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Complete List of Authors:	Liu, Anqi; Shanghai Stomatological Hospital, Department of Orthodontics; Shanghai Key Laboratory of Craniomaxillofacial Development and Diseases Zhang, Weihua; Shanghai Stomatological Hospital, Department of Orthodontics; Shanghai Key Laboratory of Craniomaxillofacial Development and Diseases Shi, Shuangshuang; Shanghai Stomatological Hospital, Department of Orthodontics; Shanghai Key Laboratory of Craniomaxillofacial Development and Diseases Chen, Zhuoyue; Shanghai Stomatological Hospital, Department of Orthodontics; Shanghai Key Laboratory of Craniomaxillofacial Development and Diseases Liu, Yuehua; Shanghai Stomatological Hospital, Department of Orthodontics; Shanghai Key Laboratory of Craniomaxillofacial Development and Diseases Lu, Yun; Shanghai Stomatological Hospital, Department of Orthodontics; Shanghai Key Laboratory of Craniomaxillofacial Development and Diseases
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Efficacy of a modified Twin Block appliance compared to the traditional Twin Block appliance in children with hyperdivergent mandibular retrognathia: a single-center, single-blind, randomized controlled trial

Anqi Liu[1,2] , Weihua Zhang[1,2], Shuangshuang Shi[1,2], Zhuoyue Chen[1,2], Yuehua Liu[1,2*], Yun Lu[1,2*]

[1] Department of Orthodontics, Shanghai Stomatological Hospital & School of Stomatology, Fudan University, Shanghai, China

[2] Shanghai Key Laboratory of Craniomaxillofacial Development and Diseases, Fudan University, Shanghai, China

*Correspondance:

1. Dr. Yun Lu,

Shanghai Stomatological Hospital & School of Stomatology, Fudan University

No.356 East Beijing Road, Shanghai 200001, China

Tel.: +86-18817878669 Email: luyun@fudan.edu.cn

2. Prof. Yuehua Liu,

Shanghai Stomatological Hospital & School of Stomatology, Fudan University

No.356 East Beijing Road, Shanghai 200001, China

Tel.: +86-13818889988 Email: liuyuehua@fudan.edu.cn

ABSTRACT

Introduction

Compensatory mouth breathing, caused by nasopharyngeal obstructive disease, is the main cause of hyperdivergent mandibular retrognathia in children. Such deformities require effective growth guidance before pubertal growth peaks. The traditional mandibular advancement device (MAD), Twin Block (TB), can guide the forward development of the mandible, but the side effect of increasing the vertical dimension of the lower facial third, worsens the facial profile of children with divergent growth trends. To solve this problem, a modified Twin Block (LLTB) appliance was designed to control the vertical dimension by intruding incisors and inhibiting the elongation of posterior teeth during the advancement of the mandible. This avoids the side effects of traditional appliances and effectively guides the growth of the mandible in a normal direction.

Methods and analysis

The study is designed as a single-center, single-blind, randomized, parallel controlled trial. We aim to enroll 60 children aged 9-14 years with hyperdivergent skeletal Class II malocclusion, using a 1:1 allocation ratio. Participants will be randomly assigned to receive either the TB or LLTB treatment. The primary outcome will be a change in the angle of the mandibular plane relative to the anterior cranial base. The secondary outcomes will include changes in the sagittal maxillomandibular relation, occlusal plane, facial height, morphology of the mandible, and upper airway width. Safety endpoints will also be evaluated.

Ethics and dissemination

Ethical approval was obtained from the ethics committee of Shanghai Stomatological Hospital. All participants and their guardians will be fully informed of the study and sign an informed consent form before joining the trial. The results will be publicly available in peer-reviewed scientific journals.

Trial registration number: ChiCTR2000035882

Key words: hyperdivergent mandibular retrognathia, mandibular advancement, modified Twin Block, vertical control, randomized controlled trial

Strengths and limitations of this study

- Selection bias will be minimized by designing a randomized controlled trial to compare the efficacy of modified LLTB with conventional TB in children with hyperdivergent mandibular retrognathia.
- This study will provide a new method and evidence-based basis for the treatment of mandibular advancement in children with long-face growth patterns.
- A key limitation is the inability to blind the researchers involved in treatment.

INTRODUCTION

Convex deformity is a common facial deformity in children, and the treatment of children with long-face growth patterns is a challenging clinical problem. In recent years, the number of children with nasopharyngeal airway obstructive disease has been increasing, and the resulting compensatory mouth breathing is the main cause of dental and maxillofacial deformities in these children[1].

We investigated the prevalence of deciduous dentition malocclusion among children aged 3-5 years in Shanghai and analyzed the correlation between malocclusion and oral habits, dietary structure, and upper respiratory diseases[2]. Research has indicated that chronic rhinitis and adenotonsillar hypertrophy are highly correlated with mouth breathing[3], accompanied by a higher prevalence of hyperdivergent malocclusion[4].

Children are in an important stage of dental and maxillofacial development and respiratory pattern formation[5]. Long-term airway obstruction and mouth breathing can cause narrowing of the maxillary dental arch, increased anterior face height, lip incompetence, and backward and downward mandibular rotation, resulting in mandibular retrognathia[6 7]. Mandibular retrognathia is an important risk factor for sleep apnea, which can affect children's behavioral psychology and social ability[8]. Such deformities have serious physical and psychological effects on children and their parents[9]. If effective growth modification is not carried out before the adolescent growth spurt, only orthognathic surgery can achieve satisfactory results in adulthood[10].

Hyperdivergent convex deformity in children, caused by long-term mouth breathing, is one of the difficulties in orthodontic treatment[11 12]. The clinical methods for mandibular growth guidance mainly include Twin Block (TB), activator, and Herbst, whose main function is to protrude the mandible and stimulate its growth[13-15]. However, the above traditional mandibular advancement devices (MADs) have obvious limitations in children with long-face growth patterns. In children with deep overbite before treatment, the forward movement of the mandible is accompanied by an open bite of the posterior teeth, which leads to continued elongation of the posterior teeth, an increase in the inferior height, and deterioration of the profile[16]. Therefore, traditional MADs are not applicable to patients with hyperdivergent mandibular retrognathia[17].

To overcome these difficulties, the modified Twin Block (LLTB, figure 1) appliance

has been designed and patented (Yun Lu, Yuehua Liu, Qiang Li, Tingchao Lan, Min Zhao, Huanhuan Li. Double-occlusal pad appliance, 2019.11.12, China, ZL201821348135.7). In the process of guiding the forward development of the mandible, the LLTB appliance can simultaneously intrude the upper and lower anterior teeth, flatten the inclined occlusal plane, avoid elongation of the posterior teeth during the occlusal adjustment process, and effectively guide the growth direction of the mandible. LLTB has been used in clinical cases of hyperdivergent mandibular retrognathia, and the effect of this modified appliance needs to be systematically analyzed. This study aims to analyze and compare the clinical effects of TB and LLTB in children with hyperdivergent mandibular retrognathia. This comparison will provide valuable information to guide the clinical treatment of such cases.

METHODS AND ANALYSIS

Study design

This study is designed as a single-center, single-blind, randomized parallel controlled trial, aiming to evaluate the efficacy of a modified LLTB and compare its effect with the traditional TB in children with hyperdivergent mandibular retrognathia. The study is registered at http://www.chictr.org.cn/index.aspx, which can be accessed online. The trial will be performed in the Department of Orthodontics at Shanghai Stomatological Hospital. We will recruit 60 patients who meet the inclusion criteria and randomly assign them to one of two treatment groups, TB or LLTB, in a 1:1 ratio. Treatment in both groups will last for 12 months, with follow-up visits every 2 months. Participants will be assessed at the following time points: the baseline (before treatment), the end of the treatment (after 12 months of treatment), and follow-up (6 months after treatment finishes). A brief flowchart of the study is provided in figure 2 and the trial schedule is presented in table 1. The design adheres to the Consolidated Standards of Reporting Trials (CONSORT) statement recommendations.

Table 1 Trial schedule chart

	Screening	Enrollment	Randomization	Treatment			Follow-up		
				0 month	6 month	12 month	2 month	4 month	6 month
Informed consent	O								
Demographic characteristic	O								
Medical history	O								
Oral/facial examination	O					O	O	O	O
Photograph	O					O			O
Dental cast	O					O			
Cephalometrics	O					O			
CBCT	O					O			
Inclusion criteria		O							
Exclusion criteria		O							
Allocation			O						
Orthodontic treatment				O	O	O			
Questionnaire						O			
Safety assessment					O	O			
Compliance of participants					O	O			

CBCT, cone beam CT

Patient and public involvement

There was no patient or public involvement in the design, recruitment, or conduct of this study. After the treatment, researchers will communicate with the participants and their guardians about the efficacy and follow-up arrangements.

Study patient

A total of 60 eligible patients will be recruited for the study after screening. The following eligibility criteria were developed to ensure the precision of the results:

Inclusion criteria:

1. Aged 9-14 years, no gender limit.

2. Protrusion deformity, poor chin morphology, mandibular retrusion, ANB > 5°, and normal maxillary development.

3. Children with a high mandibular plane angle (SN-MP), 35°< SN-MP < 45°. Ethical considerations: children treated with traditional TB are prone to elongation of the posterior teeth, causing the backward and downward rotation of the mandible. The increase in facial height will aggravate the original long face and cause ethical issues; therefore, the SN-MP is controlled within 45°. Participants included in this study are children showing a tendency of a long-face growth pattern, but have not yet developed

into severe long faces. Even if the facial height increases after treatment with TB, it is still acceptable.

4. Narrow upper airway.

5. Participants have good compliance and are able to wear appliances as required and rechecked regularly.

Exclusion criteria:

1. Children who have passed pubertal peak according to the modified cervical spine analysis method (Cvs4 stage).

2. Children who have symptoms of temporomandibular joint disorders.

3. Children with loose deciduous molar.

4. Patients with systemic disease.

Recruitment and randomization process

Participants will be recruited through outpatient clinics and hospital-based advertisements. If patients with mandibular retrognathia are interested in participating in the trial, a pretreatment screening visit with a clinical research assistant will be conducted in the outpatient clinic before enrollment. Once considered eligible for enrollment, the participants and their guardians will sign an informed consent form after fully understanding the study. The enrolled participants will be randomly assigned to one of the two treatment groups, either TB or LLTB, in a 1:1 ratio with block randomization. Random assignment will be performed by an independent statistician using the central randomization website (Public Health of Biological Statistics Platt, Fudan, http://redcap.fudan.edu.cn). Allocation concealment will be used to avoid the potential selection bias.

