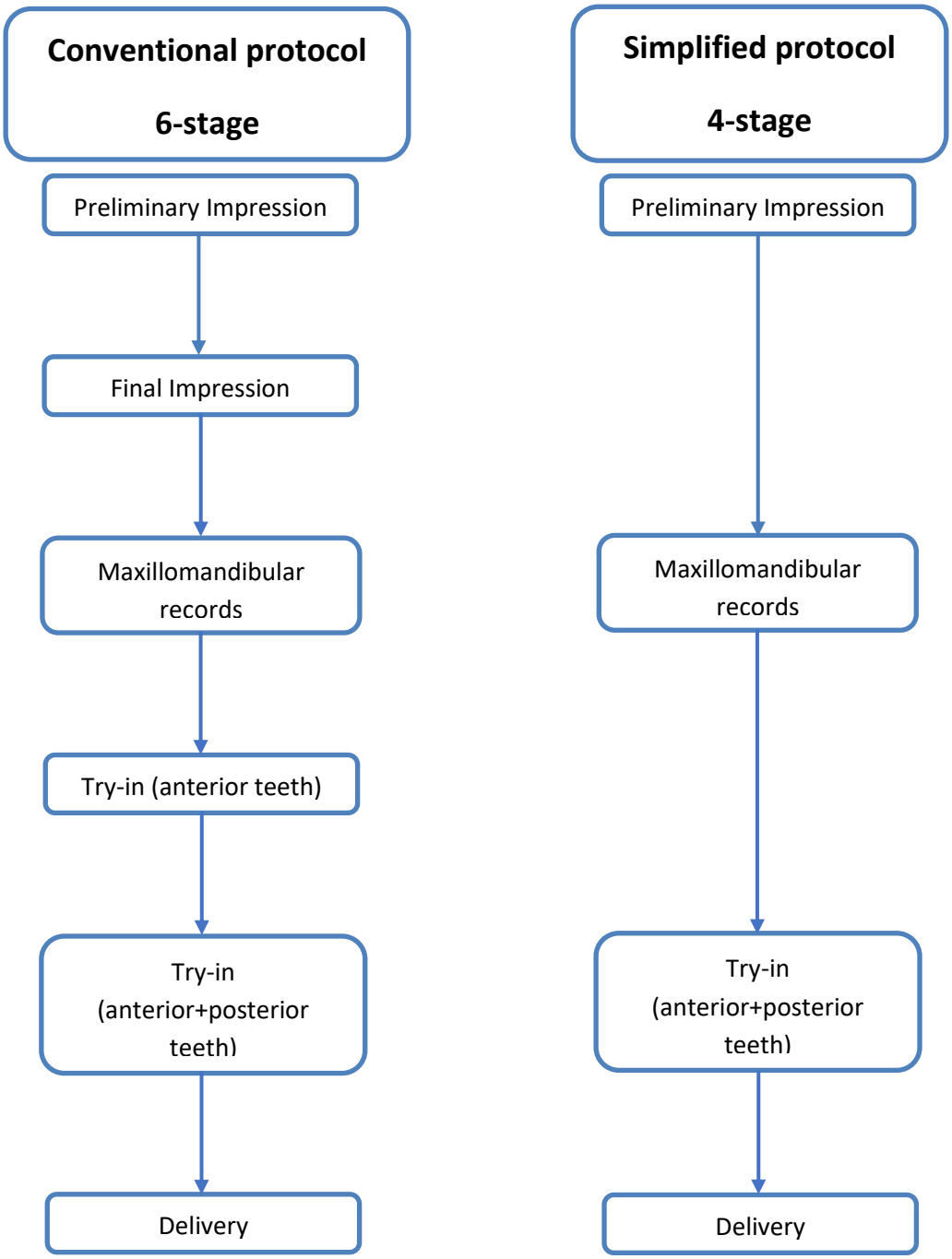
In order to replace an established protocol with a new one, it is necessary to have adequate evidence that the new protocol offers the same outcome with the previous

one, if not better. In other words, does the simplified technique for the fabrication of complete dentures have better outcomes compared to the conventional technique? The aim of this systematic review is to report on the current evidence and evaluate the differences between the simplified and the conventional method for fabrication of complete dentures and do a narrative comparison in order to conclude if the simplified technique is equal to or better than the conventional one. The outcomes to be evaluated are masticatory performance and ability, patient satisfaction, oral health related quality of life (OHRQoL), denture quality, time, cost, and cost effectiveness. The null-hypothesis is that the simplified protocol results in superior outcomes compared to the conventional protocol.

Table 1: Stages of conventional and simplified complete denture fabrication protocol

	Conventional protocol		**Simplified protocol**			
Sessions	**6 stages**	**5 stages**	**5 stages**	**4 stages**	**3 stages**	**2 stages**
Preliminary impression	X	X	X	X	X	X
Final impression	X	X				
Maxillomandibular records	X	X	X	X	X	X
Try-in (anterior teeth)	X		X		X	X
Try-in (anterior+posterior teeth)	X	X	X	X		
Delivery	X	X	X	X	X	X
Comments	Most common	Not common	Lira-Oetiker 2018	Most common	Owen & MacEntee	SET Ceruti 2017

Fig. 1: Flowchart of the conventional and the simplified protocol



MATERIAL AND METHODS

The present systematic review has been conducted according to the PRISMA instructions.[13] The protocol of this systematic review was submitted to PROSPERO (ID 160603), an international prospective register of systematic reviews and meta-analyses. An electronic search of the MEDLINE-PubMed, Scopus and Europe PMC databases was conducted by two independent researchers (PE and SA). The inclusion criteria were randomized clinical trials, cohort clinical studies and clinical studies of complete dentures fabricated either with the conventional or the simplified method. The PICO details can be seen in Table 2. The PICO question was formed as such: 'Does the simplified technique for fabrication of complete dentures provide equal or even better outcomes than the conventional technique to the treatment of the edentulous patients?' All relevant studies should have been published in English from January 1950 to January 2020. The keywords used in the search included a combination of the following terms: Simplified OR conventional (technique OR method OR fabrication OR construction) AND complete dentures AND patient satisfaction AND/OR cost AND/OR time AND/OR masticatory ability AND/OR ability to speak AND/OR success of the complete dentures AND/OR performance ability. The results from the electronic search were screened based on the relevance of the titles to our topic. Any disagreement between the two reviewers was solved in consensus by discussion or by a third reviewer (CA). Articles that appeared multiple times during the search were considered only once. Following that, the abstracts of the articles chosen were read to identify if they met the inclusion criteria. The full-text articles were then obtained and reviewed if this determination could not be made only with the abstracts. Excluded were articles written in other languages than English and studies referring to implants, overdentures, immediate dentures and/or fixed partial dentures. Furthermore, studies that did not compare the two aforementioned methods were excluded, even if they could provide information about each technique separately.

The main difference between the two protocols -conventional and simplified- is the session of the final impression. If the clinician performs two impression sessions-one preliminary and one final- then the protocol used, is called conventional. When the clinician takes only one impression from which the final casts will be fabricated, then we have the simplified protocol.

The outcomes evaluated were masticatory performance and ability, patient's satisfaction, oral health related quality of life (OHRQoL), denture quality, time, cost, and cost effectiveness.

As part of the data extraction process, two reviewers (PE, SA) independently assessed the risk of bias in the included studies individually. Bias is defined as the tendency for the study results to differ systematically from the result expected from a randomized trial (RT) conducted on the same participant group that has no flows in its conduct. This could be avoided in a trial with a very large number of participants, where all people involved were blinded throughout the whole process and all the findings were

registered. The aim of a study group is to include participants who represent the general population. The larger the number of the participants, the more likely it is to have a representative sample. Simultaneously it is more likely to have selected people with similar characteristics which otherwise could be held as confounding to the result. It is equally important for all the people included to be blinded. This refers not only to the participants but also to the researchers who conduct the trial, the professionals who assist during the trial and even the outcome assessors. By registering all the data, even if they seem irrelative during the trial, it is assured that nothing is overlooked, and everything can be compared. In that way the researchers can result to more valid conclusions. Taking all these aspects into serious consideration, factors that could affect the result are eliminated or at least constricted, the risk of bias is reduced, and the results of the study are useful.[14]

In the present study, the risk of bias for randomized clinical trials was assessed according to ROBINS 2 (RoB 2). The tool consists of twenty-two (22) questions organized in five domains. The purpose is to discover biases that affect the result. Such biases can be found in every step of a trial therefore the questions refer to all the stages, from the planning of the trial to the results found. More specifically, the domains aim to cover all types of biases i.e.: a) bias arising from the randomization process (3 questions), b) bias due to deviations from the intended interventions (7 questions), c) bias due to missing outcome data (4 questions), d) bias in measurement of the outcome (5 questions) and e) bias in selection of the reported results (3 questions). There are five possible responses for each question: Yes (Y), Probably Yes (PY), Probably No (PN), No (N) and No Information (NI). 'Yes (Y)' and 'Probably Yes (PY)' are answers with the same impact because the term 'probably' implies that the aspect questioned has been taken under consideration from the researchers, can be retrieved from the context, but is not mentioned clearly in their publication. The same applies to the answers 'No (N)' and 'Probably No (PN)'. The answer 'No Information (NI)' is used in cases of absence of the information asked. In cases where clarifications are needed, the reviewer can and should contact the researchers for further details. The answers in each domain are combined through an algorithm and result to a risk-of-bias judgement. In the end, another algorithm combines the risk-of-bias assessment of each domain and gives an overall risk-of-bias assessment of the study. As the questions are predetermined and the same for every evaluation, there is a section in each domain where the reviewer can write comments and clarifications which, according to his opinion, have to be mentioned. Moreover, the reviewer characterizes the risk of bias in each domain and overall, irrespectively of the result of the algorithm. More important is the fact that the reviewer can overcome the algorithm and change the assessment if he judges this is appropriate. The risk-of-bias assessment can be low, high or with some concerns. The lower the risk of bias, the more valid the result of the trial. In order to characterize a trial as of 'low risk' of bias, all domains should be separately judged at 'low risk'. If at least one domain is judged 'with some concerns' or at 'high risk' of bias, then the overall assessment is 'with some concerns' or at 'high risk' accordingly. The trials that are judged with some concerns

in several domains are also at high risk of bias. In other words, the most severe assessment in a domain defines the overall assessment. The questions of each domain with elaboration and a diagram of the algorithm can be seen in Appendix 1.[15]

The study of Duncan et al 2001[20] was the only study included in this systematic review which was not randomized. Therefore, a different tool for accessing the risk of bias was used (ROBINS-I). ROBINS-I is based on the Cochrane ROBINS 2 (RoB 2) and therefore there are similarities. It is used for Non-Randomized Studies of Interventions (NRSI) and aims to evaluate the effect of an intervention in a quantitative study. To evaluate the result of a study, the effect of the intervention has to be applicable to the general population. In the non-randomized trials, the participants are not randomly chosen. This could lead to a serious bias. In order to overcome this and evaluate the risk of bias of the study, the reviewer traces the non-randomized trial to a hypothetical randomized one. More specifically, the reviewer tries to control the confounding factors between the participants. This is done with precaution and only to make it possible to run the test. Contrary to the RoB 2, ROBINS-I covers seven domains: a) bias due to confounding-(8 questions), b) bias in selection of participants into the study-(5 questions), c) bias in classification of interventions-(3 questions), d) bias due to deviations from intended interventions-(6 questions), e) bias due to missing data-(5 questions), f) bias in measurement of outcomes-(4 questions), and g) bias in selection of the reported result-(3 questions). The first two domains-bias due to confounding and bias in selection of participants into the study-include questions about the planning of the study before the intervention. The first domain includes eight questions and aims to examine the possible confounding factors that may influenced the study. 'Bias in selection of participants into the study' consists of five questions investigating if the exclusion of some participants prior the study could have influenced the outcome. The third domain-bias in classification of interventions-focuses on the intervention itself and if it was somehow misclassified prior the study. It is important to collect information about the intervention and if this was clearly defined from the beginning of the study so as not to interfere with the outcome. In these three domains, the hypothetical pragmatic randomized trial is formed, and the lack of randomization is overcome. The remaining four domains are similar to the domains of the RoB 2 and address issues after the start of the interventions. 'Bias due to deviations from intended interventions' evaluates through six questions if the intervention is the only care that the participants received. In order to obtain this information, detailed data should be collected. Generally, the most difficult part of an observational study is the collection of the data because some of them may not be recorded. Missing data can cause bias in a study and this is tried to be assessed through the next five questions ('bias due to missing data'). The last two domains refer to the outcome. 'Bias in measurement of the outcome' consists of four questions about possible errors when measuring the outcome. Possible errors could arise from the participants or the researchers being aware of the intervention and/or the method used. The last domain ('bias in selection of the reported result') includes three questions about the possibility of using more than one methods to measure the

outcome. It has to be clarified which method is the most appropriate one and if this one has been used in all subgroups of the participants and the impact on the results in case different methods have been used. The possible responses do not differ between the two assessment tools {Yes (Y), Probably Yes (PY), Probably No (PN), No (N), No Information (NI)}, but the risk-of-bias assessment does. In each domain and overall, the possible assessments are low risk of bias, moderate risk of bias, serious risk of bias, critical risk of bias and no information. The assessments are presented progressively. A study can be judged at an overall 'low risk' of bias only if all domains are at 'low risk'. In case, all domains are at 'low' or 'moderate risk' of bias, the overall risk of bias is 'moderate'. At least one domain at 'serious risk' is enough to characterize the study at an overall 'serious risk' of bias. The same happens with critical risk of bias. As it was mentioned for ROBINS 2 tool (RoB 2), the most severe assessment in a domain defines the overall assessment. A study at 'low risk' of bias means that it is comparable to a randomized one. This is especially rare because of the numerous confounding factors between the participants which are often not mentioned. A study at 'moderate risk' of bias is a sound study but cannot be equalized with a randomized one. In the other three assessments options ('serious risk of bias', 'critical risk of bias', 'no information'), the study presents such important problems that their evidence on the effect of the intervention should be presented either with precaution or is not useful at all. These seven domains and their questions with elaboration can be seen in Appendix 2.[14]

The risk of bias across the studies was evaluated by GRADE, which is a system for rating the quality of a body of evidence in a systematic review. The quality of evidence reflects the extent to which the reviewers are confident that an estimate of the effect is correct. The importance of the GRADE system is that clinical recommendations can be given only after completing the evaluation of the outcomes through the GRADE system. To begin with, PICO question has to be clarified. According to the GRADE system, the outcomes are categorized as critical, important but not critical and not important. The last-mentioned category will not be included in the evaluation. The characterization of each outcome is according to the importance of the outcome for the decision making for the treatment of a patient. The rating of the quality of the evidence begins with the study design. Randomized clinical trials (RCTs) provide stronger evidence than observational studies. The GRADE system consists of eight factors: five of them can possibly lower the quality of evidence and three of them can increase it. The five factors that can negatively affect the quality are: the risk of bias of each study individually, the inconsistency of the results, the indirectness of evidence, the imprecision and the publication bias. On the other hand, the large magnitude of the effect, the dose-response gradient and the confounders can increase the quality of evidence. The real effect of each factor on the evaluation is under the reviewers' judgement. All the outcomes included in the GRADE system, are evaluated by the reviewers separately and summarized in a table. The evaluation of evidence can be rated as high, moderate, low or very low. The lowest rating of the critical outcomes defines the overall rating. High GRADE means stronger evidence. The next

step is to make recommendations and formulate guidelines. The GRADE approach can lead to clinical recommendations, which is the next step, however this cannot be done through a systematic review and it is assigned to the guideline developers.[16]

The different studies included in the present review examined different factors. Due to this reason, they were compared in subgroups. The studies that evaluated similar factors and outcomes were grouped together for further analysis and narrative description. The presence of multiple factors and therefore subgroups made it impossible to conduct a statistical analysis of the results.