Description of the interventions

Orthodontic treatments in both groups will be performed by experienced orthodontists following a consistent protocol. In the test group, a LLTB appliance combined with brackets and archwires will be used to intrude the upper anterior teeth, flatten the inclined occlusal plane, and guide the mandible to rotate counterclockwise with the adjustment of the blocks. Participants in the control group will wear the TB appliance every day without adjustment of the anterior teeth. The treatments will continue for 12 months, with follow-up every 2 months. Dental casts, digital oral and facial photographs, lateral radiographs, and cone beam CT (CBCT) images will be obtained

before and after treatment. Third-party interpreters will perform cephalometrics, and the dental-skeletal-soft tissue parameters will be comprehensively analyzed in the sagittal, transverse, and vertical dimensions.

Treatment group

Participants in the trial group will be treated with LLTB for mandibular advancement. The fixed LLTB appliance is designed with two double buccal tubes in the posterior region, which are connected to the anterior brackets by an archwire. The primary archwire is 0.012- or 0.014-inch nickel-titanium wire for aligning the anterior teeth, and the intrusion archwire is 0.016 stainless steel wire for intruding the upper anterior teeth and leveling the occlusal plane in the anterior region. Along with the intrusion of the anterior teeth, occlusal pads will be grinded to lower the height and guide the mandible to rotate forward and upward to improve the chin profile.

Control group

The participants in the control group will be treated with TB for mandibular advancement. The removable TB is unable to achieve anterior teeth adjustment and, thus, will not guide the mandible to rotate counterclockwise during treatment. Only the adam clasps will be adjusted for good retention at each follow-up visit.

Outcome measures

The measurement outcomes in this study are mainly derived from the comparison of cephalometric measurements on lateral radiographs before and after treatment, with photographs and dental casts as auxiliary references.

Primary outcome

The primary outcome of this study is the degree of change in the SN-MP. SN-MP is the angle of intersection of the mandibular plane and the anterior cranial base plane, which indicates the steepness of the mandibular plane and the height of the lower facial third and thus can reflect the vertical growth pattern. The larger the SN-MP, the greater the amount of vertical growth and the corresponding increase in treatment difficulty. The SN-MP is a commonly used parameter for evaluating the downward and backward rotation of the mandible and is also a valid indicator for assessing the efficacy of vertical control.

Secondary outcomes

The secondary outcomes include the following:

1. The ANB angle represents the anterior-posterior relationship between the maxilla and mandible.
2. The angle of the occlusal plane (OP-SN) represents the inclination of the occlusal plane. The larger the angle, the steeper the occlusal plane and the more serious the tendency of the protrusion type.
3. Tooth height analysis: The vertical height of the teeth will be analyzed by measuring the distance of the upper and lower anterior teeth and the posterior teeth relative to the reference plane using U1-PP, U6-PP, L1-MP, and L6-MP.
4. Facial height analysis: Facial height will be analyzed by two parameters, S-Go/N-Me and ANS-Me/N-Me, which represent the ratio of posterior face height to anterior face height and the percentage of lower face height to total face height, respectively.
5. Mandibular morphology: The changes in mandibular morphology will be analyzed by measuring the mandibular length (Co-Gn), ramus height (Ar-Go), mandibular body length (Go-Me), and Gonial angle (Ar-Go'-Me).
6. The facial convexity angle (Ns-Sn-Pos) will be measured to assess lateral protrusion of the soft tissue.
7. Upper airway analysis: TB-TPPW and V-LPW measurements will be used to assess the widths of the middle and lower segments of the upper airway.

Safety monitoring

The MADs used in both groups in this study have no obvious adverse effects on the participants if they are worn according to the doctor's advice. Possible risks are mainly the adverse effects of poor oral hygiene during orthodontic treatment, such as enamel demineralization and gingivitis. Timely measures such as oral cleaning and hygiene promotion can reduce symptoms.

Sample size calculation

Based on data from a pilot study, the primary outcome is SN-MP at 12 months post-treatment relative to that before treatment, with a mean difference of 1.5° and a standard deviation (SD) of 1.87°. Using a conventional α of 5% and β of 20%, 26 participants are required per group. With a dropout rate of 10%, the number of participants in each group is 30, and the final sample size for this study is 60 participants, randomized in a

1:1 ratio.

Statistical analysis

During the measurement process, statistical analysts will be blinded to the participants' personal information and group assignments. Statistical significance will be set at $p<0.05$, based on a two-sided test. Continuous variables will be described as mean ± SD or median (range), depending on whether they conform to a normal distribution. The t-test or rank sum test will be used to compare continuous data between groups. The $\chi 2$ test or Fisher's exact test will be used to analyze categorical variables. All statistical analyses will be performed using the statistical software SPSS V.26.0.

ETHICS AND DISSEMINATION

The study has been approved by the ethics committee of Shanghai Stomatological Hospital (approval no. [2021]023; [2022]005) and will comply with the Declaration of Helsinki. All amendments to the program will be implemented with the approval of the ethics committee. All participants and their guardians will be fully informed of the study and sign an informed consent form before joining the study. They will be informed that they can withdraw from the study at any time without explanation.

The results will be publicly available in peer-reviewed scientific journals and presented at academic conferences.

DISCUSSION

The influence of breathing patterns on maxillofacial growth and development has been confirmed by past studies. Compared with nasal breathing, mouth breathing causes children and adolescents to show vertical growth patterns with increased facial height and a retrognathic mandible with a high mandibular plane angle due to backward and downward rotation[18 19].

Currently, children with hyperdivergent mandibular retrognathia are difficult to treat. Orthodontists can guide and improve mandibular growth in the adolescent growth spurt by making good use of the growth potential[20]. Due to the backward rotation of the mandible and infra-anterior inclination of the occlusal plane, the effect of mandibular advancement in children with hyperdivergent mandibular retrognathia is not

satisfactory[21]. Traditional MADs such as activator or TB, not only stimulate mandibular growth in the sagittal direction but also cause an increase in the vertical direction, which makes the long-face pattern more severe[16 22]. Studies have shown that patients of long-face type are more susceptible to vertical growth stimuli. It has been reported that the high-pull headgear and chin cup can control the vertical growth of the mandible[23]. Lione confirmed that posterior bite-blocks could reduce the vertical dimension in children with a high mandibular angle after treatment with rapid maxillary expansion[24]. However, the study of Jung-Yul Cha revealed that patients with severe hyperdivergent mandibular retrognathia showed very similar vertical maxillofacial results regardless of whether they were treated with functional appliances or not, manifesting a clinical tendency for a higher mandibular plane and excessive eruption of teeth after treatment[25].

Therefore, the treatment for children with long-face growth patterns should incorporate vertical control methods that may help prevent the continued increase in the mandibular plane and improve the facial profile in both sagittal and vertical dimensions. Most studies on vertical control have focused on orthognathic surgery and compensatory orthodontic treatment in adult patients with high mandibular plane angles[26 27]. Few studies have investigated the improvement in mandibular advancement in children with hyperdivergent mandibular retrognathia. Zervas found that the cervical headgear showed more control over the vertical dimension and produced more favorable changes in mandibular position by normalizing the occlusal plane in children with Class II Division 1 malocclusion[28]. However, this study did not involve a significant sagittal discrepancy between the maxilla and the mandible. A review of the literature found that studies on modified functional appliances were limited to patients with normal growth patterns[29 30], and there was a lack of systematic high-quality studies on children of long-face growth patterns.

For children with hyperdivergent mandibular retrognathia, a modified LLTB appliance was designed to take vertical control measures to intrude incisors and inhibit the elongation of posterior teeth during mandibular advancement, which can avoid the side effects of the traditional appliance and effectively guide the growth of the mandible in a normal direction. The comparison of treatment mechanisms between LLTB and TB is shown in figure 3. The effect of LLTB on growth improvement and vertical control needs to be systematically analyzed and evaluated in a large number of cases. In this

study, a single-center, randomized, single-blind, parallel controlled trial is conducted to verify the efficacy of the new appliance in improving dentomaxillofacial growth guidance in children with hyperdivergent retrusive mandibles. This study focuses on comparing the efficacy of modified and traditional appliances. This randomized controlled trial is expected to clarify the potential benefits of the modified appliance over conventional appliances. The evaluation will include sagittal and vertical analysis of the teeth, jaws, facial soft tissues, and upper airway width measurement.

Since the primary difference between the two groups is the appliance and procedure, it is not possible to blind the orthodontists who will perform the treatment. To minimize trial bias, we will blind the patients and data surveyors, and the data will be averaged from repeated measurements by a third-party reader.

Authors' contributions:
YLu was responsible for the trial design and protocol writing, YLiu supervised the study protocol, and read and reviewed the manuscript. AL participated in the study design and helped draft the manuscript; WZ obtained ethical approval; and SS participated in the study and coordination. All authors have read and approved the final manuscript.

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Competing interests: None declared.

Patient consent for publication: Not required.