Table 2: PICO question

Participants/**P**opulation	Patients in need of a complete denture.
Intervention	Patients treated with a complete denture fabricated by the simplified technique.
Comparison	Patients treated with a complete denture fabricated by the conventional technique.
Outcome	Masticatory performance and ability, patient satisfaction, oral health related quality of life (OHRQoL), denture quality, time, cost and cost effectiveness.

RESULTS

The electronic search of databases produced 474 titles of articles relevant to the topic. 403 articles were duplicated and therefore excluded. After reading the abstracts, 22 articles were rejected because they also referred to other prosthetic rehabilitations (apart from complete dentures) such as overdentures and fixed partial dentures. Full text was obtained from the remaining 49 articles and only 19 of these fulfilled the inclusion criteria. All of the included studies were clinical trials, 18 of which were randomized clinical trials (RCT). The electronic search resulted also in the identification of two systematic reviews and one meta-analysis on the comparison between the conventional versus the simplified technique for complete denture fabrication. Their limitation was that none of these papers examined all the outcomes, but rather they focused on some of them. Furthermore, additional research has led to newer evidence on the topic since then. Our systematic review aims to overcome this limitation and include all the available information. We included these papers in the discussion section of the present review in order to compare their results with ours and identify any differences. The flowchart for the selected articles used in this systematic review can be seen in Figure 2. The characteristics of the studies included are listed in Table 3.

In the same table the risk of bias of each study individually is presented. All the included randomized studies except of the one, were at low risk of bias. The RoB 2 assessment results applied to 18 of the included studies are presented in Table 4. For the study of Krishna at al[27] there were some concerns about the risk of bias. This doubt was raised from the randomization process because of lack of information. More specifically, the patients were divided randomly, but it was not mentioned whether they were informed about receiving the intervention or not prior to the start of the trial. Moreover, it was not mentioned if there were any confounding factors in the demographic characteristics between the groups. As stated in the Material and Methods section, the most severe assessment defines the overall risk of bias. Therefore, the study of Krishna et al[27] is characterized 'with some concerns' although all the other domains are at low risk. However, it is worth mentioning that no study was at high risk.

The study of Duncan et al[20] was the only one evaluated with a different risk of bias assessment tool (ROBINS-I). According to the algorithm of the tool, one domain is characterized as 'no information' and another one is at 'serious risk'. In the fifth domain there is lack of information about exclusion of possible participants. The authors do not mention if the participants selected were chosen after excluding some others perhaps because of missing records. In this case it is possible to also have excluded participants due to their answers and that could set the study at critical risk. There is no information about possible exclusion and therefore the domain is characterized accordingly. The sixth domain results at serious risk. The reason for that is the second question. It is impossible for the outcome assessors not to be aware of the intervention that each participant received. The positive answer to this question automatically rises the risk of bias at serious. However, the trial focuses on the number of visits needed for the fabrication of the denture and after its delivery, and the need

for reline. These information were recorded prior to the start of the research and it is highly improbable that these could be anyhow affected. The fact that the researchers knew about the intervention received could not affect the outcomes or their interpretation. Therefore, the authors of the present review concluded that the algorithm overestimated the risk of bias of this domain, and this should be low. Nevertheless, the fifth domain remains as 'no information' and as mentioned in the Material and Methods section the most severe assessment in a domain defines the overall assessment. Therefore, the overall assessment for this study is 'no information' and its results should be presented with precaution. The results of ROBINS-I are presented in Table 5.

Table 6 presents the impression techniques and the different materials used for final impression in each study. The study of Hyde et al[21] is not included in Table 6 because it is not possible to include it in any of the mentioned categories. The reason is that the authors compared both impression materials (alginate, silicone) in the impression stage with a custom tray.

The study of Mengatto et al[28] could not be enlisted in any category of the materials used for the final impression, because the materials used were not clarified, but rather were mentioned under the general term 'compound with an impression material'. As observed from the same table, Ceruti et al[11] used the SET method for the test group. SET stands for simplified edentulous treatment and it is performed with a multilayer impression material. This material is formed intraorally and then polymerized and used as a baseplate. On this baseplate, an occlusal rim is placed in order to record the maxillomandibular relationship and after that a polysulfide is used to take an impression of the intaglio surface. Although the SET protocol is only used by one study, it still remains a simplified procedure for fabricating complete dentures and therefore this study meets the inclusion criteria of the present review and can be compared with the other studies. Interestingly, in the test group of the study of the de Resende et al[19] group, the baseplate in the clinical session of the try-in was relined with zinc oxide and eugenol. However, the procedure was defined and considered as simplified by the authors.

As observed in Table 3, the included studies examined different variables. In an effort to assess the studies' outcomes more comprehensively, the different studies were categorized based on their examined outcomes (Table 7). It is worth mentioning that five outcomes (complete denture's functional activity, clinical outcomes, occlusal contact area/maximum occlusal force, cost effectiveness, and need for reline) were examined only by one different research each. This probably occurs because the definition of each outcome differs between the study groups. Therefore, we included studies, that examined similar variables but named them differently, in the same category in order to draw more robust conclusions (Table 8).

Complete denture's functional activity and clinical outcomes studied by de Resende et al[19] and de Villa Camargos et al[17] respectively, can be summarized under the general term 'quality of the complete dentures'.

Komagamine et al[26] focused on the masticatory performance of the patients but the authors also added two extra variables, i.e. the occlusal contact area and the

maximum occlusal force. According to our opinion these two factors were in fact the other side of the same coin. According to Lepley et al[33], the greater the occlusal contact and the bite force, the better the masticatory performance. Horie et al[34] also exhibited that the occlusal contact and the near occlusal contact areas related significantly with the mixing ability. However, the study involved dentate patients. Since a relevant study for denture wearers does not exist, we have to consider their results with precaution.

Comfort, stability, esthetics, ability to speak and chew different specific items and ease to clean are examined with questionnaires and therefore their evaluation is based on subjective information. We agreed that each one of these factors expresses part of the satisfaction that the patient gets with their complete dentures. Therefore, they could be grouped under the general term 'patient satisfaction', despite the fact they were examined separately in some of the included studies (Kawai et al 2005[23], Kawai et al 2010[24], Lira-Oetiker et al 2018[8] and Mengatto et al 2017[28]).

Cost effectiveness and the need for reline were analyzed separately and individually.

Hyde and Krishna[21,27] focused only on the impression stage and tried to find differences in that stage only. The research group of Hyde[21] examined the influence of the material used on the dentures that were delivered. More specifically, Hyde et al[21] delivered two sets of complete dentures to all the participants. One set was fabricated from an alginate impression and the other from a silicone impression. They examined which denture was superior according to the patients. The impression material of choice in the simplified protocol is the alginate. Therefore, it is implied that the dentures fabricated from an alginate impression represent the simplified method, whether the silicone impression represents the conventional one. On the other hand, Krishna et al[27] did made only one impression in the tested group in contrary to the control group where two impressions -a preliminary and a final- were made. The difference of this trial is that the impression used in the simplified method is silicone and not alginate. The fact that Hyde et al[21] examined the same subject from an indirect aspect and that Krishna et al[27] used materials that no other research group used, are the reasons why these studies are mentioned separately. Although the differences in their trial protocol, they focused on outcomes already existing in the first categorization (Table 7) and so they are enlisted accordingly.

It is evident that the majority of the studies focused mainly on aspects of patient quality of life (patient satisfaction and OHRQoL).

The quality of evidence is examined for each outcome separately. According to Table 8 cost-effectiveness and the need of reline were examined only by one study and therefore the GRADE approach cannot be used for them. Moreover, as mentioned before the studies of Hyde and Krishna[21,27] were categorized separately in Table 8 under the term 'impression' although the impression method is not an outcome. The GRADE results can be summarized in the Summary of Findings (SoF) table (Table 9). The quality of evidence in this systematic review was high for each outcome, mainly due to the low risk of bias of all but two studies and the homogeneity in their respective design. The fact that all studies did a power analysis to determine the study

sample size and used a level of significance at 5% affected positively the quality of evidence. The study of Krishna et al[27] and Duncan et al[20] did not result in low risk of bias, however that did not affect the GRADE evaluation according to the reviewers' judgement.

Masticatory performance

Alves[7] tried to associate the masticatory ability based on the method used (simplified versus conventional) and on some sociodemographic characteristics. These characteristics were: age, gender, bone height and previous complete dentures. No difference on masticatory ability was found between the two techniques. When evaluating the sociodemographic variables, only gender was found to have a statistically significant difference with women presenting lower masticatory performance than men.

Cuhna et al[18] differentiated the masticatory ability from the masticatory performance. According to this study, masticatory performance is something objective that can be tested by the clinicians. In contrary, the masticatory ability refers to the patients' opinion of how they perceive their masticatory function. Although masticatory performance was measured according to different number of chewing cycles (20 and 40) the researchers could not find a difference between the two groups. There was also a third group in this study that consisted of dentate patients. As expected, there was a significant difference between the dentate patients and the patients wearing a complete denture. However, there was an improvement when the patients with complete dentures chewed 40 rather than 20 times and this suggests that these patients can achieve a good masticatory performance if they have patience and persistence. Subjectively, patients with complete dentures fabricated with the simplified technique are presumed to have no difficulties in mastication in contrary to the control group. This was the only difference between the groups which did not affect the overall insignificant score.

Interestingly, Komagamine et al[26] included as their study outcomes the occlusal contact area and the maximum occlusal force apart from the masticatory performance. It was an attempt to examine masticatory performance from other measurable aspects and probably an attempt to associate the results, which they failed to show. More specifically, dentures fabricated by the conventional method had a statistically higher occlusal contact area than the simplified dentures, but this did not relate with a better mixing of the food. This was attributed to the fact that all the measurements were performed only 1 month after delivery and this interval may have been too short and that the final impression may provide more stable acrylic resin bases and occlusion rims during the following sessions.

Similar to de Villa Camargos et al[17], Mengatto et al[28] found no difference in the masticatory performance depending on the protocol used. In other words, there is evidence in all these studies that the method used to fabricate a complete denture does not affect the masticatory performance and ability and both techniques are held as equal.

Patient satisfaction

Many studies focused on the patient satisfaction and the influence that the fabrication method has on it. Only two of them found a significant difference between the two methods. Jo et al[22] documented that the conventional method was preferred among the patients because the final impression ensured more detailed borders and therefore increased stability and comfort of the complete denture. Hyde et al[21] emphasized on the impact of the impression material. His team fabricated two sets of complete dentures for each patient, one obtained after an alginate impression and the other obtained from a silicone impression. He concluded that the patients preferred the dentures fabricated from a silicone impression. All the other studies proved the two methods to be equal (Komagamine et al[26], Kawai et al[23,25], Krishna et al[27], Lira-Oetiker et al[8], Mengatto et al[28], Nunez et al[30], Regis et al[31]). The only difference was that the satisfaction increased in both groups respectively following the time and the use of the complete dentures (Nunez et al[30], Regis et al[31]). Kawai et al.[23] on the other hand concluded that there is increase of satisfaction in 3 months compared to the baseline, but they found a significant decrease in 6 months. This phenomenon was noticed in both categories making them not to differentiate. It is remarkable that after 10 years Kawai et al[25] still found no difference between the control and test group except of esthetics. Patients with simplified dentures were significantly more satisfied with the maxillary denture's esthetics after 10 years. Komagamine et al[26] and Krishna et al[27] failed to prove the improvement over time because of the short-term follow up.

Oral Health Related Quality of Life (OHRQoL)

The OHRQoL test is performed by a series of questionnaires. The basic questions are universal (OHIP-Edent) but every country has added questions relevant to their population and their lifestyle in order to get more specific answers. OHRQoL showed no difference between the two examined methods among all the studies. Nunez[30] discovered a decrease of OHRQoL over the months which means an improvement in quality of life for all the patients regardless of the method used. Hyde et al[21] compared the two methods indirectly emphasizing on the impression stage. He evaluated the OHRQoL with the OHIP-Edent questionnaire and found a difference between the two techniques in favor of the denture fabricated from a silicone impression.

Quality of complete dentures

The complete dentures included in each trial were fabricated by the same technicians, therefore it was highly improbable to find a difference among the complete dentures. As expected, none of the trials found a difference in the quality of the complete dentures. Impeccable proof for this was provided by the study group of Kawai et al.[23] They let prosthodontists, blinded the trial, to objectively examine the quality of the dentures and the results were similar for conventional and simplified dentures.

Time

Five clinical trials focused on the time spent for the treatment plan. Kawai et al[24] used a more general term and measured the time spent for the treatment plan. On the other hand, Ceruti et al[11] measured the time needed for each step, such as clinical time, number of clinical sessions but also the laboratory time and the laboratory returns. The research group of de Resende et al[19] separated time in two major categories: the time needed from the consultation until the delivery of the dentures and the time needed for adjustments. The latter is something very important because it reflects also on the quality of the denture in terms of stability and retention. It is beneficial to mention the adjustment period separately. The two methods have to be compared regarding the need for adjustments after delivery. Most of them had a strict protocol with three or four visits. However, all studies mentioned that the clinicians continued the follow-up appointments until the patient was feeling comfortable with the dentures. If the number of visits for adjustments was outnumbered for one method, then this could be a critical clinical issue. If simplified dentures reduced time until delivery but needed more sessions after delivery, then it cannot be cost effective but such a difference between the two methods was not proven. Such a differentiation in time did also Duncan et al[20]. The researchers caclulated the visits needed to fabricate the complete denture and separately the visits needed for adjustments. The results in both outcomes were statistically significant favoring the simplified protocol. Krishna et al[27] limited their evaluation to the number of visits. Generally, it was agreed in all studies that the simplified method was faster in clinical time and clinical sessions than the conventional method.

Cost

Cost of denture fabrication was evaluated in three clinical trials. All of them agreed that the cost of a conventional method was significantly higher than the cost of the simplified one. Kawai et al[24] attributed the difference in cost to the final impression step and to the remount of the denture before the delivery. Miyayasu et al[29] and Vecchia et al[32] considered also under the term of cost the time spent from the professionals. Vecchia et al[32] evaluated also the time that a patient needs to spend for their treatment from the time a patient exits their house until their return. Although the interpretation of cost differs between the studies, all three came to the same conclusion, that conventional method costs more than the simplified method.

Cost effectiveness

It is rational to think that studies which examined cost and time would have also evaluated cost effectiveness. However, the only study group that referred to cost effectiveness was Miyayasu et al[29]. According to them cost effectiveness is a combination of cost and patient satisfaction where time is also considered under the term of cost. Miyayasu et al[29] found cost to be statistically higher in the conventional group. In a previous study (Jo et al 2015[22]), the same study group found satisfaction

of the conventional method to be statistically higher than the simplified method. To result in a conclusion about cost effectiveness, we have to quantify the cost and the patient satisfaction, as cost effectiveness is the result of the division of the cost with the satisfaction. Following this simple mathematical procedure, the authors concluded that cost effectiveness is higher for the conventional group.

Need for reline

The study by Duncan et al[20] was the only one referring to the need of reline. This need and more specifically the time when this occurs, reflects not only the quality of the denture but also the effectiveness and precision of the impression technique. Although the thought is very good in this case, we cannot draw any conclusion because the evaluation happened three months after the delivery. It is impossible in such a short time to occur the need of the reline of the denture base.

Impressions

The electronic search resulted in two articles relevant to our topic and included in the present review that focused on the stage of final impression. Hyde et al[21] and Krishna et al[27] studied the effect of the presence or absence of the final impression on the denture delivered. In an indirect way, they compared simplified and conventional method and that is why we included them in this systematic review. Hyde et al[21] concluded that the conventional method resulted in superior dentures according to the patients. Krishna et al[27] found only a statistically significant difference in time but except from that the two methods did not differ. This outcome is in agreement with the rest of the literature.

Fig. 2: Flowchart illustrating study selection process.