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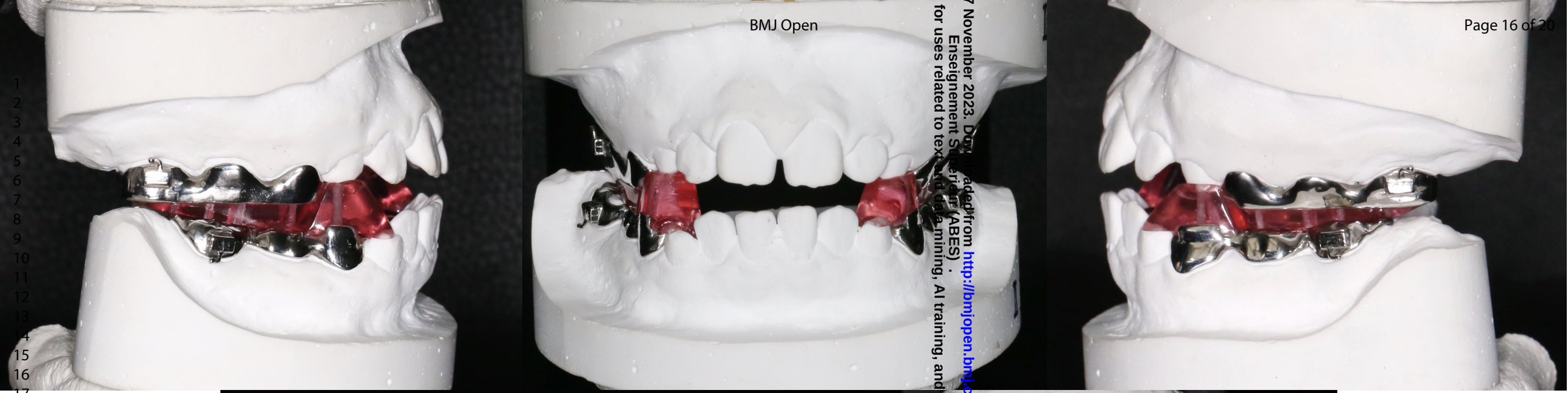
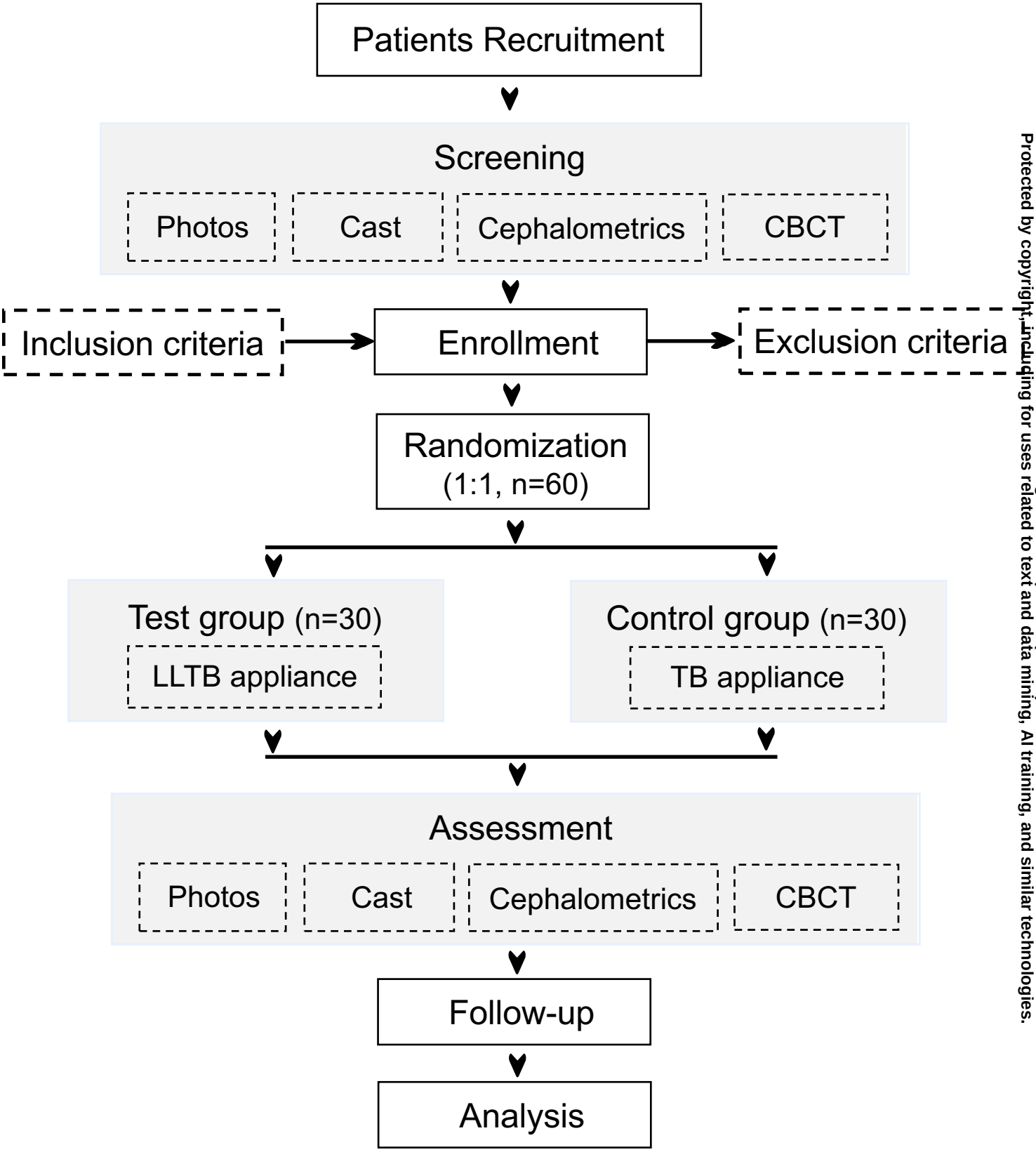
Figure 1: Modified Twin Block (LLTB) appliance

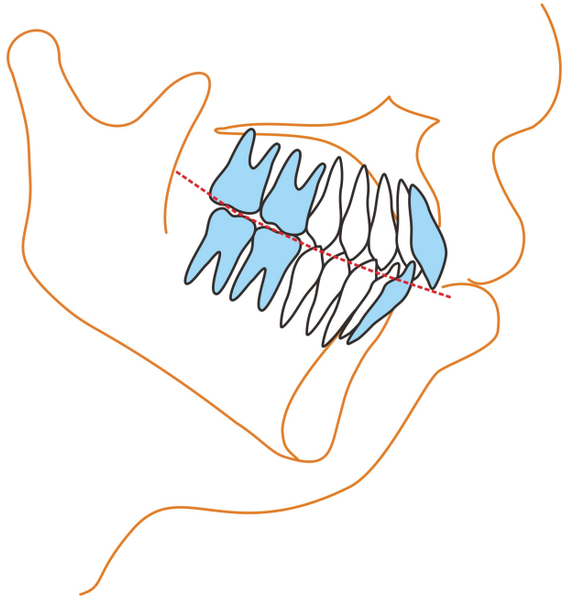
Figure 2: Flowchart of the study. CBCT, cone beam CT; TB, Twin-Block

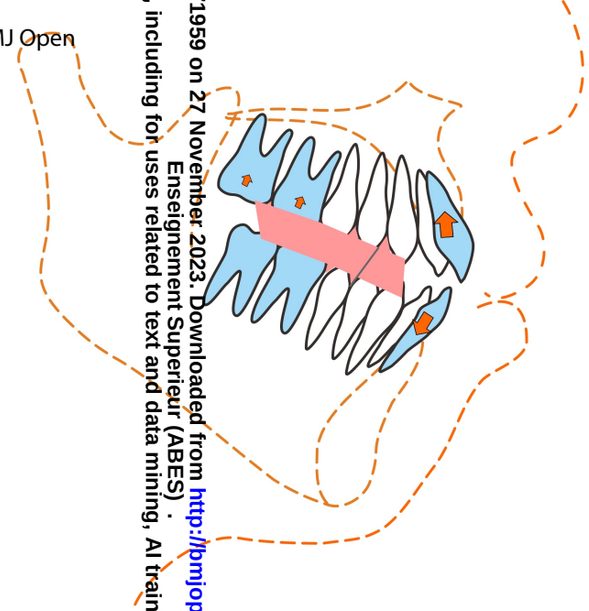
Figure 3: The comparison of treatment mechanisms between LLTB and TB

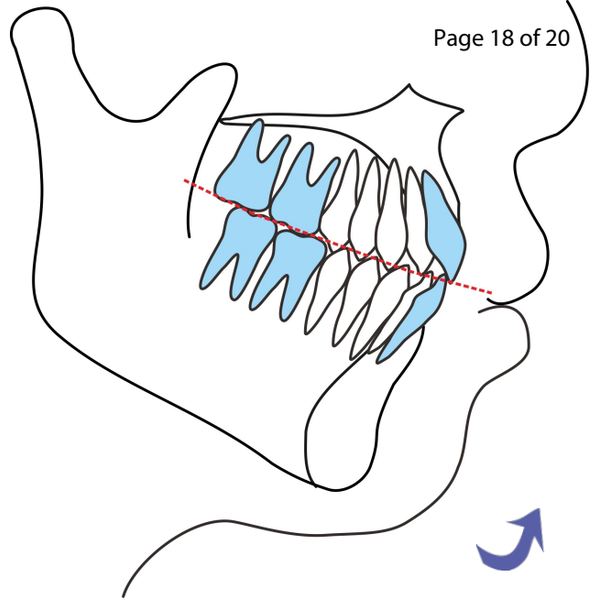




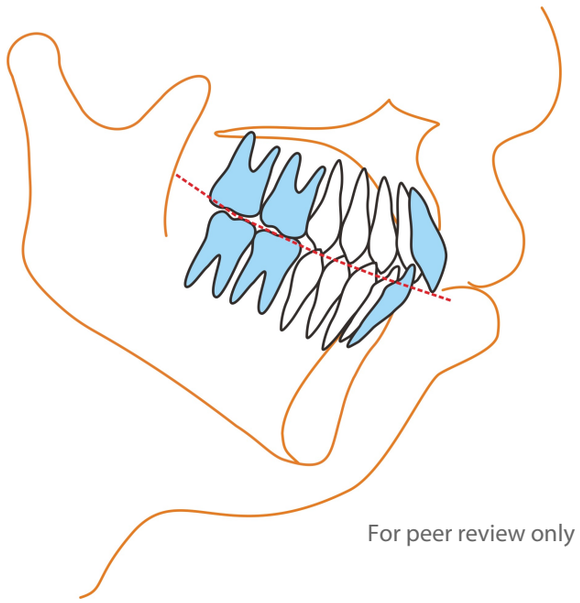
LLTB

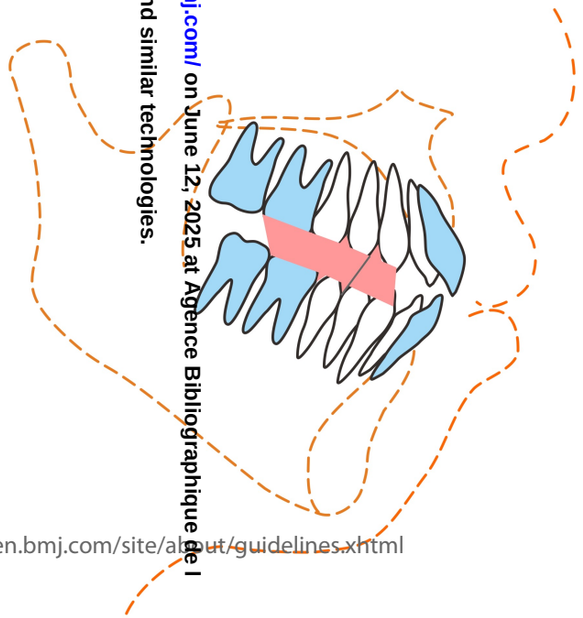


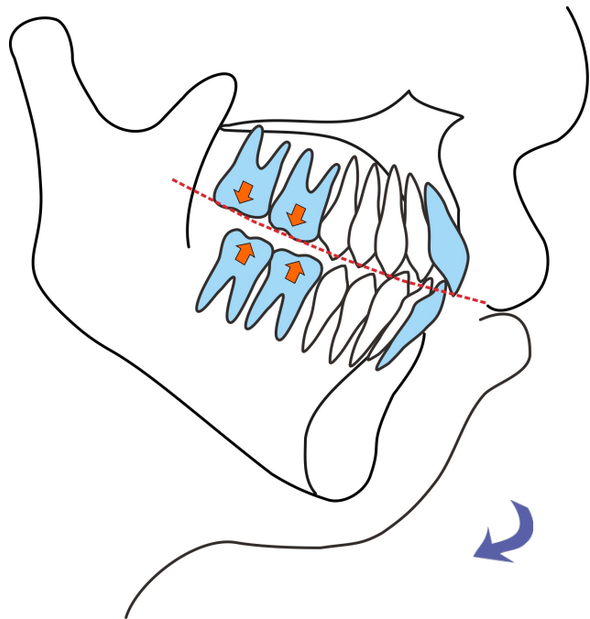




TB







CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	2
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	6
Participants	4a	Eligibility criteria for participants	6
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	7
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	8
	6b	Any changes to trial outcomes after the trial commenced, with reasons	8&9
Sample size	7a	How sample size was determined	9
	7b	When applicable, explanation of any interim analyses and stopping guidelines	9
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	6&7
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	6&7
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	7
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	6&7
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	9&11