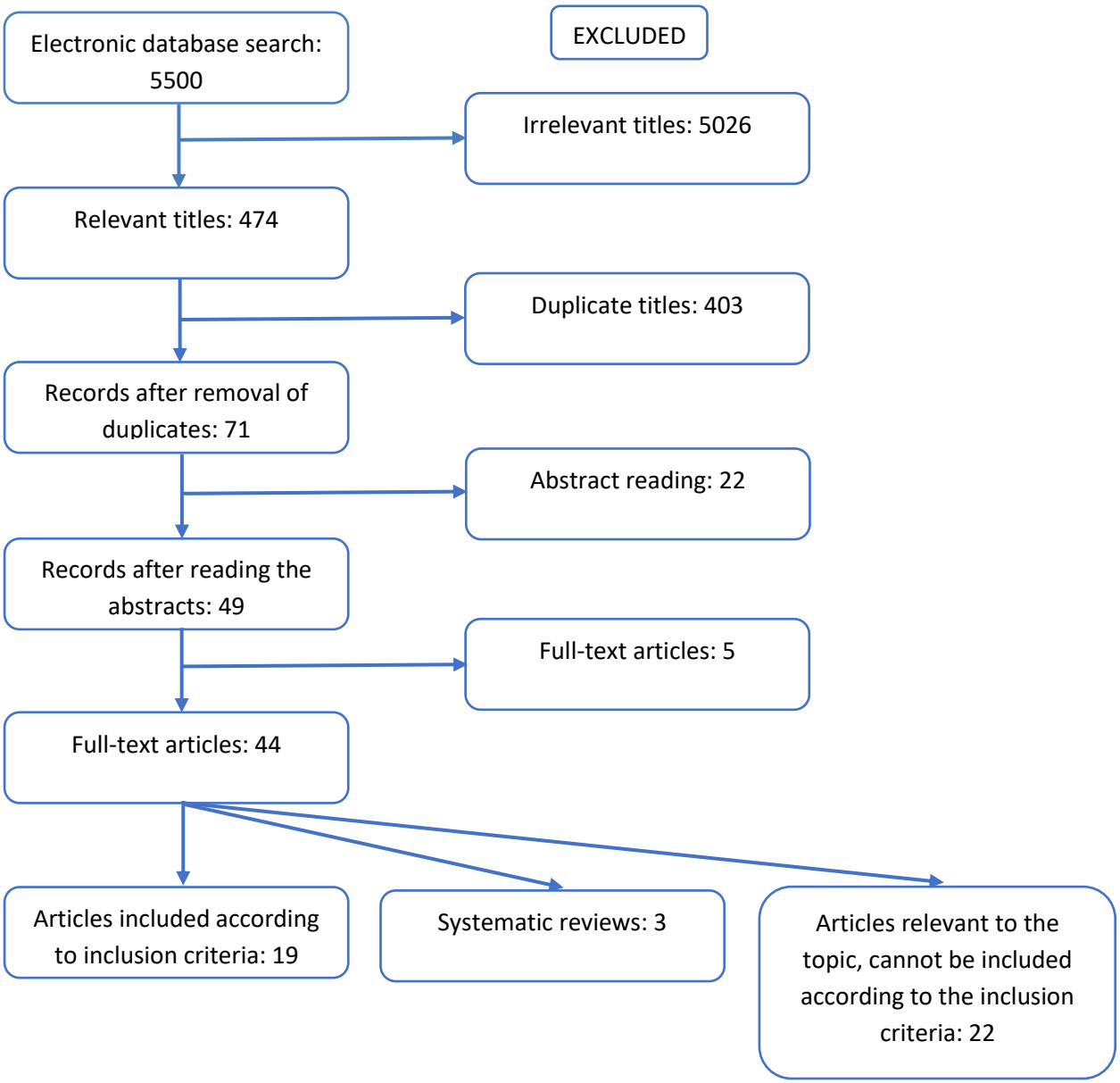


Table 3: Summary of the study characteristics included in the systematic review

Study	Study size	PICOs	Baseline	Follow up period	Risk of bias
Alves et al 2018[7]	38(19 C, 19 S) **pt completed the study: 29(15 C, 14 S)**	P: edentulous for at least 1 year I: S C: C O: masticatory performance	After adjustments (3-4 weeks)	4 weeks after the last adjustment =2 months after the delivery	Low
de Villa Camargos et al 2019[17]	36(18 C, 18 S) **pt completed the study: 12 C, 12 S**	P: edentulous for at least 1 year I: S C: C O: OHRQoL, Satisfaction, Denture functional quality, masticatory performance	After adjustments (2 weeks)	1, 3, 6 months after the last adjustment Masticatory performanc e only at 3 months.	Low
Ceruti et al 2017[11]	64 (32 C, 32 SET)	P: edentulous for at least 2 years I: SET=S C: C O: Clinical time, number of clinical sessions, lab time, lab returns, patient satisfaction, quality of CD	Delivery	6 months after the delivery	Low
Cuhna et al 2013[18]	42(21 S, 21 C) **pt completed the study: 19 S, 20 C**	P: edentulous for at least 1 year I: S C: C O: masticatory performance and ability	After adjustments (2 weeks)	3 months after the last adjustment	Low
de Resende et al 2019[19]	92(42 T=C, 50 S) **pt completed**	P: edentulous I: S C: C		3 months for the questionnai res	Low

	the study: 30 C, 38 S	O: Quality of CD, clinical outcomes, PROMs, time, OHRQoL			
Duncan et al 2001[20]	80(40C, 40S)	P: edentulous I: S C: C O: number of visits for fabrication, number of visits for adjustments, need for reline	Delivery	3 months after the delivery	No information
Hyde et al 2014[21]	85 **pt completed the study: 72**	P: edentulous I: dentures made from silicone impressions C: dentures made from alginate impressions O: Preference of silicone or alginate, OHRQoL, comfort, stability, chewing ability, patients' experience		Impression Habituation period Adjustment period Confirmation period	Low
Jo et al 2015[22]	27(14 C-S, 13 S-C) **pt completed the study: 13 C-S, 11 S-C**	P: edentulous I: S C: C O: General satisfaction, OHRQoL	After adjustments =4 times a week???	1st phase: C/S 1 month after adjustments ASSESSMENT Wash out phase=1 month wearing old CD 2nd phase: S/C 1 month after adjustments ASSESSMENT	Low
Kawai et al 2005[23]	119(58 T=C, 61 S) **pt completed the study:**	P: edentulous I: S C: C	Delivery	3 and 6 months after the delivery	Low

	3m 53 C, 55 S, 6m 51 C, 54 S, after 6m 42 C, 44S(quality)	O: General satisafaction, satisfaction, comfort, stability, esthetics, ability to speak, ease to clean, ability to chew bread/hard cheese/raw carrot/sausage/lettuce, quality of denture			
Kawai et al 2010[24]	119(58 T=C, 61 S) **pt completed the study: 3m 53 C, 55 S, 6m 51 C, 54 S**	P: edentulous I: S C: C O: Cost, time	Delivery	(3 and) 6 months after the delivery The statistical analysis was done at 6 months, the 3-month recall was counted as clinic time and cost.	Low
Kawai et al 2018[25]	54 (25 T, 29 S) same CDs 14 T, 21 S	P: edentulous I: S C: C O: General satisafaction, comfort, stability, esthetics, retention, ease to clean, ability to chew, OHRQoL	Delivery	10 years	Low
Komagamine et al 2019[26]	24(13 C-S, 11 S-C)	P: edentulous I: S C: C O: Masticatory function, occlusal contact area, maximum occlusal force	After adjustments (4 times a week=1 month)	1st phase: C/S 1 month adjustments ASSESSMENT Wash out phase=1 month wearing old CD 2nd phase: S/C 1 month adjustments	Low

				ASSESSMENT	
Krishna et al 2014[27]	70 (35 c, 35 s)	P: edentulous I: S impression C: C impression O: Retention, stability, perception		2 months after the delivery	Some concerns
Lira-Oetiker et al 2018[8]	40(18 C, 22 S) **pt completed the study: 17 C, 21 S**	P: edentulous I: S impression C: C impression O: Satisfaction, comfort, stability, esthetics, ability to speak, facility of cleaning, ability to chew raw carrot, raw apple, sausage, white bread, lettuce	Non defined but 2 adjustments on 7th and 14th day	3 and 6 months	Low
Mengatto et al 2017[28]	20(10 C, 10 S) **pt completed the study: 10 C, 9 S**	P: edentulous I: S impression C: C impression O: Masticatory performance, chewing ability	1 adjustment after delivery	Before (old dentures) 3 months with new CD 6 months with new CD	Low
Miyayasu et al 2018[29]	27(14 C-S, 13 S-C) **pt completed the study: 13 C-S, 11 S-C**	P: edentulous I: S impression C: C impression O: Cost= time+materials, cost effectiveness	After adjustments =4 times a week???	1st phase: C/S 1 month after adjustments ASSESSMENT Wash out phase=1 month wearing old CD 2nd phase: S/C 1 month after adjustments ASSESSMENT	Low

Nunez et al 2013[30]	50(25 C, 25 S) **pt completed the study: 23 C, 22 S**	P: edentulous I: S impression C: C impression O: OHRQoL, satisfaction	Last adjustment	1 week before insertion, 30 days and 6 months after last adjustment	Low
Regis et al 2013[31]	42(21 C, 21 S) **pt completed the study: 20 C, 19 S**	P: edentulous I: S impression C: C impression O: OHRQoL, satisfaction, denture quality		Before treatment, 3 and 6 months	Low
Vecchia et al 2014[32]	42(21 C, 21 S) **pt completed the study: 21 C, 20 S (insertion), 20 C, 19 S (adjustments)**	P: edentulous for at least 1 year I: S impression C: C impression O: direct cost, indirect cost		Before insertion (from 1st appointment till insertion), adjustment time (from 1st session till the end)	Low

S: simplified method, C: conventional method, SET: simplified edentulous treatment, pt: patients, CD: complete denture, PROMs: patient-reported outcome measurements, OHRQoL: Oral Health Related Quality of Life

Table 4: Results of ROBINS 2 tool (RoB 2)

Basic Information					Domain 1: Randomzation process				
Unique ID	**Experimental**	**Comparator**	**Aim**	**Weight**	**1.1**	**1.2**	**1.3**	**Algorithm result**	**Assessor´s Judgement**
Alves 2018	S	C	ITT	1	Y	Y	N	Low	Low
Camargos 2019	S	C	ITT	1	Y	Y	N	Low	Low
Ceruti 2017	S	C	ITT	1	Y	Y	N	Low	Low
Cuhna 2013	S	C	ITT	1	Y	NI	N	Some concerns	Low
de Resende 2019	S	C	ITT	1	Y	PY	N	Low	Low
Hyde 2014	S	C	ITT	1	Y	Y	N	Low	Low
Jo 2015	S	C	ITT	1	Y	Y	N	Low	Low
Kawai 2005	S	C	ITT	1	Y	Y	N	Low	Low
Kawai 2010	S	C	ITT	1	Y	Y	N	Low	Low
Kawai 2018	S	C	ITT	1	Y	Y	N	Low	Low
Komagamine 2019	S	C	ITT	1	Y	Y	N	Low	Low
Krishna 2014	S	C	ITT	1	Y	NI	NI	Some concerns	Some concerns
Lira-Oetiker 2018	S	C	ITT	1	Y	Y	N	Low	Low
Mengatto 2017	S	C	ITT	1	Y	Y	N	Low	Low
Miyayasu 2018	S	C	ITT	1	Y	PY	N	Low	Low
Nunez 2013	S	C	ITT	1	Y	PY	N	Low	Low
Regis 2013	S	C	ITT	1	Y	PY	N	Low	Low
Vecchia 2014	S	C	ITT	1	Y	Y	N	Low	Low

	Domain 2: Deviations from Intended Interventions								
Unique ID	**2.1**	**2.2**	**2.3**	**2.4**	**2.5**	**2.6**	**2.7**	**Algorithm result**	**Assessor´s Judgement**
Alves 2018	N	Y	N	NA	NA	Y	NA	Low	Low
Camargos 2019	N	Y	N	NA	NA	Y	NA	Low	Low
Ceruti 2017	N	Y	PN	NA	NA	Y	NA	Low	Low
Cuhna 2013	PN	Y	N	NA	NA	Y	NA	Low	Low
de Resende 2019	N	Y	N	NA	NA	Y	NA	Low	Low
Hyde 2014	N	N	NA	NA	NA	Y	NA	Low	Low
Jo 2015	N	Y	N	NA	NA	Y	NA	Low	Low
Kawai 2005	N	Y	N	NA	NA	Y	NA	Low	Low
Kawai 2010	N	Y	N	NA	NA	Y	NA	Low	Low
Kawai 2018	N	Y	N	NA	NA	Y	NA	Low	Low
Komagamine 2019	N	Y	N	NA	NA	Y	NA	Low	Low
Krishna 2014	N	Y	PN	NA	NA	PY	NA	Low	Low
Lira-Oetiker 2018	PN	Y	N	NA	NA	Y	NA	Low	Low
Mengatto 2017	PN	Y	N	NA	NA	Y	NA	Low	Low
Miyayasu 2018	N	Y	N	NA	NA	Y	NA	Low	Low
Nunez 2013	PN	Y	N	NA	NA	Y	NA	Low	Low
Regis 2013	PN	Y	N	NA	NA	Y	NA	Low	Low
Vecchia 2014	N	PY	N	NA	NA	Y	NA	Low	Low

	Domain 3: Missing Outcome Data					
Unique ID	**3.1**	**3.2**	**3.3**	**3.4**	**Algorithm result**	**Assessor´s Judgement**
Alves 2018	Y	NA	NA	NA	Low	Low
Camargos 2019	Y	NA	NA	NA	Low	Low
Ceruti 2017	Y	NA	NA	NA	Low	Low
Cuhna 2013	Y	NA	NA	NA	Low	Low
de Resende 2019	Y	NA	NA	NA	Low	Low
Hyde 2014	Y	NA	NA	NA	Low	Low
Jo 2015	Y	NA	NA	NA	Low	Low
Kawai 2005	Y	NA	NA	NA	Low	Low
Kawai 2010	Y	NA	NA	NA	Low	Low
Kawai 2018	Y	NA	NA	NA	Low	Low
Komagamine 2019	Y	NA	NA	NA	Low	Low
Krishna 2014	PY	NA	NA	NA	Low	Low
Lira-Oetiker 2018	Y	NA	NA	NA	Low	Low
Mengatto 2017	Y	NA	NA	NA	Low	Low
Miyayasu 2018	Y	NA	NA	NA	Low	Low
Nunez 2013	Y	NA	NA	NA	Low	Low
Regis 2013	Y	NA	NA	NA	Low	Low
Vecchia 2014	Y	NA	NA	NA	Low	Low

	Domain 4: Measurement of the Outcome						
Unique ID	**4.1**	**4.2**	**4.3**	**4.4**	**4.5**	**Algorithm result**	**Assessor´s Judgement**
Alves 2018	N	N	PY	PN	NA	Low	Low
Camargos 2019	N	N	PY	N	NA	Low	Low
Ceruti 2017	N	N	y	PN	NA	Low	Low
Cuhna 2013	N	N	Y	N	NA	Low	Low
de Resende 2019	N	N	Y	PN	NA	Low	Low
Hyde 2014	N	N	PN	NA	NA	Low	Low
Jo 2015	N	N	Y	N	NA	Low	Low
Kawai 2005	N	N	N	NA	NA	Low	Low
Kawai 2010	N	N	N	NA	NA	Low	Low
Kawai 2018	N	N	N	NA	NA	Low	Low
Komagamine 2019	N	N	Y	N	NA	Low	Low
Krishna 2014	N	N	Y	N	NA	Low	Low
Lira-Oetiker 2018	N	N	N	NA	NA	Low	Low
Mengatto 2017	N	N	Y	N	NA	Low	Low
Miyayasu 2018	N	N	Y	N	NA	Low	Low
Nunez 2013	N	N	Y	N	NA	Low	Low
Regis 2013	N	N	PY	N	NA	Low	Low
Vecchia 2014	N	N	PY	N	NA	Low	Low

	Domain 5: Selection of the Reported Result					Domain 6: Overall Bias	
Unique ID	**5.1**	**5.2**	**5.3**	**Algorithm result**	**Assessor´s Judgement**	**Algorithm Judgement**	**Assessor´s Judgement**
Alves 2018	Y	N	N	Low	Low	Low	Low
Camargos 2019	Y	N	N	Low	Low	Low	Low
Ceruti 2017	Y	N	N	Low	Low	Low	Low
Cuhna 2013	Y	N	N	Low	Low	Low	Low
de Resende 2019	Y	N	N	Low	Low	Low	Low
Hyde 2014	Y	N	N	Low	Low	Low	Low
Jo 2015	Y	N	N	Low	Low	Low	Low
Kawai 2005	Y	N	N	Low	Low	Low	Low
Kawai 2010	Y	N	N	Low	Low	Low	Low
Kawai 2018	Y	N	N	Low	Low	Low	Low
Komagamine 2019	Y	N	N	Low	Low	Low	Low
Krishna 2014	Y	N	N	Low	Low	Some concerns	Some concerns
Lira-Oetiker 2018	Y	N	N	Low	Low	Low	Low
Mengatto 2017	Y	N	N	Low	Low	Low	Low
Miyayasu 2018	Y	N	N	Low	Low	Low	Low
Nunez 2013	Y	N	N	Low	Low	Low	Low
Regis 2013	Y	N	N	Low	Low	Low	Low
Vecchia 2014	Y	N	N	Low	Low	Low	Low

S: Simplified, C: Conventional, ITT: Intention-To-Treat (assignment to intervention), Y: Yes, PY: Probably Yes, NI: No Information, N: No, PN: Probably No, NA: Not Applicable

Table 5: Results of ROBINS-I tool

Domains	Questions	Answers	Risk of bias
Bias due to confounding	1.1	N	Low
	1.4	NI	
	1.7	PY	
Bias in selection of participants into the study	2.1	N	Low
	2.4	PY	
Bias in classification of interventions	3.1	Y	Low
	3.2	Y	
	3.3	N	
Bias due to deviations from intended interventions	4.1	N	Low
	4.3	PY	
	4.4	Y	
	4.5	Y	
Bias due to missing data	5.1	PY	No Information
	5.2	NI	
	5.3	NI	
Bias in measurement of outcomes	6.1	N	Serious→Low
	6.2	PY	
	6.3	Y	
	6.4	N	
Bias in selection of the reported result	7.1	N	Low
	7.2	N	
	7.3	N	

Y: Yes, PY: Probably Yes, NI: No Information, N: No, PN: Probably No

Table 6: Impression technique and materials

Conventional technique		Simplified technique
Preliminary impression	**Final impression**	**Impression**
Alginate+stock tray *Alves 2018, de Villa Camargos 2019, Ceruti 2017 (no report about trays), Cuhna 2013, de Resende 2019, Jo 2015, Kawai 2005/2010/2018 (same group), Mengatto 2017 (no reports), Nunez 2013, Regis 2013, Vecchia 2014*	**Custom tray+compound+silicone** *Jo 2015 (2 compounds), Komagamine 2019 (2 compounds), Miyayasu 2018*	**Alginate+stock tray** *Alves 2018, de Villa Camargos 2019, Cuhna 2013, de Resende 2019 (+functional impression), Jo 2015, Kawai 2005/2010/2018 (same group), Mengatto 2017, Nunez 2013, Regis 2013, Vecchia 2014*
Alginate+metal edentulous impression tray *Komagamine 2019, Lira-Oetiker 2018, Miyayasu 2018*	**Custom tray+compound+polyether** *Alves 2018, de Villa Camargos 2019, Kawai 2005/2010/2018 (same group*)	**Alginate+metal edentulous impression tray** *Komagamine 2019, Lira-Oetiker 2018, Miyayasu 2018*
Compound *Krishna 2014*	**Custom tray+wax+zinc oxide impression paste** *Cuhna 2013*	**Multilayer impression tray (SET)** *Ceruti 2017*
	Custom tray+compound+zinc oxide impression paste *De Resende 2019(no report on compound), Krishna 2014, Lira-Oetiker 2018, Regis 2013, Vecchia 2014 (no report on compound)*	**Silicone (putty+light)** *Krishna 2014*
	Custom tray+compound+polysulfide *Ceruti 2017, Nunez 2013*	

Table 7: Summary of the studies and the outcomes they studied

Outcomes	Studies
Masticatory performance/ability	Alves 2018, de Villa Camargos 2019, Cuhna 2013, Komagamine 2019, Mengatto 2017
Patient satisfaction	Ceruti 2017, de Villa Camargos 2019, de Resende 2019, Jo 2015, Kawai 2005, Kawai 2018, Krishna 2014, Lira-Oetiker 2018, Nunez 2013, Regis 2013
OHRQoL	de Villa Camargos 2019, de Resende 2019, hyde 2014, Jo 2015, Kawai 2018, Nunez 2013, Regis 2013
Denture Quality	Ceruti 2017, de Resende 2019, Kawai 2005, Regis 2013
Time	Ceruti 2017, de Resende 2019, Duncan 2001, Krishna 2014, Kawai 2010
Cost	Kawai 2010, Miyayasu 2018, Vecchia 2014
Comfort/stability/esthetics/ability to speak/ease to clean/ability to chew specific foods	Hyde 2014, Kawai 2005, Kawai 2018, Lira-Oetiker 2018, Mengatto 2017
Complete dentures' functional activity	de Villa Camargos 2019
Clinical outcomes	de Resende 2019
Occlusal contact area/maximum occlusal force	Komagamine 2019
Cost effectiveness	Miyayasu 2018
Need for reline	Duncan 2001
Impressions	Hyde 2014, Krishna 2014

Table 8: Summary of the studies and the outcomes they studied revisited

Outcomes	Studies
Masticatory performance/ability, Occlusal contact area/maximum occlusal force	Alves 2018, de Villa Camargos 2019, Cuhna 2013, Komagamine 2019, Mengatto 2017
Patient satisfaction, Comfort/stability/esthetics/ability to speak/ease to clean/ability to chew specific foods	Ceruti 2017, de Villa Camargos 2019, de Resende 2019, Hyde 2014, Jo 2015, Kawai 2005, Kawai 2018, Krishna 2014, Lira-Oetiker 2018, Mengatto 2017, Nunez 2013, Regis 2013
OHRQoL	de Villa Camargos 2019, de Resende 2019, Hyde 2014, Jo 2015, Kawai 2018, Nunez 2013, Regis 2013
Denture Quality, Complete dentures' functional activity, Clinical outcomes	Ceruti 2017, de Resende 2019, Kawai 2005, Regis 2013, de Villa Camargos 2019
Time	Ceruti 2017, Duncan 2001, de Resende 2019, Kawai 2010, Krishna 2014
Cost	Kawai 2010, Miyayasu 2018, Vecchia 2014
Cost-effectiveness	Miyayasu 2018
Need of reline	Duncan 2001
Impressions	Hyde 2014, Krishna 2014

Table 9: Summary of Findings (SoF)

Outcomes	Number of studies	Study design	Number of patients	Quality of evidence (GRADE)
Masticatory performance/ability, Occlusal contact area/maximum occlusal force	5	RCTs	135	High
Patient satisfaction, Comfort/stability/esthetics/ability to speak/ease to clean/ability to chew specific foods	12	RCTs	571/568/549/517*	High
OHRQoL	7	RCTs	326	High
Quality of the complete denture, Complete dentures' functional activity, Clinical outcomes	5	RCTs	303/300/281*	High
Time	5	4 RCTs 1 observational	390/387*	High
Cost	3	RCTs	173/171/168*	High

RCT: Randomized Controlled Trial, *: Dropouts between the follow-ups

DISCUSSION

The majority of the textbooks and curriculums teach the two-staged impression for the fabrication of a complete denture. More specifically, the curriculum of all the Dental Schools in Turkey includes a preliminary impression with alginate and a final impression using a custom tray, compound for the border moulding and zinc oxide eugenol as a wash material.[35] A relevant study in the Dental Schools in Spain and Portugal revealed similar results, namely the use of alginate for the preliminary impression and border molding accompanied with an elastomeric material for the final impression.[36] Interestingly enough, Hussain et al[37] studied the same subject not only among dental schools of the United Kingdom but also among dentists who worked either on a private clinic or in the National Health System (NHS). Although the curriculum dictated the use of a custom tray with silicone for the final impression, the dentists replaced the silicone with alginate. Dentists used a custom tray and alginate, whereas silicone was their second choice, regardless of where they worked (private or NHS).[37] These results were supported by another study which included general dentists in the United Kingdom. According to this study, over 70% of the dentists asked, use a custom tray and alginate for the final impression. The use of a custom tray indicates that a preliminary impression preceded the final impression.[38] Likewise, Petrie et al[39] investigated the difference in the impression stage for the fabrication of complete dentures among prosthodontists (members of the American College of Prosthodontics-ACP) and American Dental School Students. Contrary to the results of Hussain et al[37] for the United Kingdom, Petrie et al[39] revealed similarity in the process between prosthodontists and dental school students. The vast majority (92%) of the prosthodontists used two impressions, one preliminary and one final using a custom tray. 88% of them chose compound and silicone for the final impression. That is also the curriculum taught in the dental schools. It is remarkable how rarely Americans deviate from what they were taught.[39] All the above mentioned studies indicate that dental schools all over the world consider that the final impression step is crucial and necessary for the fabrication of a well-functioning complete denture. The purpose of the impression is to make an accurate copy of the seating surface. For that purpose, the clinician makes a step-by-step impression of the surface borders with a compound and then uses a different material with the appropriate viscosity to make the impression of the surface without interfering with the border molding. This procedure is considered as leading to the most accurate impression and maximizes the stability and retention of the complete denture. If an accurate impression can be taken with a simpler procedure, then the stability and retention of the denture will not be compromised, the different outcomes will not be affected and therefore this may be suggested as an alternative.

Masticatory performance

The primary goal when fabricating a denture is to evaluate the patients' masticatory performance. The comparison of the two methods could not omit the evaluation of the masticatory performance. This evaluation is objective and subjective. Two

different tests, the sieve method and the swallowing threshold test index, are used to receive objective information about the masticatory performance. These tests quantify the pulverization of the food and therefore their results are comparable. It is equally important to collect subjective information and therefore the patients are asked to answer different simple questionnaires. They include questions about the dietary habits of the patients or direct questions on whether the patients can chew specific foods (e.g. vegetables, fruits, meat etc). Interestingly the results of the objective and subjective test do not always coincide. In other words, there is a difference between the masticatory performance and the assessment of their chewing ability.[40] The level of bone resorption did not influence the masticatory ability of the patients according to Marcello-Machado et al.[41] This is in agreement with the results of the study of Alves et al (2018)[7]. Since we did not find a significant difference in the masticatory performance combined with the fact that the population in the included studies varied in the level of the ridge resorption, our results agree the statement of Marcello-Machado et al[41].

Classification systems of complete edentulism

More specifically, the majority of the studies included used the classification system for complete edentulism of the American College of Prosthodontics (ACP)[42]. They focused on the ridge resorption as the main factor of a compromised case. However, this classification system categorizes the edentulous patients based on the complexity of the case which depends not only by the residual ridge. It is out of the scope of the present review to analyze the classification system, but it is important to mention that the participants of the clinical studies belonged to all the categories and only the minority belonged to the most favorable class (class I). This indicates that the results are not biased as they would have been if only patients with the most ideal oral condition were included.[42] Only one study, namely that of Lira-Oetiker et al[8], used the classification system of Cawood and Howell[43] instead of the ACP[42] one. According to this system the edentulous jaws are categorized based on measures on different spots of the jaw as they appear on a panoramic radiograph. There are six categories (class I to VI), with class I being the most favorable and class VI characterized by severe ridge resorption. Lira-Oetiker et al[8] included patients of class II, III and IV and therefore we could imply that the results may be optimized.[43]

Patient satisfaction

Huumonen et al[44] indirectly associated the ridge resorption with the patient satisfaction. In their study patients with severe ridge resorption complained about the stability of the mandibular denture and that caused reduced satisfaction. According to Huumonen et al[44] as severe ridge resorption was characterized by the absence of bone above the mandibular canal and/or the mental foramen.[44] In contrary, Pan et al[45] did not find a significant association between ridge height and patient satisfaction. In this study, ridge height was evaluated using four different classification systems. According to Cawood & Howell and Xie classification systems, the participants were

divided in two groups equally, half of them had adequate bone height and the other half presented with severe bone resorption. When using the other two classification systems (ACP, Wical & Swoope) only the minority of the participants had adequate bone height. So, we can conclude that their results were valid. Irrespective of the system, patient satisfaction did not show a correlation to the residual bone height[45], which comes in agreement with our result. The included studies did not evaluate patient satisfaction based only on the denture fabrication technique, but also assessed all other factors that may influence it, such as the remaining ridge height. No differences in patient satisfaction were found between all the included groups.

Oral Health Related Quality of Life (OHRQoL)

Following patient satisfaction, the oral health related quality of life (OHRQoL) was examined. OHRQoL was measured using different versions of the Oral Health Impact Profile (OHIP). OHIP-Edent is a shortened version of OHIP and focused on the edentulous patients. Moreover, OHIP-Edent can detect the differences in the quality of life of the patients after recieving a new rehabilitation. De Souza et al[46] proved the validity of the Brazilian version of the OHIP-Edent as well as the validity of the Geriatric Oral Health Assessment (GOHAI). They compared the answers of these two OHRQoL inventories with the answers of a denture satisfaction questionnaire and they found a strong correlation.[46] Likewise, Sato et al[47] found that the Japanese version of OHIP-Edent (OHIP-Edent J) demonstrated good reliability and validity.[47]

It is important to mention the study of Stober et al[48]. They correlated OHRQoL measured with OHIP-Edent with the patient satisfaction measured with questionnaires. Although they emphasized that patient satisfaction cannot per se predict the OHRQoL, they found a significant association between the two factors[48], strengthening the conclusion that the method used did not affect neither the OHRQOL nor the patient satisfaction.

Cost and time

The simplified and the conventional technique differed significantly in two outcomes, named cost and time. The simplified technique did have a significant lower cost than the conventional technique. The cost of the conventional is higher as the clinicians use extra materials. In both methods, an impression with alginate will be made. The session of the final impression includes an acrylic resin custom tray, a compound for border molding and a wash material. The use of these three additional materials inevitably increases the cost.[49]

The time needed for the conventional technique was longer, since the protocol included an extra clinical session, that of the final impression. The time increases more if we take into consideration the difficulty of the final impression. Moreover, a randomized clinical trial of Kimoto et al[50] revealed a difference in time needed based on the experience. Junior clinicians needed more time to fabricate, deliver and adjust the complete dentures than senior clinicians. Although Kimoto et al[50] did not mention the years of experience of each clinician, the time difference in the stage of the final

impression was statistically significant.[50] Therefore, they concluded that experience plays a major role. In the studies included in the present review, the practitioners varied from undergraduate students to experienced prosthodontists. Bearing in mind that the two methods differed in time, the experience of the practitioner may be a basic reason. However, no study compared students and prosthodontists directly (included students and prosthodontists). That means that the time difference was valid in all studies regardless of the clinician and therefore the simplified method is quicker.

Cost effectiveness

Cost effectiveness analysis is an economic analysis which aims to give an answer between alternative treatments. It calculates the cost and the common outcome of each treatment option. In the present review the treatment options are the two techniques examined (conventional and simplified) and the common outcome is patient satisfaction. The calculation of the cost effectiveness analysis is mathematical.[51] The simplified technique differs from the conventional only in terms of cost and time. This could lead to the assumption that the simplified technique is more cost effective. However, the cost effectiveness analysis is an economic analysis which takes into consideration also the outcome, in this case patient satisfaction. As mentioned in the results, the analysis revealed the superiority of the conventional method. We have to bear in mind however, that only one study examined this factor and therefore we cannot draw a conclusion of which treatment plan is more cost effective.