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	7
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	9
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	9
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	5&15
	13b	For each group, losses and exclusions after randomisation, together with reasons	9
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5
	14b	Why the trial ended or was stopped	9
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	16
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	5&9
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	9
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	9
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	9
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	9
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	5&11
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	10&11
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	5
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	11&12

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

BMJ Open

Efficacy of a modified Twin Block appliance compared to the traditional Twin Block appliance in children with hyperdivergent mandibular retrognathia: protocol for a single-center, single-blind, randomized controlled trial

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Complete List of Authors:	Liu, Anqi; Shanghai Stomatological Hospital, Department of Orthodontics; Shanghai Key Laboratory of Craniomaxillofacial Development and Diseases Zhang, wei; Biomedical Informatics & Statistics Center, School of Public Health, Fudan University Zhang, Weihua; Shanghai Stomatological Hospital, Department of Orthodontics; Shanghai Key Laboratory of Craniomaxillofacial Development and Diseases Shi, Shuangshuang; Shanghai Stomatological Hospital, Department of Orthodontics; Shanghai Key Laboratory of Craniomaxillofacial Development and Diseases Chen, Zhuoyue; Shanghai Stomatological Hospital, Department of Orthodontics; Shanghai Key Laboratory of Craniomaxillofacial Development and Diseases Liu, Yuehua; Shanghai Stomatological Hospital, Department of Orthodontics; Shanghai Key Laboratory of Craniomaxillofacial Development and Diseases Lu, Yun; Shanghai Stomatological Hospital, Department of Orthodontics; Shanghai Key Laboratory of Craniomaxillofacial Development and Diseases
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Efficacy of a modified Twin Block appliance compared to the traditional Twin Block appliance in children with hyperdivergent mandibular retrognathia: protocol for a single-center, single-blind, randomized controlled trial

Anqi Liu[1,2] , Wei Zhang[3], Weihua Zhang[1,2], Shuangshuang Shi[1,2], Zhuoyue Chen[1,2], Yuehua Liu[1,2*], Yun Lu[1,2*]

[1] Department of Orthodontics, Shanghai Stomatological Hospital & School of Stomatology, Fudan University, Shanghai, China

[2] Shanghai Key Laboratory of Craniomaxillofacial Development and Diseases, Fudan University, Shanghai, China

[3] Biomedical Informatics & Statistics Center, School of Public Health, Fudan University, Shanghai, China.

*Correspondance:

1. Dr. Yun Lu,

Shanghai Stomatological Hospital & School of Stomatology, Fudan University

No.356 East Beijing Road, Shanghai 200001, China

Tel.: +86-18817878669 Email: luyun@fudan.edu.cn

2. Prof. Yuehua Liu,

Shanghai Stomatological Hospital & School of Stomatology, Fudan University

No.356 East Beijing Road, Shanghai 200001, China

Tel.: +86-13818889988 Email: liuyuehua@fudan.edu.cn

ABSTRACT

Introduction

Compensatory mouth breathing, caused by nasopharyngeal obstructive diseases, is the main cause of hyperdivergent mandibular retrognathia in children. Such deformities require effective growth guidance before pubertal growth peaks. The traditional mandibular advancement device (MAD), Twin Block (TB), can guide the forward development of the mandible. However, the side effect of increasing the vertical dimension of the lower facial third, worsens the facial profile of children with divergent growth trends. To solve this problem, a modified Twin Block (LLTB) appliance was designed to control the vertical dimension by intruding incisors and inhibiting the elongation of posterior teeth during the advancement of the mandible, which could avoid the side effects of traditional appliances and effectively guide the growth of the mandible in a normal direction.

Methods and analysis

The study was designed as a single-center, single-blind, randomized, parallel controlled trial. We aim to enroll 60 children aged 9-14 years with hyperdivergent skeletal Class II malocclusion, using a 1:1 allocation ratio. The participants were will be randomly assigned to receive either the TB or LLTB treatment. The primary outcome will be a change in the angle of the mandibular plane relative to the anterior cranial base. The secondary outcomes will include changes in the sagittal maxillomandibular relation, occlusal plane, facial height, morphology of the mandible, and upper airway width. Safety endpoints will also be evaluated.

Ethics and dissemination

Ethical approval was obtained from the ethics committee of Shanghai Stomatological Hospital. Both participants and their guardians will be fully informed of the study and sign an informed consent form before participating in the trial. The results will be publicly available in peer-reviewed scientific journals.

Trial registration number: ChiCTR2000035882

Keywords: hyperdivergent mandibular retrognathia, mandibular advancement, modified Twin Block, vertical control, randomized controlled trial

Strengths and limitations of this study

- Selection bias will be minimized by designing a randomized controlled trial to compare the efficacy of modified LLTB with conventional TB in children with hyperdivergent mandibular retrognathia.
- This study will provide a new method and evidence-based basis for the treatment of mandibular advancement in children with long-face growth patterns.
- A key limitation is the inability to blind the researchers involved in treatment.

INTRODUCTION

Convex deformity is a common facial deformity in children. The treatment of children with long-face growth patterns also remains to be a challenging clinical problem. In recent years, the number of children with nasopharyngeal airway obstructive diseases has been increasing, and the resulting compensatory mouth breathing is the main cause of dental and maxillofacial deformities in these children[1].

We investigated the prevalence of deciduous dentition malocclusion among children aged between 3-5 years in Shanghai and analyzed the correlation between malocclusion and oral habits, dietary structure, and upper respiratory diseases[2]. Researchers have found that chronic rhinitis and adenotonsillar hypertrophy are highly correlated with mouth breathing[3], accompanied by a higher prevalence of hyperdivergent malocclusion[4].

Children are in an important stage of dental and maxillofacial development and respiratory pattern formation[5]. Long-term airway obstruction and mouth breathing can cause narrowing of the maxillary dental arch, increased anterior face height, lip incompetence, and backward and downward mandibular rotation, thus resulting in mandibular retrognathia[6 7]. Mandibular retrognathia is an important risk factor for sleep apnea which can affect children's behavioral psychology and social ability[8]. Such deformities have serious physical and psychological effects on children and their parents[9]. If effective growth modification is not carried out before the adolescent growth spurt, only orthognathic surgery can achieve satisfactory results in adulthood[10].

Hyperdivergent convex deformity in children, caused by long-term mouth breathing[11], is one of the difficulties in orthodontic treatment[12 13]. The current clinical methods for mandibular growth guidance mainly include Twin Block (TB), activator, and Herbst, whose main function is to protrude the mandible and stimulate its growth[14-16]. However, the above traditional mandibular advancement devices (MADs) have obvious limitations in the treatment of children with long-face growth patterns. For children with deep overbite before treatment, the forward movement of the mandible is accompanied by an open bite of the posterior teeth, which may lead to continued elongation of the posterior teeth, an increase in the inferior height, and deterioration of the profile[17]. Therefore, traditional MADs are not applicable to patients with

hyperdivergent mandibular retrognathia[18].

To overcome these difficulties, the modified Twin Block (LLTB, figure 1) appliance has been designed and patented (Yun Lu, Yuehua Liu, Qiang Li, Tingchao Lan, Min Zhao, Huanhuan Li. Double-bite blocks appliance, 2019.11.12, China, ZL201821348135.7). In the process of guiding the forward development of the mandible, the LLTB appliance can simultaneously intrude the upper and lower anterior teeth, flatten the inclined occlusal plane, avoid elongation of the posterior teeth during the occlusal adjustment process, and effectively guide the growth direction of the mandible. LLTB has been used in clinical cases of hyperdivergent mandibular retrognathia, and the effect of this modified appliance needs to be systematically analyzed. This study aims to analyze and compare the clinical effects of TB and LLTB in children with hyperdivergent mandibular retrognathia for the purpose of providing valuable information to guide the clinical treatment of such cases.

METHODS AND ANALYSIS

Study design

This study is designed as a single-center, single-blind, randomized parallel controlled trial, aiming to evaluate the efficacy of a modified LLTB and compare its effect with the traditional TB in children with hyperdivergent mandibular retrognathia. The study is registered at http://www.chictr.org.cn/index.aspx, which can be accessed online. The trial will be performed in the Department of Orthodontics at Shanghai Stomatological Hospital. We will recruit 60 patients who meet the inclusion criteria and randomly assign them to one of two treatment groups, TB or LLTB, in a 1:1 ratio. Treatment in both groups will last for 12 months, with follow-up visits every 2 months. Participants will be assessed at the following time points: the baseline (before treatment), the end of the treatment (after 12 months of treatment), and follow-up (6 months after treatment is completed). A brief flowchart of the study is provided in figure 2 and the trial schedule is presented in table 1. The design adheres to the Consolidated Standards of Reporting Trials (CONSORT) statement recommendations. If there will be significant modifications to the eligibility criteria, outcomes and analyses arising from the implementation of this study, relevant investigators, trial registries, journals and regulators will be notified.

Table 1 Trial schedule chart

	Screening	Enrollment	Randomization	Treatment			Follow-up		
				0 month	6 months	12 months	2 months	4 months	6 months
Informed consent	O								
Demographic characteristic	O								
Medical history	O								
Oral/facial examination	O					O	O	O	O
Photograph	O					O			O
Dental cast	O					O			
Cephalometrics	O					O			
CBCT	O					O			
Inclusion criteria		O							
Exclusion criteria		O							
Allocation			O						
Orthodontic treatment				O	O	O			
Questionnaire						O			
Safety assessment					O	O			
Compliance of participants					O	O			

CBCT, cone beam CT

Patient and public involvement

There was no patient or public involvement in the design, recruitment, or conduct of this study. After the treatment, researchers will communicate with the participants and their guardians about the efficacy and follow-up arrangements.

Study patient

Participants will be recruited from the Orthodontic Department of Shanghai Stomatological Hospital via a specific referral pathway. Patients and their guardians will be informed about hyperdivergent mandibular retrognathia and this study through outpatient consultations and recruitment posters in the hospital. Interested individuals will be able to meet with research assistants who will explain the study in detail, perform an initial screening and obtain informed consent. Subsequently, the orthodontists will conduct clinical examinations and cephalometric analysis for the participants to obtain parameters related to the inclusion criteria, which ultimately determine whether the participants will be included in this study. A total of 60 eligible patients will be recruited for the study after screening. The following eligibility criteria were developed to ensure the precision of the results:

Inclusion criteria:

1. Aged 9-14, no gender limit.
2. Protrusion deformity, poor chin morphology, mandibular retrusion, ANB > 5°, and normal maxillary development.
3. Children with a high mandibular plane angle (SN-MP), 35°< SN-MP < 45°. Children treated with traditional TB are prone to elongation of the posterior teeth, causing the backward and downward rotation of the mandible. The increase in facial height will aggravate the original long face and cause ethical issues; therefore, the SN-MP is controlled within 45°. Participants included in this study are children showing a tendency of a long-face growth pattern, but have not yet developed into severe long faces. Even if the facial height increases after treatment with TB, it is still acceptable.
4. Narrow upper airway.
5. Participants have good compliance and are able to wear appliances as required and rechecked regularly.

Exclusion criteria:

1. Children who have passed pubertal peak according to the modified cervical spine analysis method (Cvs4 stage).
2. Children who have symptoms of temporomandibular joint disorders.
3. Children with loose deciduous molar.
4. Patients with systemic disease.

Recruitment and randomization process

Participants will be recruited through outpatient clinics and hospital-based advertisements. If the participants and their guardians are interested in participating in the trial, they will sign an informed consent form after fully understanding the study. A pretreatment screening visit with a clinical research assistant will be conducted in the outpatient clinic before enrollment. Once considered eligible for enrollment, the enrolled participants will be randomly assigned to one of the two treatment groups, either TB or LLTB, in a 1:1 ratio with block randomization method. The independent statistician will use SAS 9.4 software to generate a random allocation table with flexible block size according to the total sample size. Random assignment and concealment will be performed by IWRS(interactive web response system) system (http://redcap.fudan.edu.cn).

Description of the interventions

Orthodontic treatments in both groups will be performed by experienced orthodontists following a consistent protocol. In the test group, a LLTB appliance combined with brackets and archwires will be used to intrude the upper anterior teeth, flatten the inclined occlusal plane, and guide the mandible to rotate counterclockwise with the adjustment of the blocks. Participants in the control group will wear the TB appliance every day without adjustment of the anterior teeth. The treatments will last for 12 months, with follow-up every 2 months. Dental casts, digital oral and facial photographs, lateral radiographs, and cone beam CT (CBCT) images will be obtained before and after treatment. Third-party interpreters will perform cephalometrics, and the dental-skeletal-soft tissue parameters will be comprehensively analyzed in the sagittal, transverse, and vertical dimensions.

Treatment group

Participants in the trial group will be treated with LLTB for mandibular advancement. The LLTB appliance in the trial group provides three-dimensional guidance and control to the growing children from vertical, sagittal and transverse directions by the auxiliary intrusion archwire, bite blocks and rapid maxillary expansion respectively, which is different from the traditional TB appliance focusing on sagittal advancement. The fixed LLTB appliance is designed with two double buccal tubes in the posterior region, which are connected to the anterior brackets by an archwire. We use 0.012- or 0.014-inch nickel-titanium wire as primary archwire to align the anterior teeth, and 0.016-inch stainless steel wire as intrusion archwire to intrude the upper anteriors and level the occlusal plane in the anterior region. Along with the intrusion of the anterior teeth, bite blocks will be grinded successively to lower the height and guide the mandible to rotate forward and upward to improve the chin profile.

Control group

The participants in the control group will be treated with TB for mandibular advancement. The TB appliance consists of removable maxillary and mandibular plates with ramps that guide the mandible forward. The maxillary plate incorporates an expansion screw to increase posterior arch width. Due to the limitations of the removable appliance, TB cannot achieve a large amount of maxillary expansion. In addition, the removable TB is unable to achieve anterior teeth adjustment and, thus,

will not guide the mandible to rotate counterclockwise during the treatment. Only the Adams clasps will be adjusted for good retention at each follow-up visit.

Outcome measures

The measurement outcomes in this study are mainly derived from the comparison of cephalometric measurements on lateral radiographs before and after treatment, with photographs and dental casts as auxiliary references.

Primary outcome

The primary outcome of this study is the degree of change in the SN-MP. SN-MP is the angle of intersection of the mandibular plane and the anterior cranial base plane, which indicates the steepness of the mandibular plane and the height of the lower facial third and thus can reflect the vertical growth pattern. The larger the SN-MP, the greater the amount of vertical growth and the corresponding increase in treatment difficulty. The SN-MP is a commonly used parameter for evaluating the downward and backward rotation of the mandible and is also a valid indicator for assessing the efficacy of vertical control.

Secondary outcomes

The secondary outcomes include the following aspects:

1. The ANB angle : In cephalometric analysis, points A and B represent the sagittal position of the maxilla and mandible, respectively. The ANB angle represents the anterior-posterior relationship between the maxilla and mandible.
2. The angle of the occlusal plane (OP-SN): The angle OP-SN is used to establish the relationship of the occlusal plane to the cranial base. OP-SN represents the inclination of the occlusal plane, reflecting the relative relationship between the vertical dimension of the anterior and posterior teeth. The larger the angle, the steeper the occlusal plane and the more serious the tendency of the protrusion type.
3. Tooth height analysis: The vertical height of the teeth will be analyzed by measuring the distance of the upper and lower anterior teeth and the posterior teeth relative to the reference plane using U1-PP, U6-PP, L1-MP, and L6-MP. The analyses of the above parameters before and after treatment reflect the influence of different appliances on tooth heights.
4. Facial height analysis: Facial height will be analyzed by two parameters, S-Go/N-Me and ANS-Me/N-Me, which represent the ratio of posterior face height to

anterior face height and the percentage of lower face height to total face height, respectively. MADs have effects on posterior face height (S-Go) and lower face height (ANS-Me). In order to reflect the effect of face height changes on facial contours, the ratio of S-Go and ANS-Me to total face height (N-Me) will be evaluated.

5. Mandibular morphology: The changes in mandibular morphology will be analyzed by measuring the mandibular length (Co-Gn), ramus height (Ar-Go), mandibular body length (Go-Me), and Gonial angle (Ar-Go'-Me). The mandibular morphology will be evaluated by the combination of linear and angular measures. Co-Gn represents the overall length of the mandible, while Ar-Go and Go-Me reflect the vertical and sagittal development of the mandible respectively. Ar-Go'-Me reflects the morphology of the chin, a parameter that has a critical influence on the lateral profile.
6. The facial convexity angle (Ns-Sn-Pos): The angle Ns-Sn-Pos will be measured to assess lateral protrusion of the soft tissue. This parameter is based on nassion of soft tissue (Ns), subnasal (Sn) and pogonion of sott tissue (Pos), and evaluates the sagittal change of soft tissue chin with respect to the lateral profile.
7. Upper airway analysis: MADs can adjust the position of the hyoid bone by stimulating mandibular growth, increasing glossopharyngeal and hypopharyngeal airway. TB-TPPW and V-LPW measurements will be used to assess the widths of the middle and lower segments of the upper airway.

Safety monitoring

The MADs used in both groups in this study have no obvious adverse effects on the participants if they are worn according to the doctor's advice. Possible risks are mainly the adverse effects of poor oral hygiene during orthodontic treatment, such as enamel demineralization, gingivitis and gingival hyperplasia. Mild enamel demineralization and gingivitis can be alleviated by timely measures such as oral cleaning and hygiene promotion. Participants with severe enamel demineralization and caries should stop wearing the appliance and continue with mandibular advancement after filling treatment. Patients suffering from severe gingivitis with gingival hyperplasia should be terminated from the study and undergo periodontal scaling. Gingival trimming will be performed to cure gingival hyperplasia in patients with no obvious relief after periodontal scaling for one month.

Sample size calculation

Based on the data from a pilot study, the primary outcome is the change of SN-MP at 12 months post-treatment relative to that before treatment, with a mean difference of 1.5° and a standard deviation (SD) of 1.87°. Using a conventional α of 5% and β of 20%, 26 participants are required for each group. With a dropout rate of 10%, the number of participants in each group is 30, and the final sample size for this study is 60 participants, randomized in a 1:1 ratio.

Statistical analysis

During the measurement process, statistical analysts will be blinded to the participants' personal information and group assignments. Statistical significance will be set at $p<0.05$, based on a two-sided test. Continuous variables will be described as mean ± SD or median (P25-P75), depending on whether they conform to a normal distribution. All statistical analyses will be performed using the statistical software SPSS V.26.0.

All analyses will be based on ITT(Intention-to-Treat) principle. The primary analysis strategy for the primary and secondary outcomes will be the mixed-effect model with baseline adjustment. Multiple imputation will be used as sensitivity analysis. Safety endpoints will be compared by $\chi 2$ test or Fisher's exact test. Subgroup analysis stratified by age and gender is pre-planned.

ETHICS AND DISSEMINATION

The study has been approved by the ethics committee of Shanghai Stomatological Hospital (approval no. [2021]023; [2022]005) and will comply with the Declaration of Helsinki. All amendments to the program will be implemented with the approval of the ethics committee. All the participants and their guardians will be fully informed of the study and sign an informed consent form before joining the study. They will be informed that they can withdraw from the study at any time without explanation.

The results will be publicly available in peer-reviewed scientific journals and presented at academic conferences. Any public reporting of study results will not disclose personal information about participants.

DISCUSSION

The influence of breathing patterns on maxillofacial growth and development has been confirmed by the previous studies. Compared with nasal breathing, mouth breathing causes children and adolescents to show vertical growth patterns with increased facial height and a retrognathic mandible with a high mandibular plane angle due to backward and downward rotation[19 20].