Post-insertion visits and need for reline

An indirect method to evaluate the success of a method is the number of post-insertion visits for adjustments and the need for reline and even the time when this need occurs. Only the study of Duncan et al[20] evaluated the post-insertion visits and the need for reline. They concluded that the simplified technique obviously required less visits not only for the fabrication of the denture but also for the necessary adjustments and there was no difference in the need for reline. During the first three months patients still try to adjust to the new rehabilitation so it is impossible to testify the need for reline. Less post-insertion visits for the simplified technique may be explained by the fact that the final impression with border molding leads often to overextended dentures.

Facebow

In a lot of studies in the intervention group face bow record was also omitted besides the final impression. Farias-Neto et al[52] and Prakash et al[53] concluded in their systematic review accordingly that the use of a face bow does not result in a better outcome for the complete dentures.[52,53] This comes in agreement with our results, but it logically raises the question if the results are valid as there is no included study which examines the use or not of only the facebow. Kumar and Souza[54] provided the answer with their study where the only difference between the two groups was the use of the

facebow. According to them the complete dentures fabricated without the use of the facebow were better than the dentures of the control group, proving that a complete denture can also be fabricated with simple methods avoiding the use of a facebow. The differences found between the two groups were also attributed to the fact that the mandibular cast of the control group was articulated with centric, lateral and protrusive records. This is very demanding especially in edentulous patients where the records are made with record bases and occlusal rims which are impossible to be stable during the procedure.[54]

Remount

It was not feasible to assess the importance of the remount due to the concomitant presence of other confounding factors (example use of facebow). A valid evaluation about the importance of the remount could occur if that was the only difference between the control and the test group. Such a study was performed by Shigli et al[55] and they found the superiority of the remount process. The test group in which laboratory and clinical remount found place had significantly better results. The patients of this group needed less post-insertion visits, experienced less pain and discomfort during mastication and presented less sore spots. These results were statistically significant. The remount process was the only difference among the edentulous participants and its superiority was evident.[55] In the present review such a difference was not noticed. However, we have to see this result with precaution as the influence of the remount could be lost among the influence of other factors.

Systematic reviews and meta-analysis

Paulino et al[56] conducted the first systematic review for the simplified technique. They concluded that the simplified technique does not compromise patient satisfaction and masticatory ability with the complete dentures, nor does it affect the quality of the denture. Therefore, they concluded that some of the clinical and laboratory steps in the fabrication of a complete denture may be unnecessary.[56] Ye et al[57] in the systematic review published in 2017, found differences between the two technique in cost and time. All the other factors (patient satisfaction, OHRQoL, denture quality, masticatory ability) did not differ among the two methods. Their database search was completed before April 2014, only four months after the completion of the search of Paulino et al[56], and since then have been published a lot of new randomized clinical trials on the same topic.[57] The most recent-in the searching period of the present review- publication comparing the two methods is a meta-analysis of Al- Ansari et al (2019).[58] They included 11 studies and drew conclusions about patient satisfaction, quality of life, cost, and time. For the first two outcomes the researchers found no statistically significant difference between conventional and simplified technique contrary to the other two. The simplified technique had statistically lower cost and required less time for completion.[58] The results of our systematic review are more comprehensive and they are in agreement with the results of the aforementioned studies. Cost and time are the only outcomes with a difference in favor of the

simplified dentures. Apart from that, conventional and simplified method of fabrication of complete dentures have equal outcomes.

A systematic review and a meta-analysis of the same topic was published in September 2020 by Sanjeevan et al.[59] This paper is mentioned in the discussion of the present review as relevant, but it is out of the searching period selected. Although the two reviews were conducted almost simultaneously, there are some differences worth mentioning. The searching period of the two reviews differed by two months (January 2020-the present review, February 2020-Sanjeevan's et al[59] review). The search was conducted in two common databases (Pubmed, Scopus) and one different (Europe PMC-the present review, Cochrane-Sanjeevan's et al[59] review). These differences may explain the slight difference in the selected articles although in both reviews 19 articles met the inclusion criteria. Sanjeevan et al[59] included the studies of Heydecke et al 2008[60] and Matsuda et al 2015[61], which are not included in the present review. The study of Heydecke et al 2008[60] was included as a relevant to the topic title but excluded after reading the abstract. The reason was that the difference between the two protocols used was focused on the anatomy of the teeth and the occlusal pattern used rather than the impression stage. The conventional protocol of Heydecke et al[60] included a facebow transfer, tracings on the bases for the maxillomandibular records and semi-anatomic teeth in a lingualised and balanced occlusal pattern. Contrary, the simplified protocol did not include a facebow transfer, the maxillomandibular records were made with occlusal rims and the anatomic teeth were selected and setted in a canine-premolar guidance. As concluded, the anatomy of the teeth did not affect the patient satisfaction. The fact that the study defined the protocols completely different in contrary to all the other studies was the reason of exclusion. The study of Matsuda et al 2015[61] was not found in the electronic search of the present review. The reason may be the different database among the two reviews or/and the fact that one article included in the review of Sanjeevan et al[59] was found by hand searching. It is not mentioned whether this article is the study of Matsuda et al[61] but it should be held as probable. In the present review were included the studies of Hyde et al 2014[21] and Duncan et al 2001[20]. The latter one was excluded by Sanjeevan et al[59] because it is not a randomized trial but an observational study. The reasons of the exclusion of the study of Hyde et al 2014[21] are not mentioned. The main difference among the two reviews is the assessment of the risk of bias. Both review groups used the same assessment tool. However, the results differ. Sanjeevan et al[59] characterized the majority of the included studies at 'high risk' of bias (12 studies) and the minority of them at 'low risk' of bias (3 studies). The remaining 4 studies were assessed with 'some concerns'. Therefore, the quality of evidence according to the GRADE system was low and all these results suggest a heterogeneity of the studies included. There could be a lot of reasons explaining the contrary results, but these could only be assumed. A valid explanation mentioned in the article of Sanjeevan et al[59] is that this review group did not pool the information and the results between the studies included, while in the present review the outcomes were analysed and categorized according to their meaning and not only by the definition per se given by

the researchers (Table 7,8). Despite the differences between the two reviews and the reasons for them, Sanjeevan's et al[59] conclusions are in agreement with the results of the present study and the aforementioned systematic reviews and meta-analysis but suggested to consider them with precaution.

There are two established protocols for fabricating complete dentures, the conventional and the simplified. Their main difference is the omission of the final impression in the simplified technique. Apart from cost and time, the two methods are equal. None of the other outcomes is affected by the method of fabrication. The simplified technique prerequisites a perfect impression with alginate. This requires excellent knowledge of the anatomy of the oral cavity and experience. Therefore, we are still reluctant if the simplified protocol is suitable for an undergraduate curriculum or clinicians with limited experience.

Limitations

There are some limitations that could affect the power of the present systematic review. All the studies included share common characteristics such as the population (edentulous patients), the intervention (the simplified technique) and the comparison group (the conventional technique). They all focus on the same question: 'Is simplified or conventional method better?' and they all attempt to answer to this specific question. However, they evaluate different factors and even studies focusing on the same outcomes used different test methods. Due to the fact that they differed also in other aspects as for example the materials used, the studies could only be compared in subgroups. There is also a lot of heterogeneity among the studies. Even the fact that a lot of researchers omitted not only the final impression but also the use of a facebow and the remount, makes the test and control group differ in more than one factor. Therefore, the impact of each factor on the result cannot be evaluated. In addition, as mentioned before, the clinicians varied from undergraduate students to experienced prosthodontists, a fact which could affect the results. It was even the topic of some studies which method is suitable and more predictable for an undergraduate curriculum as border molding is held one of the most challenging tasks in dentistry. A lot of studies held the simplified technique as easier for the students, especially the undergraduate ones. But the simplified technique requires a perfect first impression with alginate which is not necessary an easy task. At least it requires profound knowledge of the anatomy, which can only be obtained through practice. It is therefore incorrect to consider the impression of the edentulous jaw as a simple task. Moreover, all of the studies had a follow up of at most 6 months which is very short.

A lot of outcomes were evaluated based on the patient interpretation and the information collected was subjective. If we bear in mind each patient's complexity and personality, we have to agree that the answers are not comparable. Patient self-report outcomes could be evaluated with caution. However, those results should not be undermined, since all the researchers emphasize that the acceptance of the complete denture is up to the ability of the patient to adjust with the new prosthesis. In addition, in cases where an outcome was evaluated based on subjective and objective test (e.g.

masticatory performance), the subjective information gave better results. This indicates that the perception of the patients does not always coincide with reality and they tend to be more optimistic about their oral situation and treatment outcome.

As already mentioned, simplified is called every protocol for the fabrication of a complete denture that requires less than six clinical sessions. According to that definition, the fabrication of a complete denture using CAD/CAM technology uses a simplified technique as different sessions are omitted. Technology can be used either for designing the complete denture (CAD) or for manufacturing it (CAM) but also in a combination where the whole process of fabricating a complete denture will be done digitally (CAD/CAM). The digital workflow can be a two-, three- or four-visits protocol. The systematic review of Kattadiyil et al[62] included four studies, three of them followed a two-visit protocol and one of them a four-visit one. In all of these studies it is admitted that there was a deviation in the number of the clinical sessions as in some cases more visits were required. However, even considering the additional appointments the average of the clinical sessions was less than the conventional protocol.[62] It is interesting to elaborate the different protocols in order to identify which sessions are omitted. In the two-visits protocols, the complete denture will be delivered in the second appointment following the session of the impression, omitting any try-ins will. The impression can be either digital using an oral scan or conventional. In the second case, a cast will be fabricated and then scanned. Either way the subsequent procedure is the same.[63] The mobility of the soft tissues and the absence of immobile benchmarks are some of the limitations of the intraoral scanning of an edentulous arch and therefore the process of the conventional impression cannot be yet replaced.[64] In the three-visit protocol a try-in is included. This could be a milled or printed prototype of the complete denture. The color of soft and hard tissues of the complete denture is uniform but this prototype enables the evaluation of the esthetics in terms of shape of the teeth and their position in the stomatognathic system. This try-in is more helpful to the clinician than to the patient as he cannot imagine the final result. In a four-visit protocol there is more interaction between the conventional and digital workflow. In this protocol the clinical sessions are done conventionally, and the laboratory work is done digitally. The clinician still performs an impression and maxillomandibular records. The difference is that the base plates or even the custom tray are printed. More specifically, the clinician makes an impression, and the laboratory scans it, or the cast made of this particular impression. If the clinician will proceed with a final impression, a custom tray will be printed, a final impression will be made which will again be scanned (the impression or the cast) and a base plate will be printed. If he decides to use the preliminary cast as the final cast, then base plates are printed. Either way he proceeds with the maxillomandibular records. The laboratory work of placing the teeth will be done digitally. If the clinician decides to perform a try-in, then a prototype will be printed and used as mentioned before in the three-visit protocol. Then the complete denture will be delivered. Counting all the clinical sessions, we result in a five-stage protocol and in other words following the definition given in the introduction, this protocol cannot any more be called simplified. It could be characterized as conventional fabrication of a complete denture with a digital laboratory workflow. However, no clinician performs all the sessions. Either the

final impression or the try-in will be omitted and therefore the complete denture will be fabricated with a simplified method.

The properties, advantages and disadvanages of the CAD/CAM complete dentures are out of the scopus of this systematic review and therefore not mentioned. Although, digital workflows belong to the simplified technique, we did not include studies with CAD/CAM complete dentures in this systematic review and a new one could be beneficial.

CONCLUSION

The conclusions of the present systematic review are the following:

1) Our systematic review is in agreement with the literature of the topic.
2) The null-hypothesis was confirmed in terms of cost and time but rejected in all the other factors.
3) Cost and time differed significantly between the two methods favoring the simplified protocol.
4) Masticatory performance and ability, patient satisfaction, Oral Health Related Quality of Life (OHRQoL) and denture quality are not affected by the method of fabrication.

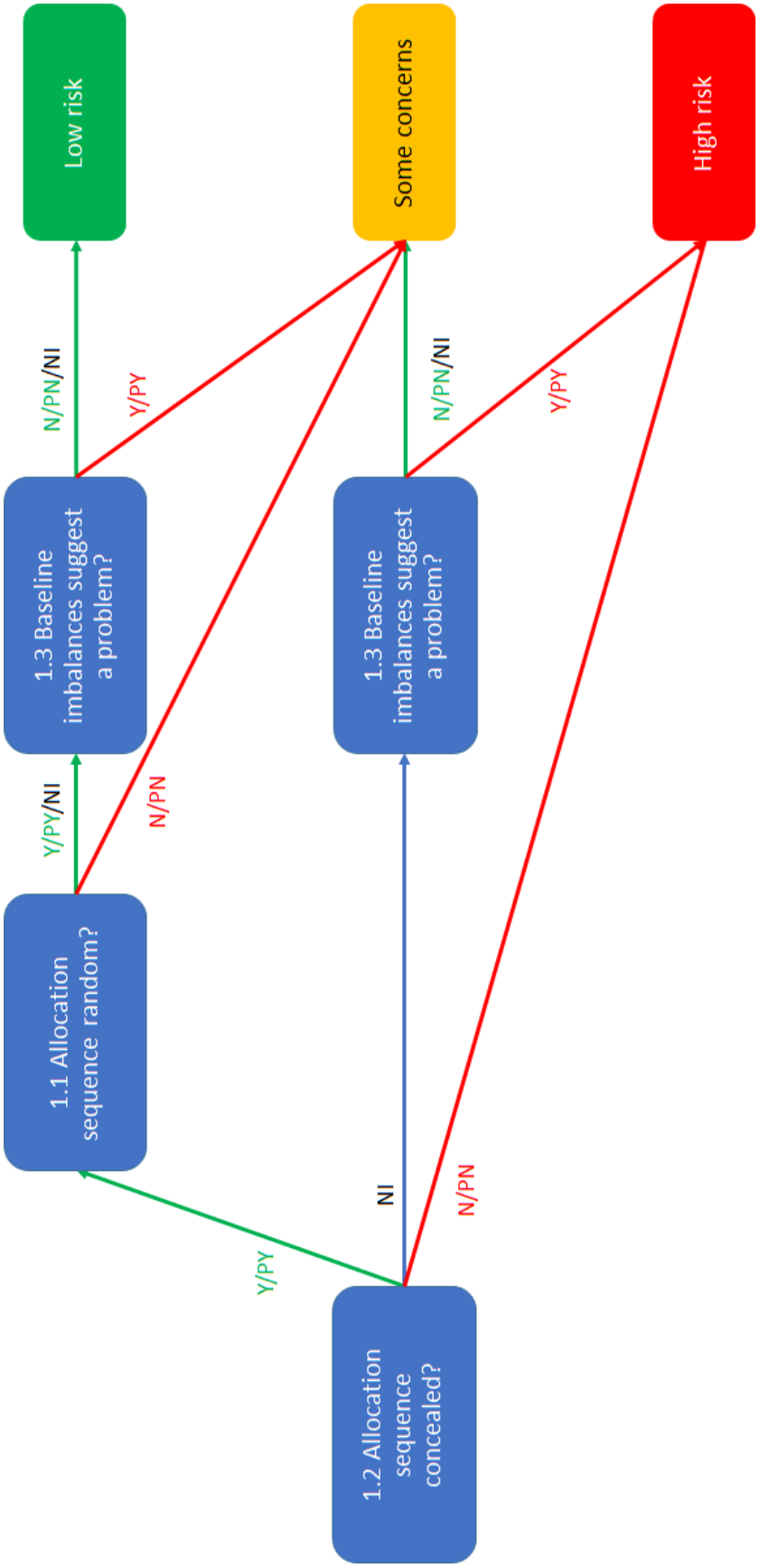
APPENDIX 1-ROBINS 2 tool (RoB 2 tool)