Currently, it is difficult to treat children with hyperdivergent mandibular retrognathia. Orthodontists can guide and improve mandibular growth in the adolescent growth spurt by making good use of the growth potential[21]. However, due to the backward rotation of the mandible and infra-anterior inclination of the occlusal plane, the effect of mandibular advancement in children with hyperdivergent mandibular retrognathia is not satisfactory[22]. Increase in vertical dimension is the most obvious change in the children with vertical growth patterns. Traditional MADs such as activator or TB, not only stimulate mandibular growth in the sagittal direction but also cause an increase in the vertical direction, which makes the long-face pattern more severe[17 23]. Studies have shown that children of long-face type are more susceptible to vertical growth stimuli[24]. It has been reported that the high-pull headgear and chin cup can control the vertical growth of the mandible[25], and present cephalometric outcome stability of treatment even after a long-term follow-up[26]. Lione confirmed that posterior bite-blocks could reduce the vertical dimension in children with a high mandibular angle after treatment with rapid maxillary expansion[27]. However, the study of Jung-Yul Cha revealed that patients with severe hyperdivergent mandibular retrognathia showed very similar vertical maxillofacial results regardless of whether or not they were treated with functional appliances, manifesting a clinical tendency for a higher mandibular plane and excessive eruption of teeth after treatment[28].

Therefore, the treatment for children with long-face growth patterns should incorporate vertical control methods that may help prevent the continued increase in the mandibular plane and improve the facial profile in both sagittal and vertical dimensions. Most studies on vertical control have focused on orthognathic surgery and compensatory orthodontic treatment in adult patients with high mandibular plane angles[29 30]. But few studies have investigated the improvement in mandibular advancement in children with hyperdivergent mandibular retrognathia. Zervas found that the cervical headgear showed more control over the vertical dimension and produced more favorable changes

in mandibular position by normalizing the occlusal plane in children with Class II Division 1 malocclusion[31]. However, this study did not involve a significant sagittal discrepancy between the maxilla and the mandible. A review of the literature found that studies on modified functional appliances were limited to patients with normal growth patterns[32 33], and there was a lack of systematic high-quality studies on children of long-face growth patterns.

For children with hyperdivergent mandibular retrognathia, a modified LLTB appliance was designed to take vertical control measures to intrude incisors and inhibit the elongation of posterior teeth during mandibular advancement, which can avoid the side effects of the traditional appliance and effectively guide the growth of the mandible in a normal direction. The comparison of treatment mechanisms between LLTB and TB is shown in figure 3. The effect of LLTB on growth improvement and vertical control needs to be systematically analyzed and evaluated in a large number of cases. In this study, a single-center, randomized, single-blind, parallel controlled trial is conducted to verify the efficacy of the new appliance in improving dentomaxillofacial growth guidance in children with hyperdivergent retrusive mandibles. This study focuses on comparing the efficacy of modified and traditional appliances. The randomized controlled trial in this study is expected to clarify the potential benefits of the modified appliance over conventional appliances. The evaluation will include sagittal and vertical analysis of the teeth, jaws, facial soft tissues, and upper airway width measurement.

Since the primary differences between the two groups are the appliance and procedure, it is not possible to blind the orthodontists who will perform the treatment. To minimize trial bias, we will blind the patients and data surveyors, and the data will be averaged from repeated measurements by a third-party reader.

Authors' contributions:

YLu was responsible for the trial design and protocol writing, YLiu supervised the study protocol, and read and reviewed the manuscript. AL participated in the study design and helped draft the manuscript; WeiZ contributed in randomization and group assignment design, statistical consultation and manuscript revision; WeihuaZ obtained ethical approval; and SS participated in the study and coordination. All authors have read and approved the final manuscript.

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Competing interests: None declared.

Patient consent for publication: Not required.

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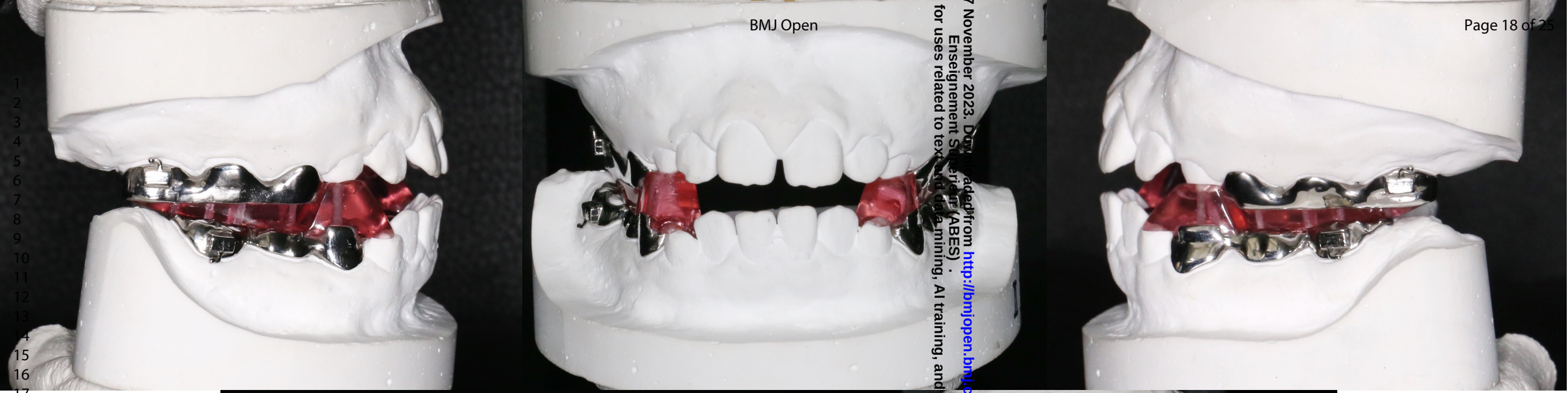
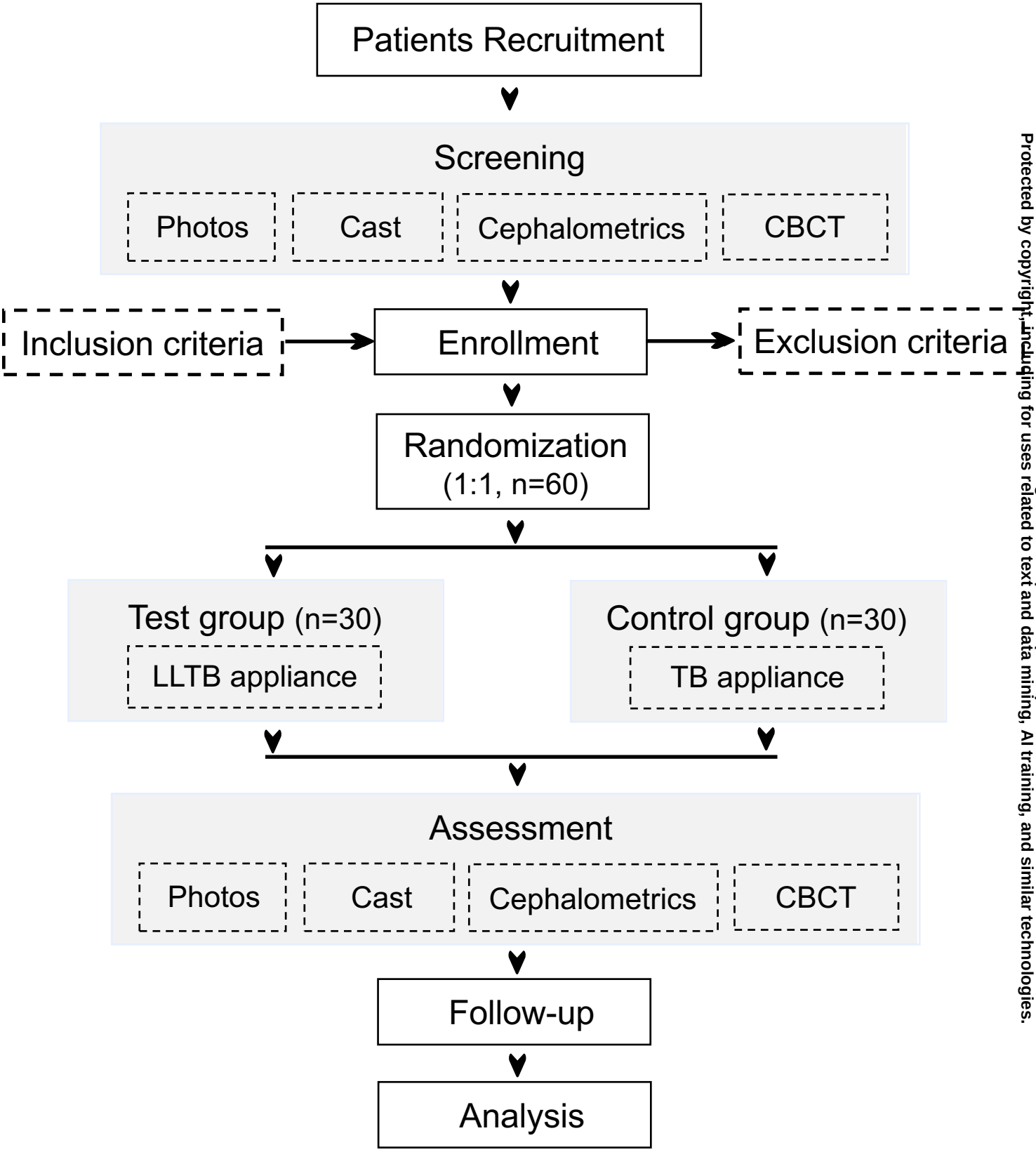
Figure 1: Modified Twin Block (LLTB) appliance

Figure 2: Flowchart of the study. CBCT, cone beam CT; TB, Twin-Block

Figure 3: The comparison of treatment mechanisms between LLTB and TB





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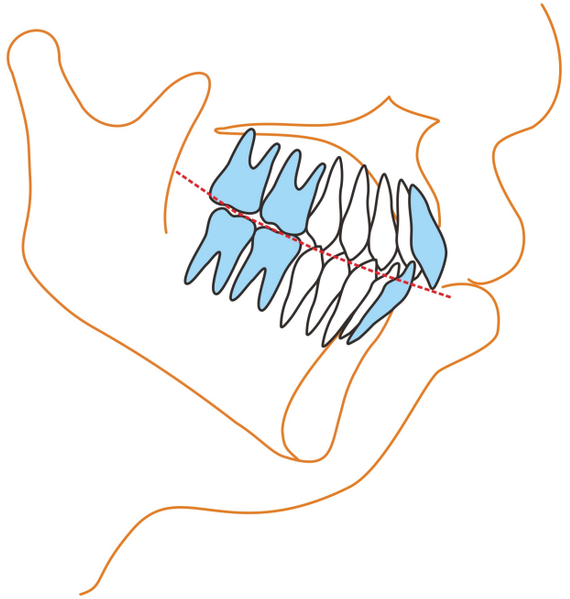