1st domain-Risk of bias arising from the randomization process

Signalling questions	**Elaboration**	**Response options**
1.1 Was the allocation sequence random?	Answer **Yes** if a random component was used in the sequence generaition process. Examples include computir-generated random numbers; reference to a random number table; shuffling cards or envelopes; throwing dice; or drawing lots. Minimazation is generally implemented with a random element (at least when the scores are equal), so an allocation sequence that is generated using minimization should generally be considered to be random. Answer **No** if no random element was used in generating the allocation sequence or the sequence is predictable. Examples include alteration; methods based on dates (of birth or admission); patient record numbers;allocation decisions made by clinician or participants; allocation based on the availability of the intervention or any other systematic or haphazard method. Answer **No Information** if the only information about randomization methods is a statement that the study is randomized. In some situations, a judgement may be made to answer **Probably No** or **Probably Yes**. For example , in the context of a large trial run by an experienced clinical trial unit, absence of specific information about generation of the randomization sequence, in a paper published in a journal with rigorously enforced word count limits, is likely to result in a response of *Probably Yes* rather than *No Information*. Alternatively, if other (contemporary) trials by the same investigator team hae clearly used non-random sequences, it might be reasonable to assume that the current study was done using similar methods.	Y/PY/PN/N/NI
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	Answer **Yes** if the trial usd any form of remote or centrally administered method to allocate interventions to participants, where the process of allocation is controlled by an external unit or organization, independent of the enrolment personel (e.g. independent central pharmacy, telephone or internet-based randomization service providers). Answer **Yes** if envelopes or drug containers were used appropriately. Envelopes should be opaque, sequentially numbered, sealed with a tamper-proof seal and opened only after the envelope has been irreversibly assigned to the participant. Drug containers should be sequentially numbered and of identical appearance, and dispensed or administered only after they have been irreversibly assigned to the participant. This level of detail is rarely provided in reports, and a judgement may be required to justify an answer of **Probably Yes** or **Probably No**. Answer **No** if there is reason to suspect that the enrolling investigator or the participant had knowledge of the forthcoming allocation.	Y/PY/PN/N/NI

Signalling questions	**Elaboration**	**Response options**
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Note that differences that are compatible with chance do not lead to a risk of bias. A small number of differences identified as statistically significant at the conventional 0.05 threshold should usually be considered to be compatible with chance. Answer **No** if no imbalances are apparent or if any observed imbalances are compatible with chance. Answer Yes if there are imbalances that indicate problems with the randomization process, including 1) Substantial differences between intervention group sizes, compared with the intended allocation ratio 2) A substantial excess in statistically significant differences in baseline characteristics between intervention groups, beyond that expected by chance 3) Imbalance un one or more key prognostic factors or baseline measures of outcome variables that is very unlikely to be due to chance and for which the between-group differences is big enough to result in bias in the intervention effect estimate. Answer **Yes** if there are other reasons to suspect that the randomization process was problematic: 4) Excessive similarity in baseline characteristics that is not compatible with chance. Answer **No Information** when there is no useful baseline information available (e.g. abstracts, studies that reported baseline characteristics of participants in the final analysis). The answer to this question should not influence answers to questions 1.1 or 1.2. For example, if the trial has large baseline imbalances, but authors report adequate randomization methods, questions 1.1 and 1.2 should still be answered on the basis of the reported adequate methods and any concerns about the imbalance should be raised in the answer to the question 1.3 and reflected in the domain-level risk-of-bias judgement. Trialists may undertake analyses that attempt to deal with flawed randomization by controlling for imbalances in prognostic factors at baseline. To remove the risk of bias caused by problems in the randomization process, it would be necessary to know, and measure all the prognostic factors that were imbalanced at baseline. It is unlikely that all important prognostic factors are known and measured so such analyses will at best reduce the risk of bias. If review authors wish to assess the risk of bias in a trial that controlled for baseline imbalances in order to mitigate failures of randomization, the study should be assessed using the ROBINS-I tool.	Y/PY/PN/N/NI

Algorithm for suggested judgement of risk of bias arising from the randomization process

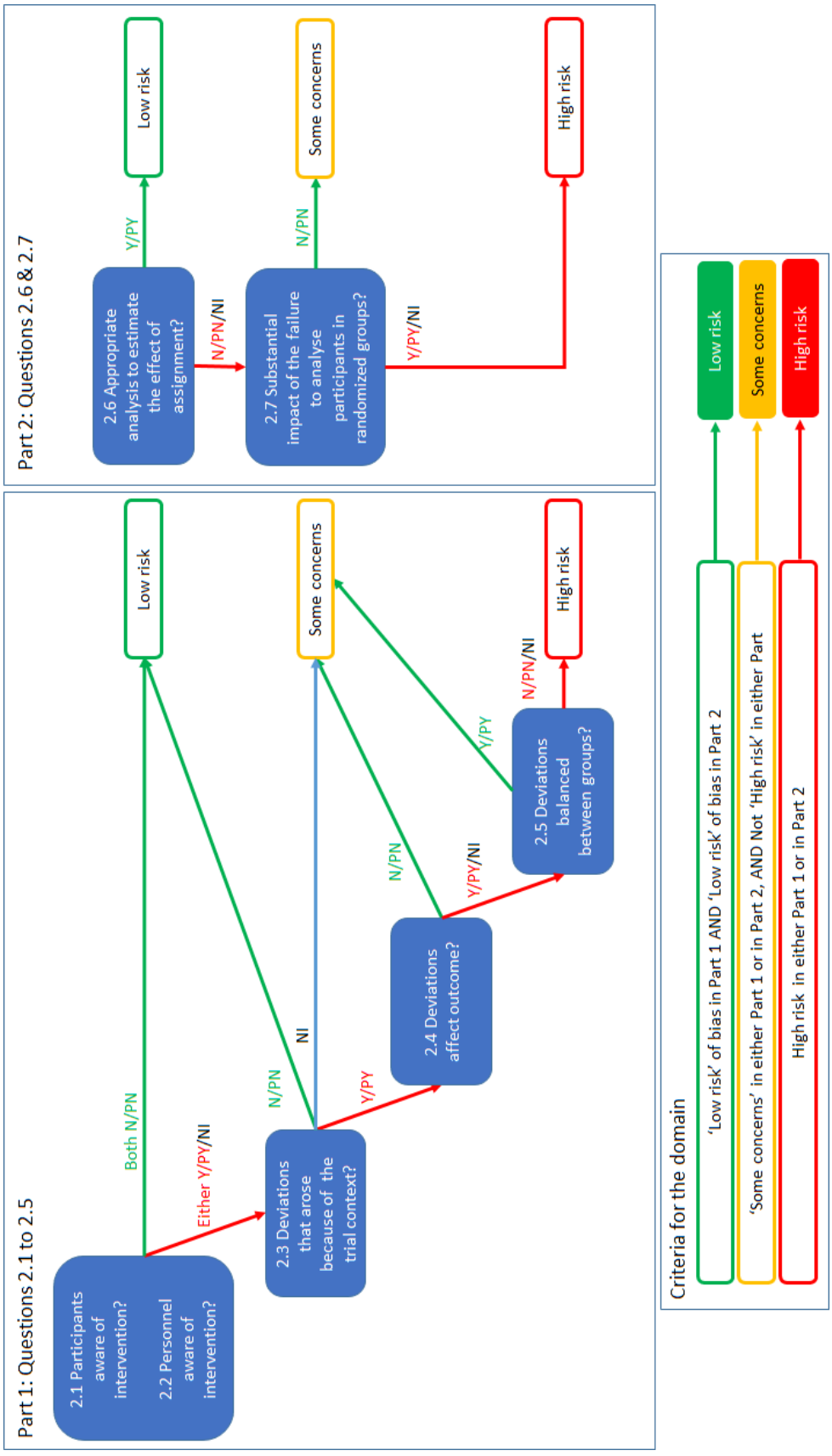


2nd domain -Risk of bias due to deviations from the intended interventions (effect to assignment of intervention)

Signalling questions	**Elaboration**	**Response options**
2.1 Were participants aware of theire assigned intervention during the trial?	If participants are aware of their assigned intervention it is more likely that health-related behaviors will differ between the intervention groups. Blinding participants, most commonly through use of a placebo or sham intervention, may prevent such differences. If participants experienced side effects or toxicities that they knew to be specific to one of the interventions, answer this question **Yes** or **Probably Yes**.	Y/PY/PN/N/NI
2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	If carers or people delivering the interventions are aware of the assigned intervention then its implementation or administration of non-protocol interventions, may differ between the intervention groups. Blinding may prevent such differences. If participants experienced side effects or toxicities that carers or people delivering the interventions knew to be specific to one of the interventions, answer question **Yes** or **Probably Yes**. If randomized allocation was not concealed, then it is likely that carers and people delivering the interventions were aware of participants' assigned intervention during the trial.	Y/PY/PN/N/NI
2.3 If Y/PY to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?	For the effect of assignment to interventions, this domain assesses problems that arise when changes from assigned intervention that are inconsistent with the trial protocol arose because of the trial context. We use the term trial context to refer to effects of recruitment and engagement activities on trial participants and when trial personnel (carers or people delivering the interventions) undermine the implementation of the trial protocol in ways that would not happen outside the trial. For example, the process of securing informed consent may lead participants subsequently assigned to the comparator group to feel unlucky and therefore seek the experimental interventionor other interventions that improve their prognosis. Answer **Yes** or **Probably Yes** only if there is evidence or strong reason to believe that the trial context led to failure to implement the protocol interventions or to implementation of interventions not allowed by the protocol. Answer **No** or **Probably No** if there were changes from assigned intervention hat are inconsistent with the trial protocol such as non-adherence to intervention, but these are consistent with what could occur outside the trial context. Answer **No** or **Probably No** for changes to intervention that are consistent with the trial protocol, for example cessation of a drug intervention because of acute toxicity or use of additional interventions whose aim is to treat consequences of one of the intended interventions. If blinding is compromised because participants report side effects or toxicities that are specific to one of the interventions, answer **Yes** or **Probably Yes** only if there were changes from assigned intervention that ae inconsistent with the trial protocol and arose because of the trial context. The answer **No Information** may be appropriate because trialists do not always report whether deviations arose because of the trial context.	NA Y/PY/PN/N/NI

Signalling questions	**Elaboration**	**Response options**
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	Changes from assigned intervention that are inconsistent with the trial protocol and arose because of the trial context will impact on the intervention effect estimate if they affect the outcome, but not otherwise.	NA Y/PY/PN/N/NI
2.5 If Y/PY to 2.4: Were these deviations from intended intervention balanced between groups?	Changes from assigned intervention that are inconsistent with the trial protocol and arose because of the trial context are more likely to impact on intervention effect estimate if they are not balanced between the intervention group.	NA Y/PY/PN/N/NI
2.6 Was an appropriate analysis used to estimate the effect of assignement to intervention?	Both intention-to-treat (ITT) analyses and modified intention-to-treat (mITT) analyses excluding participants with missing outcome data should be considered appropriate. Both naïve *per-protocol* analyses (excluding trial articipants who did not receive their assigned intervention) and *as treated* analyses (in which trial participants are grouped according to the intervention that they received rather than according to their assigned intervention) should be considered inappropriate. Analyses excluding eligible participants post-randomization should also be considered inappropriate but post-randomization exclusions of ineligible participants (when eligibility was not confirmed until after randomization and could not have been influenced by intervention group assignment) can be considered appropriate.	Y/PY/PN/N/NI
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the groups to which they were randomized?	The question addresses whether the number of participants who were analysed in the wrong intervention group or excluded from the analysis was sufficient that there could have been a substantial impact on the result. It is not possible to specify a precise rule: there may be potential for substantial impact even if fewer than 5% of participants were analysed in the wrong group or excluded f the outcome is rare or if exclusions are strongly related to prognostic factors.	NA Y/PY/PN/N/NI

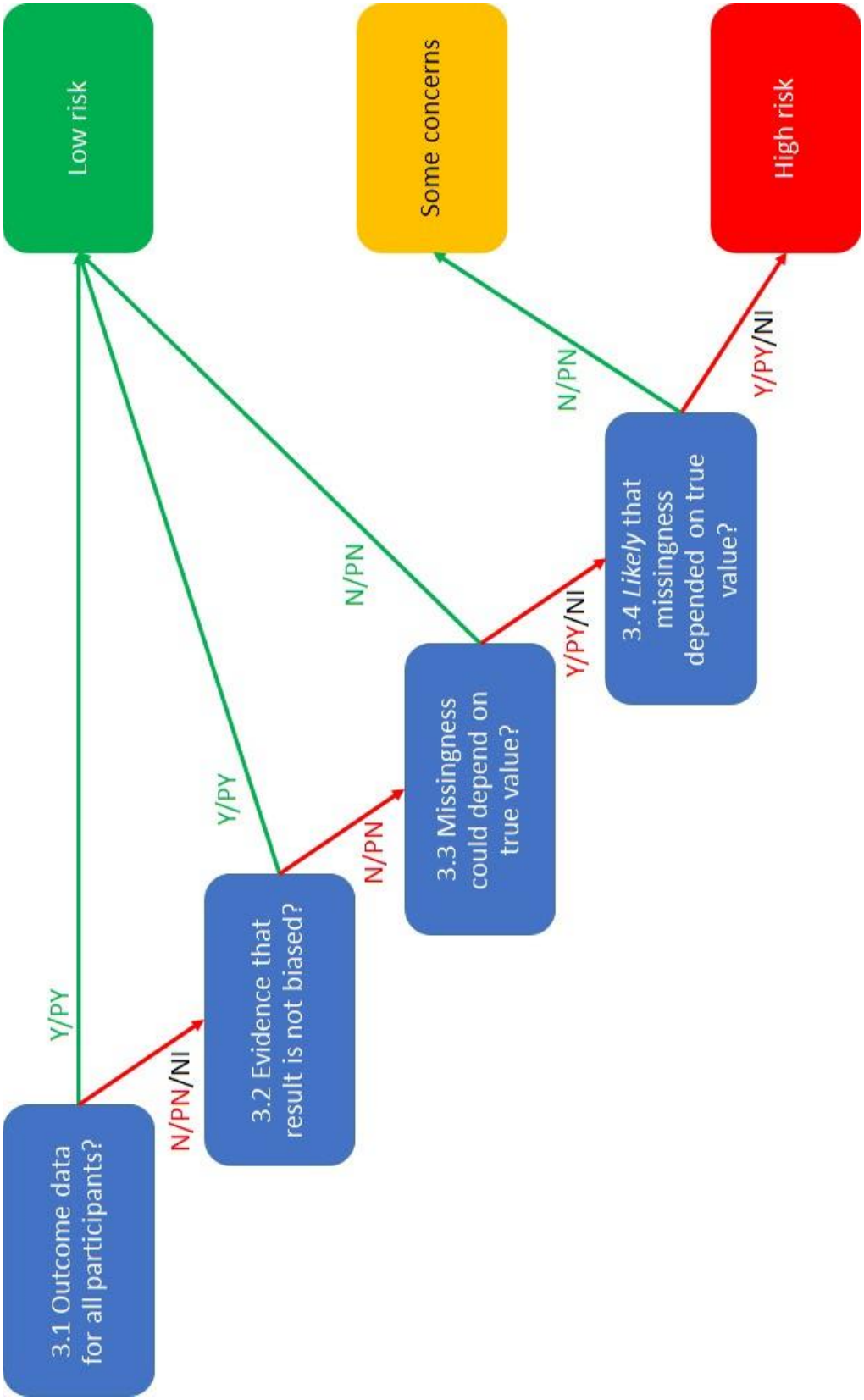
Algorithm for suggested judgement of risk of bias due to deviations from the intended interventions (effect of assignment to intervention)