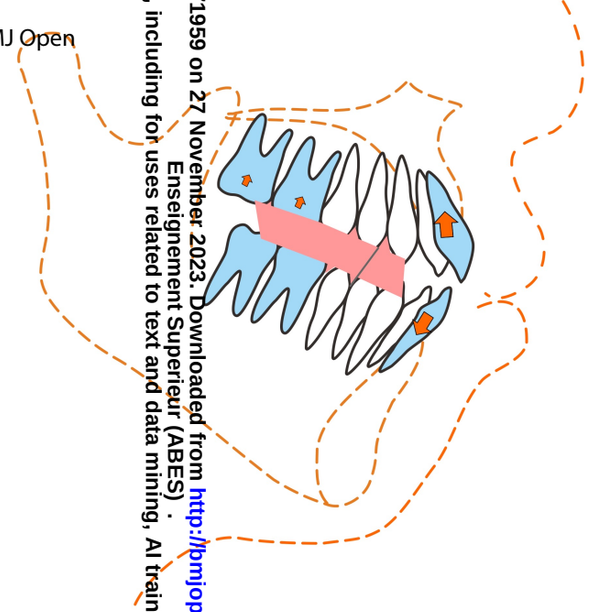

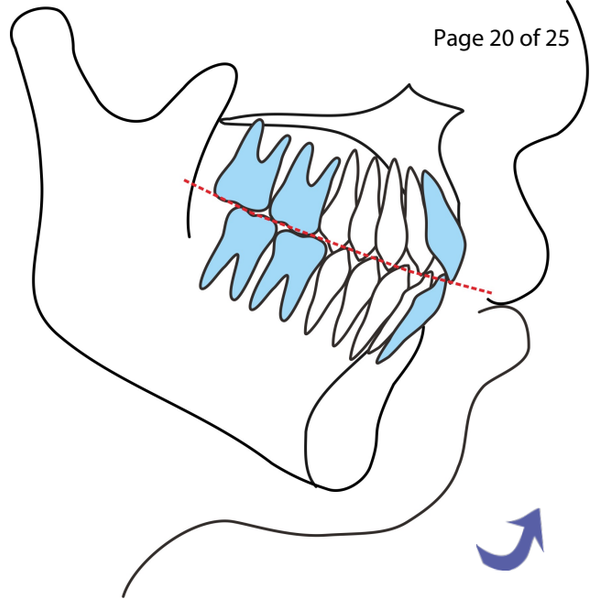

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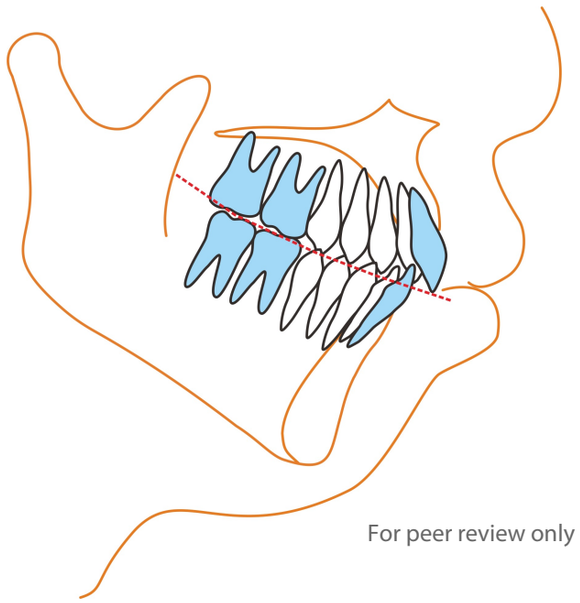

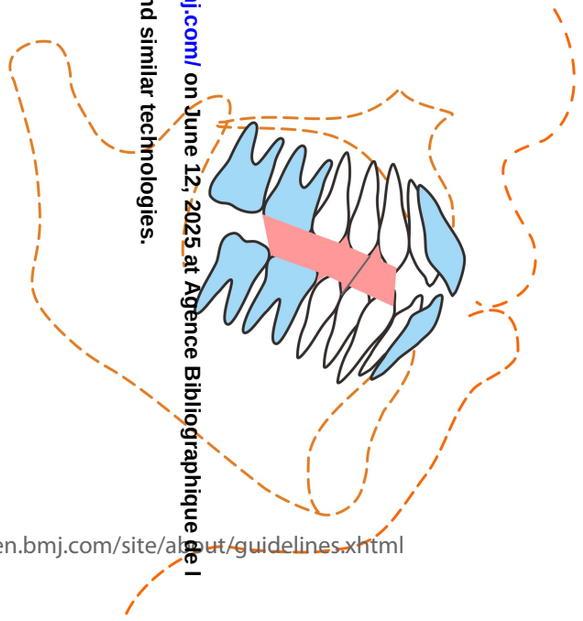

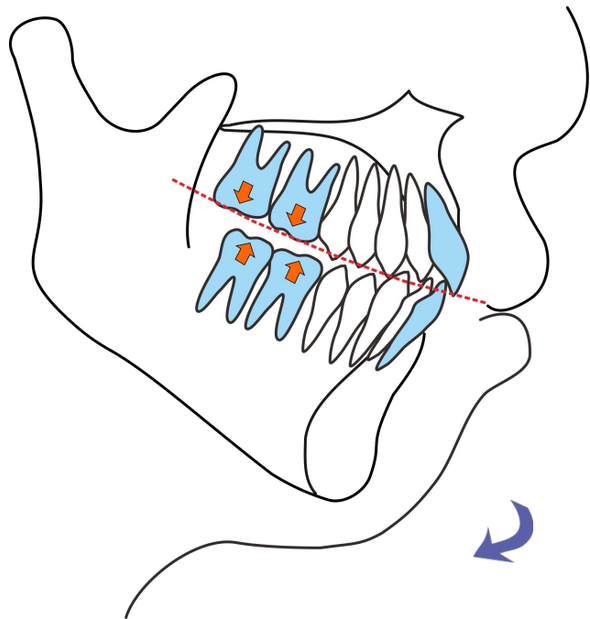

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	5
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	12
	5b	Name and contact information for the trial sponsor	12
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14 c
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	10, 11
	6b	Explanation for choice of comparators	8, 9
Objectives	7	Specific objectives or hypotheses	2, 5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	2, 5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6, 7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7, 8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7, 8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8, 9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9,10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5, 6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not applicable
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	5

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	8
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2, 10
	31b	Authorship eligibility guidelines and any intended use of professional writers	14
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	10
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Efficacy of a modified Twin Block appliance compared to the traditional Twin Block appliance in children with hyperdivergent mandibular retrognathia: protocol for a single-center, single-blind, randomized controlled trial

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Efficacy of a modified Twin Block appliance compared to the traditional Twin Block appliance in children with hyperdivergent mandibular retrognathia: protocol for a single-center, single-blind, randomized controlled trial

Anqi Liu[1,2] , Wei Zhang[3], Weihua Zhang[1,2], Shuangshuang Shi[1,2], Zhuoyue Chen[1,2], Yuehua Liu[1,2*], Yun Lu[1,2*]

[1] Department of Orthodontics, Shanghai Stomatological Hospital & School of Stomatology, Fudan University, Shanghai, China

[2] Shanghai Key Laboratory of Craniomaxillofacial Development and Diseases, Fudan University, Shanghai, China

[3] Biomedical Informatics & Statistics Center, School of Public Health, Fudan University, Shanghai, China.

*Correspondance:

1. Dr. Yun Lu,

Shanghai Stomatological Hospital & School of Stomatology, Fudan University

No.356 East Beijing Road, Shanghai 200001, China

Tel.: +86-18817878669 Email: luyun@fudan.edu.cn

2. Prof. Yuehua Liu,

Shanghai Stomatological Hospital & School of Stomatology, Fudan University

No.356 East Beijing Road, Shanghai 200001, China

Tel.: +86-13818889988 Email: liuyuehua@fudan.edu.cn

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ABSTRACT

Introduction

Compensatory mouth breathing, caused by nasopharyngeal obstructive diseases, is the main cause of hyperdivergent mandibular retrognathia in children. Such deformities require effective growth guidance before pubertal growth peaks. The traditional mandibular advancement device (MAD), Twin Block (TB), can guide the forward development of the mandible. However, the side effect of increasing the vertical dimension of the lower facial third, worsens the facial profile of children with divergent growth trends. To solve this problem, a modified Twin Block (LLTB) appliance was designed to control the vertical dimension by intruding incisors and inhibiting the elongation of posterior teeth during the advancement of the mandible, which could avoid the side effects of traditional appliances and effectively guide the growth of the mandible in a normal direction.

Methods and analysis

The study was designed as a single-center, single-blind, randomized, parallel controlled trial. We aim to enroll 60 children aged 9-14 years with hyperdivergent skeletal Class II malocclusion, using a 1:1 allocation ratio. The participants were will be randomly assigned to receive either the TB or LLTB treatment. The primary outcome will be a change in the angle of the mandibular plane relative to the anterior cranial base. The secondary outcomes will include changes in the sagittal maxillomandibular relation, occlusal plane, facial height, morphology of the mandible, and upper airway width. Safety endpoints will also be evaluated.

Ethics and dissemination

Ethical approval was obtained from the ethics committee of Shanghai Stomatological Hospital. Both participants and their guardians will be fully informed of the study and sign an informed consent form before participating in the trial. The results will be publicly available in peer-reviewed scientific journals.

Trial registration number: ChiCTR2000035882

Keywords: hyperdivergent mandibular retrognathia, mandibular advancement, modified Twin Block, vertical control, randomized controlled trial

Strengths and limitations of this study

- Selection bias will be minimized by designing a randomized controlled trial to compare the efficacy of modified LLTB with conventional TB in children with hyperdivergent mandibular retrognathia.
- This study will help orthodontists choose mandibular advancement devices especially for those children with long-face growth patterns.
- A key limitation is the inability to blind the researchers involved in treatment.

INTRODUCTION

Convex deformity is a common facial deformity in children. The treatment of children with long-face growth patterns also remains to be a challenging clinical problem. In recent years, the number of children with nasopharyngeal airway obstructive diseases has been increasing, and the resulting compensatory mouth breathing is the main cause of dental and maxillofacial deformities in these children[1].

We investigated the prevalence of deciduous dentition malocclusion among children aged between 3-5 years in Shanghai and analyzed the correlation between malocclusion and oral habits, dietary structure, and upper respiratory diseases[2]. Researchers have found that chronic rhinitis and adenotonsillar hypertrophy are highly correlated with mouth breathing[3], accompanied by a higher prevalence of hyperdivergent malocclusion[4].