Signalling questions	**Elaboration**	**Response options**
3.1 Were data for this outcome available for all or nearly all participants randomized?	The appropriate study population for an analysis of the intention to treat effect is all randomized participants. Nearly all should be interpreted as that the number of participants with missing outcome data is sufficiently small that their outcomes, whatever they were, could have made no important difference to the estimated effect of intervention. For continuous outcomes, availability of data from 95% of the participants will often be sufficient. For dichotomous outcomes, the proportion required is directly linked to the risk of the event. If the observed number of events is much greater than the number of participants with missing outcome data, the bias would necessarily be small. Only answer **No Information** if the trial report provides no information about the extent of missing outcome data. This situation will usually lead to a judgement that there is a high risk of bias due to missing outcome data. Note that imputed data should be regarded as missing data and not considered as outcome data in the context of this question.	Y/PY/PN/N/NI
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?	Evidence that the result was not biased by missing outcome data may come from: 1) Analysis methods that correct for bias 2) Sensitivity analyses showing that results are little changed under a range of plausible assumptions about te relationship between missingness in the outcome and its true value. However, imputing the outcome variable either through methods such as last-observation-carried-forward or via multiple imputation based only on intervention group, should not be assumed to correct for bias due to missing outcome data.	NA Y/PY/PN/NI
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	If loss to follow up or withdrawal from the study could be related to participants' health status, then it is possible that missingness in the outcome was influenced by its true value. However, if all missing outcome data occurred for documentes reasons that are unrelated to the outcome then the risk of bias due to missing outcome data wil be low (for example, failure of a measuring device or interruptions to routine data collection). In time-to-event analyses, participants censored during trial follow-up, for example because they withdrew from the study should be regarded as having missing outcome data, even though some of their follow up is included in the analysis. Notethat such participants may be shown as included in analyses in CONSORT flow diagrams.	NA Y/PY/PN/N/NI

Signalling questions	**Elaboration**	**Response options**
3.4 If N/PN/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	This question distinguishes between situations in which (i) missingness in the outcome could depend on its true value (assessed as *Some Concerns*) from those in which (ii) it is likely that missingness in the outcome depended on its true value (assessed as *High risk of bias*). Five reasons for answering Yes are: 1) Differences between intervention groups in the proportions of missing outcome data. If there is a difference between the effects of the experimental and comparator interventions on the outcome and the missingness in the outcome is influenced by its true value, then the proportions of missing outcome data are likely to differ between intervention groups. Such a difference suggests a risk of bias due to missing outcome data outcome data, because the trial result will be sensitive to missingness in the outcome being related to its true value. For time-to event-data, the analogue is that rates of censoring (loss to follow-up) differ between the intervention groups. 2) Reported reasons for missing outcome data provide evidence that missingness in the outcome depends on its true value. 3) Reported reasons for missing outcome data differ between the intervention groups. 4) The circumstances of the trial make it likely that missingness in the outcome depends on its true value. 5) In time-to-event analyses, participants' follow up is censored when they stop or change their assigned intervention, for example because of drug toxicity . Answer **No** if the analysis accounted for participant characteristics that are likely to explain the relationship between missingness in the outcome and its true value.	NA Y/PY/PN/N/NI

Algorithm for suggested judgement of risk of bias for bias due to missing outcome data

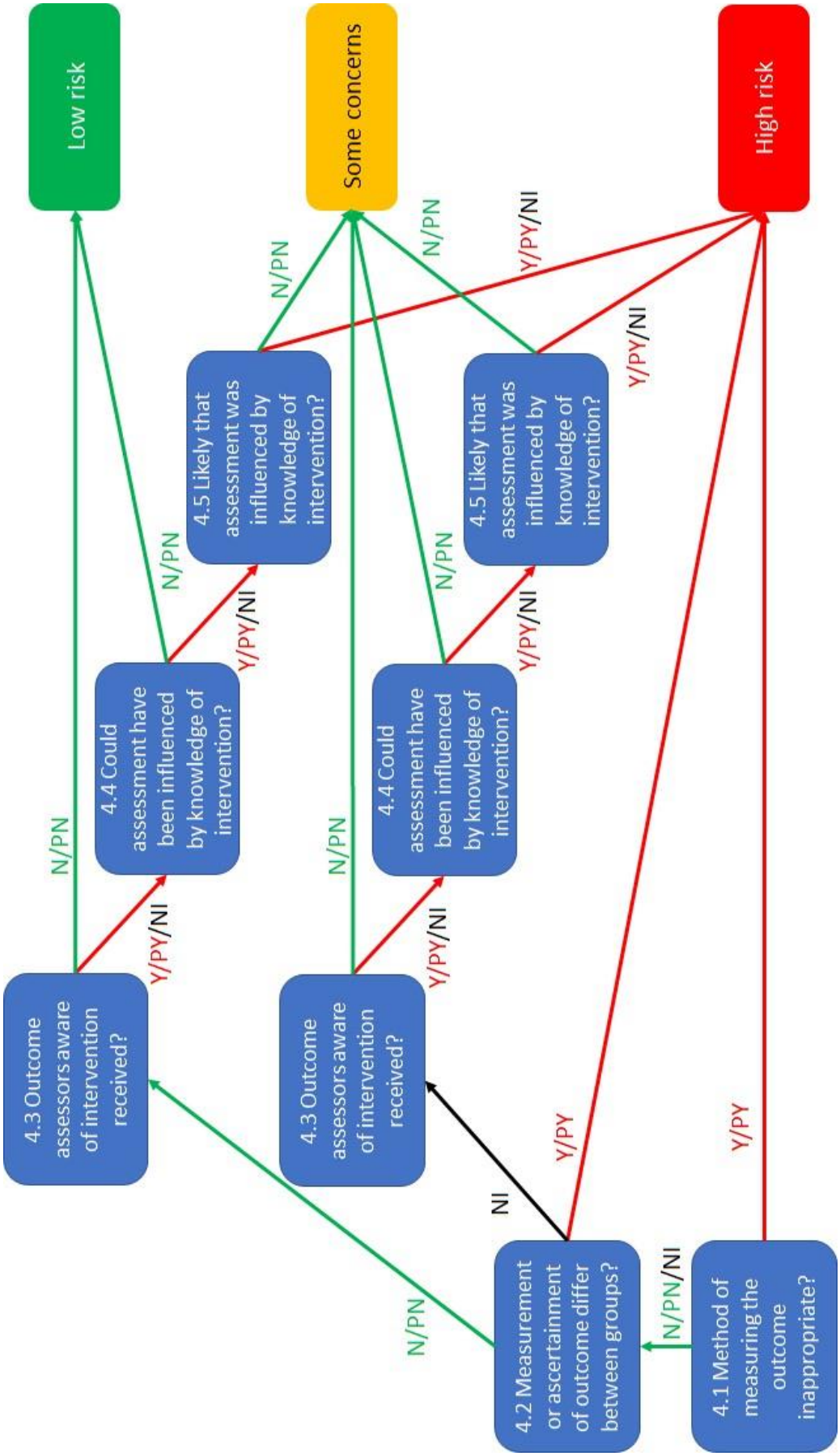


4th domain -Risk of bias in measurement of the outcome

Signalling questions	**Elaboration**	**Response options**
4.1 Was the method of measuring the outcome inappropriate?	This question aims to identify methods of outcome measurement (data collection) that are unsuitable for the outcome they are intended to evaluate. The question dies not aim to assess whether the choice of outcome being evaluated was sensible (e.g. because it is a surrogate or proxy for the main outcome of interest). In most circumstances, for the pre-specified outcomes,the answer to this question will be **No** or **Probably No**. Answer Yes or Probably Yes if the method of measuring the outcome is inappropriate, for example because: 1) It is unlikely to be sensitive to plausible intervention effects (e.g. important ranges of outcomevalues fall outside levels that are detectable using this measurement method) 2) The measurement instrument has been demonstrated to have poor validity.	Y/PY/PN/N/NI
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	Comparable methods of outcome measurement (data collection) involve the same measurement methods and thresholds, used at comparable time points. Differences between intervention groups may arise because of diagnostic detection bias in the context of passive collection of outcome data or if an intervention involves additional visits to a healthcare provider, leading to additional opportunities for outcome events to be identified.	Y/PY/PN/N/NI
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	Answer No if outcome assessors were blinded to intervention status. For participant-reported outcomes, the outcome assessor is the study participant.	NA Y/PY/PN/N/NI

Signalling questions	**Elaboration**	**Response options**
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	Knowledge of the assigned intervention could influence participant-reported outcoms (such as level of pain), observer-reported outcomes involving some judgement and intervention provider decision outcomes. They are unlikely to influence observer-reported outcomes that do not involve judgement, for example all-cause mortality.	NA Y/PY/PN/N/NI
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention recieved?	This question distinguishes between situations in which (i) knowledge of intervention status have influenced outcome assessment but there is no reason to believe that it did (assessed as Some concerns) from those in which (ii) knowledge of intervention status was likely to influence outcome assessment (assessed as High risk of bias). When there are strong levels of belief in either beneficial or harmful effects of the intervention, it is more likely that the outcome was influenced by knowledge of the intervention received.	NA Y/PY/PN/N/NI

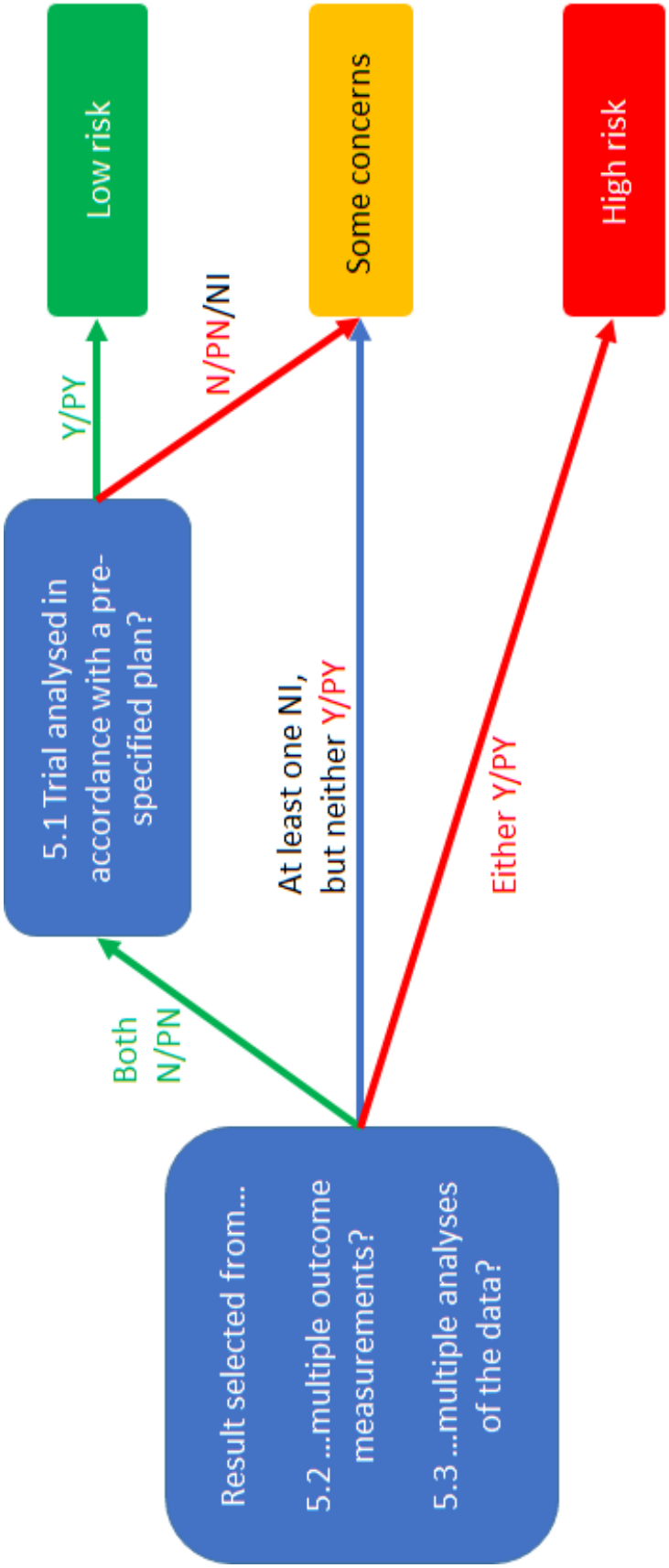
Algorithm for suggested judgement of risk of bias in measurement of the outcome



Signalling questions	**Elaboration**	**Response options**
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	If the researchers' pre-specified intentions are available in sufficient detail, then planned outcome measurements and analyses can be compared with those presented in the published report(s). To avoid the possibility of selection of the reported result, finalization of the analysis intentions must precede availability of unblinded outcome data to the trial investigators. Changes to analysis plans that were made before unblinded outcome data were available or that were clearly unrelated to the result (e.g. due to a broken machine making data collection impossible) do not raise concerns about bias in selection of the reported result.	Y/PY/PN/N/NI
5.2 Is the numerical result being assessed likely to have been selected on the basis of the results from multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	A particular outcome domain (i.e. a true state of endpoint of interest) may be measured in multiple ways.For example the domain pain may be measured using multiple scales (e.g. a visual analogue scale and the McGill Pain Questionnaire) each at multiple time points. If multiple measurements were made but only one or a subset is reported on the basis of the results (e.g. statistical significance) there is a high risk of bias in the fully reported result. Attention should be restricted to outcome measurements that are eligible for consideration by the RoB 2 tool user. For example, if only a result using a specific measurement scale is eligible for inclusion in a meta-analysis and this is reported by the trial, then there would not be an issue of selection even if this result was reported in preference to the result from a different measurement scale. Answer **Yes** or **Probably Yes** if: there is a clear evidence (usually through examination of a trial protocol or statistical analysis plan) that a domain was measured in multiple eligible ways, but data for only one or a subset of measures is fully reported (without justification) and the fully reported results is likely to have been selected on the basis of the results. Selection on the basis of the results can arise from a desire for findings to be newsworthy, sufficiently noteworthy to merit publication or to confirm a prior hypothesis. For example, trialists who have a preconception or vested interest in showing that an experimental intervention is beneficial may be inclined to report outcome measurements selectively that are favorable o the experimental intervention. Answer **No** or **Probably No** if: 1) there is clear evidence (usually through examination of a trial protocol or statistical analysis plan) that all eligible reported results for the outcome domain correspond to all intended outcome measurements. 2) there is only one possible way in which the outcome domain can be measured (hence there is no opportunity to select from multiple measures) 3) outcome measurements are inconsistent across different reports on the same trial but the trialists have provided the reason for the inconsistency and it is not related to the nature of the results. Answer **No Information** if: Analysis intentions are not available or the analysis intentions are not reported in sufficient detail to enable an assessment and there is no more than one way in which the outcome domain could have been measured.	Y/PY/PN/N/NI

Signalling questions	**Elaboration**	**Response options**
5.3 Is the numerical result being assessed likely to have been selected on the basis of the results from multiple eligible analyses of the data?	A particular outcome measurement may be analysed in multiple ways. Examples include: unadjusted and adjusted models; final value vs change from baseline vs analysis of covariance; transformations of variables; different definitions of composite outcomes; conversion of continuously scaled outcome to categorical data with different cut-points; different sets of covariates for adjustment; and different strategies for dealing with missing data. Application of multiple methods generates multiple effect estimates for a specific outcome measurement. If multiple estimates are generated but only one or a subset is reported on the basis of the results (e.g. statistical significance), there is a high risk of bias in the fully reported result. Attention should be restricted to analyses that are eligible for consideration by the RoB 2 tool user. For example, if only the result from an analysis of post-intervention values is eligible for inclusion in a meta-analysis and this is reported by the trial then there would not be an issue of selection even if this result was reported in preference to the result from an analysis of changes from baseline. Answer **Yes** or **Probably Yes** if: there is clear evidence (usually through examination of a trial protocol or statistical analysis plan) that a measurement was analysed in multiple eligible ways, but data for only one or a subset of analyses is fully reported (without justification) and the fully reported result is likely to have been selected on the basis of the results. Selection on the basis of the results arises from a desire for findings to be newsworthy, sufficiently noteworthy to merit publication or to confirm a prior hypothesis. For example, trialists who have a preconception or vested interest in showing that an experimental intervention is beneficial may be inclined to selectively report analyses that are favorable to the experimental intervention. Answer **No** or **Probably No** if: 1) there is clear evidence (usually through examination of a trial protocol or statistical analysis plan) that all eligible reported results for the outcome measurement correspond to all intended analyses. 2) there is only one possible way in which the outcome measurement can be analysed (hence there is no opportunity to select from multiple analyses). 3) analyses are inconsistent across different reports on the same trial, but the trialists have provided the reason for the inconsistency and it is not related to the nature of the results. Answer **No Information** if: analysis intentions are not available or the analysis intentions are not reported in sufficient detail to enable an assessment and there is moire than one way in which the outcome measurement could have been analysed.	Y/PY/PN/N/NI

Algorithm for suggested judgement of risk of bias in selection of the reported result



APPENDIX 2-ROBINS-I tool

Bias domains

Domain	**Explanation**
Pre-intervention Bias due to confounding	Baseline confounding occurs when one or more prognostic variables (factors that predict the outcome of interest) also predicts the intervention received at baseline. ROBINS-I can also address time-varying confounding, which occurs when individuals switch between the interventions being compared and when post-baseline prognostic factors affect the intervention received after baseline.
Bias in selection of participants into the study	When exclusion of some eligible participants or the initial follow up time of some participants or some outcome events is related to both intervention and outcome, there will be an association between interventions and outcome even if the effects of the interventions are identical. This form of selection bias is distinct from confounding. A specific example is bias due to the inclusion of prevalent users, rather than new users, of an intervention.
At intervention Bias in classification of interventions	Bias introduced by either differential or non-differential misclassification of intervention status. Non-diferential is unrelated to the outcome and will usually bias the estimated effect of intervention towards the null. Differential misclassification occurs when misclassification of intervention status is related to the outcome of the risk of the outcome and is likely to lead to bias.
Post-intervention Bias due to deviations from intended interventions	Bias that arises when there are systematic differences between experimental intervention and comparator groups in the care provided, which represent a deviation from the intended intervention(s). Assessment of bias in this domain will depend on the type of effect of interest (either the effect of assignment to intervention or the effect of starting and adhering to intervention).
Bias due to missing data	Bias that arises when later follow-up is missing for individuals initially included and followed (e.g. differential loss to follow-up that is affected by prognostic factors); bias due to exclusion of individuals with missing information about intervention status or other variables such as cofounders.
Bias in measurement of outcomes	Bias introduced by either differential or non-differential errors in measurement of outcome data. Such bias can arise when outcome assessors are aware of intervention groups, or if measurement errors are related to intervention status or effects.
Bias in selection of the reported result	Selective reporting of results in a way that depends on the findings.

Signalling questions	Elaboration	Response options
1.1 Is there potential for confounding of the effect of intervention in this study? If N/PN: the study can be considered at low risk of bias due to confounding and no further signalling questions need to be considered.	In rare situations, such as when studying harms that are very unlikely to be related to factors that influence treatment decisions, no confounding is expected and the study can be considered to be at low risk of bias due to confounding, equivalent to a fully randomized trial. There is no NI option for this signalling question.	Y/PY/PN/NI
1.2 If Y/PY to 1.1: Was the analysis based on splitting participants' follow up time according to intervention received? If N/PN answer question 1.4 to 1.6	If participants could switch between intervention groups then associations between interventionand outcome may be biased by time-varying confounding. This occurs when prognostic factors influence switches between intended interventions.	NA Y/PY/PN/N/NI
1.3 If Y/PY to 1.2: Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? If N/PN answer questions 1.4 to 1.6 If Y/PY answer questions 1.7 and 1.8	If intervention switches are unrelated to the outcome, for example when the outcome is an unexpected harm, then time-varying confounding will not be present and only control for baseline confounding is required.	NA Y/PY/PN/N/NI
1.4 Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Appropriate methods to control for measured confounders include stratification, regression, matching, standardization and inverse probability weighting. They may control for individual variables or for the estimated propensity score. Inverse probability weighting is based on a function of the propensity score. Each method depends on the assumption that there is no unmeasured or residual confounding.	NA Y/PY/PN/N/NI

Signalling questions	**Elaboration**	**Response options**
1.5 If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the vaiables available in this study?	Appropriate control of confounding requires that the variables adjusted for are valid and reliable measures of the confounding domains. For some topics, a list of valid and reliable measures of confounding domians will be specified in the review protocol but for others such a list may not be available. Study authors may cite references to support the use of a particular measure. If authors control for confounding variables with no indication of their validity or reliability pay attention to the subjectivity of the measure. Subjective measures (e.g. based on self-report) may have lower validity and reliability than objective measures such as lab findings.	NA Y/PY/PN/N/NI
1.6 Did the authors control for any post-intervention variables that could have been affected by the intervention?	Controlling for post-intervention variables that are affected by intervention is not appropriate. Controlling for mediating variables estimates the direct effect of intervention and may introduce bias. Controlling for common effects of intervention and outcome introduces bias.	NA Y/PY/PN/N/NI
1.7 Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Adjustment for time-varying confounding is necessary to estimate the effect of starting and adhering to intervention in both randomized trials and NRSI. Appropriate methods include those based on inverse probability weighting. Standard regression models that include time-updated confounders may be problematic if time-varying confounding is present.	NA Y/PY/PN/N/NI
1.8 If Y/PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Appropriate control of confounding requires that the variables adjusted for are valid and reliable measures of the confounding domains. For some topics, a list of valid and reliable measures of confounding domians will be specified in the review protocol but for others such a list may not be available. Study authors may cite references to support the use of a particular measure. If authors control for confounding variables with no indication of their validity or reliability pay attention to the subjectivity of the measure. Subjective measures (e.g. based on self-report) may have lower validity and reliability than objective measures such as lab findings.	NA Y/PY/PN/N/NI

2nd domain-Risk of bias in selection of participants into the study

Signalling questions	Elaboration	Response options
2.1 Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to 2.1: go to 2.4?	This domain is concerned only with selection into the study based on participant characteristics observed after the start of intervention. Selection based on characteristics observed before the start of intervention can be addressed by controlling for imbalances between experimental intervention and comparator groups in baseline characteristics that are prognostic for the outcome (baseline confounding)	Y/PY/PN/N/NI
2.2 If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	Selection bias occurs when selection is related to an effect of either intervention or a cause of intervention and an effect of either the outcome or a cause of the outcome. Therefore, the result is at risk of selection bias if selection into the study is related to both the intervention and the outcome.	NA Y/PY/PN/N/NI
2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?		NA Y/PY/PN/N/NI
2.4 Do the start of follow-up and start of intervention coincide for most participants?	If participants are not followed from the start of the intervention then a period of follow-up has been excluded and individuals who experienced the outcome soon after intervention will be missing from analyses. This problem may occur when prevalent rather than new (incident) users of the intervention are included in analyses.	Y/PY/PN/N/NI
2.5 If Y/PY to 2.2 and 2.3 or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	It is principle possible to correct for selection biases for example by using inverse probability weights to create a pseudo-population in which the selection bias has been removed or by modelling the distributions of the missing participants or follow up times and outcome events and including them using missing data methodology. However, such methods are rarely used and the answer to this question will usually be **No**.	NA Y/PY/PN/N/NI

Signalling questions	Elaboration	Response options
3.1 Were intervention groups clearly defined?	A prerequisite for an appropriate comparison of interventions is that the interventions are well defined. Ambiguity in the definition may lead to bias in the classification of participants. For individual-level intervention, criteria for considering individuals to have received each intervention should be clear and explicit covering issues such as type, setting, dose, frequency, intensity and/or timing of intervention. For population-level interventions (e.g. measures to control air population), the question relates to whether the population is clearly defined, and the answer is likely to be **Yes**.	Y/PY/PN/N/NI
3.2 Was the information used to define intervention groups recorded at the start of the intervention?	In general, if information about interventions received is available from sources that could not have been affected by subsequent outcomes, then differential misclassification of intervention status is unlikely. Collection of the information at the time of the intervention makes it easier to avoid such misclassification. For population-level interventions (e.g. measures to control air population), the answer to this question is likely to be **Yes**.	Y/PY/PN/N/NI
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Collection of the information at the time of the intervention may not be sufficient to avoid bias. The way in which the data are collected for the purposes of the NRSI should also avoid misclassification.	Y/PY/PN/N/NI

Signalling questions	Elaboration	Response options
4.1 Were there deviations from the intended intervention beyond what would be expected in usual practice?	Deviation that happen in usual practice following the intervention (for example, cessation of a drug intervention because of acute toxicity) are part of the intended intervention and therefore do not lead to bias in the effect of assignment to intervention. Deviations may arise due to expectations of a difference between intervention and comparator (for example because participants feel unlucky to have been assigned to the comparator group and therefore seek the active intervention or components of it or other interventions). Such deviations are not part of usual practice so may lead to biased effect estimates. However, these are not expecte in observational studies of individuals in routine care.	Y/PY/PN/N/Ni
4.2 If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Deviations from intended interventions that do not reflect usual practice will be important if they affect the outcome, but not otherwise. Furthermore, bias will arise only if there is imbalance in the deviations across the two groups.	NA Y/PY/PN/N/NI
4.3 Were important co-interventions balanced across intervention groups?	Risk of bias will be higher if unplanned co-interventions were implemented in a way that would bias the estimated effect of intervention. Co-interventions will be important if they affect the outcome, bt not otherwise. Bias will arise only if there is imbalance in such co-interventions between the intervention groups. Consider the co-interventions including any administered in this study. Consider whether these co-interventions are balanced between intervention groups.	Y/PY/PN/N/NI
4.4 was the intervention implemented successfully for most participants?	Risk of bias will be higher if the intervention was not implemented as intended by, for example, the health care professionals delivering care during the trial. consider whether implementation of the intervention was successful for the most participants.	Y/PY/PN/N/NI
4.5 Did study participants adhere to the assigned intervention regimen?	Risk of bias will be higher if participants did not adhere to the intervention as intended. Lack of adherence includes imperfect compliance, cessation of intervention, crossovers to the comparator intervention and switches to another active intervention. Consider available information on the proportion of study participants who continued with their assigned intervention throughout follow up and answer **No** or **Probably No** if this propostion is high enough to raise concerns. Answer **Yes** for studies of interventions that are administered once so that imperfect adherence is not possible. We distinguish between analyses where follow-up time after interventions switches (including cessation of intervention) is assigned to: 1) The new intervention 2) The original intervention 3) Is addressed under time-varying confounding and should not be considered further here.	Y/PY/PN/N/NI

Signalling questions	**Elaboration**	**Response options**
4.6 If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	It is possible to conduct an analysis that corrects for some types of deviation from the intended intervention. Examples of appropriate analysis strategies include inverse probability weighting or instrumental variable estimation. It is possible that a paper reports such an analysis without reporting information on the deviations from intended intervention but it would be hard to judge such an analysis to be appropriate in the absence of such information. Specialist advice may be needed to assess studies that used these approaches. If everyone in one group received a co-intervention, adjustments cannot be made to overcome this.	NA Y/PY/PN/N/NI

5th domain-Risk of bias due to missing data

Signalling questions	Elaboration	Response options
5.1 Were outcome data available for all or nearly all participants?	Nearly all should be interpreted as enough to be confident of the findings and a suitable proportion depends on the context. In some situations, availability of data from 95% (or possibly 90%) of the participants may be sufficient, providing that events of interest are reasonably common in both intervention groups. One aspect of this is that review authors would ideally try and locate an analysis plan for the study.	Y/PY/PN/N/NI
5.2 Were participants excluded due to missing data on intervention status?	Missing intervention status may be a problem. This requires that the intended study sample is clear which it may not be in practice.	Y/PY/PN/N/NI
5.3 Were participants excluded due to missing data on other variables needed for the analysis?	This question relates particularly to participants excluded from the analysis because of missing information on confounders that were controlled for in the analysis.	Y/PY/PN/N/NI
5.4 If PN/N to 5.1 or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	This aims to elicit whether either (i) differential proportion of missing observations or (ii) differences in reasons for missing observations could substantially impact on our ability to answer the question being addressed. Similar includes some minor degree of discrepancy across intervention groups as expected by chance.	NA Y/PY/PN/N/NI
5.5 If PN/N to 5.1 or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Evidence for robustness may come from how missing data were handled in the analysis and whether sensitivity analyses were performed by the investigators or occasionally from additional analyses performed by the systematic reviewers. It is important to assess whether assumptions employed in analyses are clear and plausible. Both content knowledge and statistical expertise will often be required for this. For instance, use of a statistical method such as multiple imputation does not guarantee an appropriate answer. Review authors should seek naïve (complete-case) analyses for comparison and clear differences between complete-case and multiple imutation-based findings should lead to careful assessment of the validity of the methods used.	NA Y/PY/PN/N/NI

Signalling questions	Elaboration	Response options
6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Some outcome measures involve negligible assessor judgement e.g. all-cause mortality or non-repeatable automated laboratory assessments. Risk of bias due to measurement of these outcomes would be expected to be low.	Y/PY/PN/N/NI
6.2 Were outcome assessors aware of the intervention received by study participants?	If outcome assessors were blinded to intervention status, the answer to this question would be **No**. in other situations, outcome assessors may be unaware of the intervention being received by participants despite there being no active blinding by the study investigators; the answer to this question would then also be **No**. In studies where participants report their outcomes themselves for example in a questionnaire, the outcome assessor is the study participant. In an observational study, the answer to this question will usually be **Yes** when the participants report their outcomes themselves.	Y/PY/PN/N/NI
6.3 Were the methods of outcome assessment comparable across intervention groups?	Comparable assessment methods (i.e. data collection) would involve the same outcome detection methods and thresholds, same time point, same definition, and same measurements.	Y/PY/PN/N/NI
6.4 Were any systematic errors in measurement of the outcome related to intervention received?	This question refers to differential misclassification of outcomes. Systematic errors in measuring the outcome, if present could cause bias if they are related to intervention or to a confounder of the intervention-outcome relationship. This will usually be due either to outcome assessors being aware of the intervention received or to non-comparability of outcome assessment methods, but there are examples of differential misclassification arising despite these controls being in place.	Y/PY/PN/N/NI

Signalling questions	Elaboration	Response options
7.1 Is the reported effect estimate likely to be selected, on the basis of the results from multiple outcome measurements within the outcome domain?	For a specified outcome domain, it is possible to generate multiple effect estimates for different measurements. If multiple measurements were made but only one or a subset is reported, there is a risk of selective reporting on the basis of results.	Y/PY/PN/N/NI
7.2 Is the reported effect estimate likely to be selected, on the basis of the results from multiple analyses of the intervention-outcome relationship?	Because of the limitations of using data from non-randomized studies for analyses of effectiveness (need to control confounding, substantial missing data, etc), analysts may implement different analytic methods to address these limitations. Examples include unadjusted and adjusted models; use of final value vs change from baseline vs analysis of covariance; different transformations of variables; a continuously scaled outcome converted to categorical data with different cut-points; different sets of covariates used for adjustment; and different analytic strategies for dealing with missing data. Application of such methods generates multiple estimates of the effect of the intervention vwersus the comparator on the outcome. If the analyst does not pre-specify the methods to be applied and multiple estimates are generated but only one or a subset is reported, there is a risk of selective reporting on the basis of results.	Y/PY/PN/N/NI
7.3 Is the reported effect estimate likely to be selected, on the basis of the results from different subgroups?	Particularly with large cohorts often available from routine data sources, it is possible to generate multiple effect estimates for different subgroups or simply to omit varying proportions of the original cohort. If multiple estimates are generated but only one or a subset is reported, there is a risk of selective reporting on the basis of results.	Y/PY/PN/N/NI

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