Children are in an important stage of dental and maxillofacial development and respiratory pattern formation[5]. Long-term airway obstruction and mouth breathing can cause narrowing of the maxillary dental arch, increased anterior face height, lip incompetence, and backward and downward mandibular rotation, thus resulting in mandibular retrognathia[6 7]. Mandibular retrognathia is an important risk factor for sleep apnea which can affect children's behavioral psychology and social ability[8]. Such deformities have serious physical and psychological effects on children and their parents[9]. If effective growth modification is not carried out before the adolescent growth spurt, only orthognathic surgery can achieve satisfactory results in adulthood[10].

Hyperdivergent convex deformity in children, caused by long-term mouth breathing[11], is one of the difficulties in orthodontic treatment[12 13]. The current clinical methods for mandibular growth guidance mainly include Twin Block (TB), activator, and Herbst, whose main function is to protrude the mandible and stimulate its growth[14-16]. However, the above traditional mandibular advancement devices (MADs) have obvious limitations in the treatment of children with long-face growth patterns[17]. For children with deep overbite before treatment, the forward movement of the mandible is accompanied by an open bite of the posterior teeth, which may lead to continued elongation of the posterior teeth, an increase in the inferior height, and

deterioration of the profile[18]. Therefore, traditional MADs are not applicable to patients with hyperdivergent mandibular retrognathia[19].

To overcome these difficulties, the modified Twin Block (LLTB, figure 1) appliance has been designed and patented (Yun Lu, Yuehua Liu, Qiang Li, Tingchao Lan, Min Zhao, Huanhuan Li. Double-bite blocks appliance, 2019.11.12, China, ZL201821348135.7). In the process of guiding the forward development of the mandible, the LLTB appliance can simultaneously intrude the upper and lower anterior teeth, flatten the inclined occlusal plane, avoid elongation of the posterior teeth during the occlusal adjustment process, and effectively guide the growth direction of the mandible. LLTB has been used in clinical cases of hyperdivergent mandibular retrognathia, and the effect of this modified appliance needs to be systematically analyzed. This study aims to analyze and compare the clinical effects of TB and LLTB in children with hyperdivergent mandibular retrognathia for the purpose of providing valuable information to guide the clinical treatment of such cases. Compared with the previous studies that emphasized sagittal orientation[18 20 21], this study focuses on the vertical control in the mandibular advancement of hyperdivergent mandibular retrognathia.

METHODS AND ANALYSIS

Study design

This study is designed as a single-center, single-blind, randomized parallel controlled trial, aiming to evaluate the efficacy of a modified LLTB and compare its effect with the traditional TB in children with hyperdivergent mandibular retrognathia. The study is registered at http://www.chictr.org.cn/index.aspx, which can be accessed online. The trial will be performed in the Department of Orthodontics at Shanghai Stomatological Hospital. We will recruit 60 patients who meet the inclusion criteria and randomly assign them to one of two treatment groups, TB or LLTB, in a 1:1 ratio. Treatment in both groups will last for 12 months, with follow-up visits every 2 months. Participants will be assessed at the following time points: the baseline (before treatment), the end of the treatment (after 12 months of treatment), and follow-up (6 months after treatment is completed). A brief flowchart of the study is provided in figure 2 and the trial schedule is presented in Supplementary Table 1. The design adheres to the Consolidated Standards of Reporting Trials (CONSORT) statement recommendations. If there will

be significant modifications to the eligibility criteria, outcomes and analyses arising from the implementation of this study, relevant investigators, trial registries, journals and regulators will be notified.

Patient and public involvement

There was no patient or public involvement in the design, recruitment, or conduct of this study. After the treatment, researchers will communicate with the participants and their guardians about the efficacy and follow-up arrangements.

Study patient

Participants will be recruited from the Orthodontic Department of Shanghai Stomatological Hospital via a specific referral pathway. Patients and their guardians will be informed about hyperdivergent mandibular retrognathia and this study through outpatient consultations and recruitment posters in the hospital. Interested individuals will be able to meet with research assistants who will explain the study in detail, perform an initial screening and obtain informed consent. Subsequently, the orthodontists will conduct clinical examinations and cephalometric analysis for the participants to obtain parameters related to the inclusion criteria, which ultimately determine whether the participants will be included in this study. A total of 60 eligible patients will be recruited for the study after screening. The following eligibility criteria were developed to ensure the precision of the results:

Inclusion criteria:

1. Aged 9-14, no gender limit.
2. Protrusion deformity, poor chin morphology, mandibular retrusion, ANB > 5°, and normal maxillary development.
3. Children with a high mandibular plane angle (SN-MP), 35°< SN-MP < 45°. Children treated with traditional TB are prone to elongation of the posterior teeth, causing the backward and downward rotation of the mandible. The increase in facial height will aggravate the original long face and cause ethical issues; therefore, the SN-MP is controlled within 45°. Participants included in this study are children showing a tendency of a long-face growth pattern, but have not yet developed into severe long faces. Even if the facial height increases after treatment with TB, it is still acceptable.
4. Narrow upper airway.
5. Participants have good compliance and are able to wear appliances as required and

rechecked regularly.

Exclusion criteria:

1. Children who have passed pubertal peak according to the modified cervical spine analysis method (Cvs4 stage).
2. Children who have symptoms of temporomandibular joint disorders.
3. Children with loose deciduous molar.
4. Patients with systemic disease.

Recruitment and randomization process

Participants will be recruited through outpatient clinics and hospital-based advertisements. If the participants and their guardians are interested in participating in the trial, they will sign an informed consent form after fully understanding the study. A pretreatment screening visit with a clinical research assistant will be conducted in the outpatient clinic before enrollment. Once considered eligible for enrollment, the enrolled participants will be randomly assigned to one of the two treatment groups, either TB or LLTB, in a 1:1 ratio with block randomization method. The independent statistician will use SAS 9.4 software to generate a random allocation table with flexible block size according to the total sample size. Random assignment and concealment will be performed by IWRS(interactive web response system) system (http://redcap.fudan.edu.cn).

Description of the interventions

Orthodontic treatments in both groups will be performed by experienced orthodontists following a consistent protocol. In the test group, a LLTB appliance combined with brackets and archwires will be used to intrude the upper anterior teeth, flatten the inclined occlusal plane, and guide the mandible to rotate counterclockwise with the adjustment of the blocks. Participants in the control group will wear the TB appliance every day without adjustment of the anterior teeth. The treatments will last for 12 months, with follow-up every 2 months. Dental casts, digital oral and facial photographs, lateral radiographs, and cone beam CT (CBCT) images will be obtained before and after treatment. Third-party interpreters will perform cephalometrics, and the dental-skeletal-soft tissue parameters will be comprehensively analyzed in the sagittal, transverse, and vertical dimensions.

Treatment group

Participants in the trial group will be treated with LLTB for mandibular advancement. The LLTB appliance in the trial group provides three-dimensional guidance and control to the growing children from vertical, sagittal and transverse directions by the auxiliary intrusion archwire, bite blocks and rapid maxillary expansion respectively, which is different from the traditional TB appliance focusing on sagittal advancement. The fixed LLTB appliance is designed with two double buccal tubes in the posterior region, which are connected to the anterior brackets by an archwire. We use 0.012- or 0.014-inch nickel-titanium wire as primary archwire to align the anterior teeth, and 0.016-inch stainless steel wire as intrusion archwire to intrude the upper anteriors and level the occlusal plane in the anterior region. Along with the intrusion of the anterior teeth, bite blocks will be grinded successively to lower the height and guide the mandible to rotate forward and upward to improve the chin profile.

Control group

The participants in the control group will be treated with TB for mandibular advancement. The TB appliance consists of removable maxillary and mandibular plates with ramps that guide the mandible forward. The maxillary plate incorporates an expansion screw to increase posterior arch width. Due to the limitations of the removable appliance, TB cannot achieve a large amount of maxillary expansion. In addition, the removable TB is unable to achieve anterior teeth adjustment and, thus, will not guide the mandible to rotate counterclockwise during the treatment. Only the Adams clasps will be adjusted for good retention at each follow-up visit.

Outcome measures

The measurement outcomes in this study are mainly derived from the comparison of cephalometric measurements on lateral radiographs before and after treatment, with photographs and dental casts as auxiliary references.

Primary outcome

The primary outcome of this study is the degree of change in the SN-MP. SN-MP is the angle of intersection of the mandibular plane and the anterior cranial base plane, which indicates the steepness of the mandibular plane and the height of the lower facial third and thus can reflect the vertical growth pattern. The larger the SN-MP, the greater the amount of vertical growth and the corresponding increase in treatment difficulty. The

SN-MP is a commonly used parameter for evaluating the downward and backward rotation of the mandible and is also a valid indicator for assessing the efficacy of vertical control.

Secondary outcomes

The secondary outcomes include the following aspects:

1. The ANB angle : In cephalometric analysis, points A and B represent the sagittal position of the maxilla and mandible, respectively. The ANB angle represents the anterior-posterior relationship between the maxilla and mandible.
2. The angle of the occlusal plane (OP-SN): The angle OP-SN is used to establish the relationship of the occlusal plane to the cranial base. OP-SN represents the inclination of the occlusal plane, reflecting the relative relationship between the vertical dimension of the anterior and posterior teeth. The larger the angle, the steeper the occlusal plane and the more serious the tendency of the protrusion type.
3. Tooth height analysis: The vertical height of the teeth will be analyzed by measuring the distance of the upper and lower anterior teeth and the posterior teeth relative to the reference plane using U1-PP, U6-PP, L1-MP, and L6-MP. The analyses of the above parameters before and after treatment reflect the influence of different appliances on tooth heights.
4. Facial height analysis: Facial height will be analyzed by two parameters, S-Go/N-Me and ANS-Me/N-Me, which represent the ratio of posterior face height to anterior face height and the percentage of lower face height to total face height, respectively. MADs have effects on posterior face height (S-Go) and lower face height (ANS-Me). In order to reflect the effect of face height changes on facial contours, the ratio of S-Go and ANS-Me to total face height (N-Me) will be evaluated.
5. Mandibular morphology: The changes in mandibular morphology will be analyzed by measuring the mandibular length (Co-Gn), ramus height (Ar-Go), mandibular body length (Go-Me), and Gonial angle (Ar-Go'-Me). The mandibular morphology will be evaluated by the combination of linear and angular measures. Co-Gn represents the overall length of the mandible, while Ar-Go and Go-Me reflect the vertical and sagittal development of the mandible respectively. Ar-Go'-Me reflects the morphology of the chin, a parameter that has a critical influence on the lateral profile.

6. The facial convexity angle (Ns-Sn-Pos): The angle Ns-Sn-Pos will be measured to assess lateral protrusion of the soft tissue. This parameter is based on nassion of soft tissue (Ns), subnasal (Sn) and pogonion of sott tissue (Pos), and evaluates the sagittal change of soft tissue chin with respect to the lateral profile.
7. Upper airway analysis: MADs can adjust the position of the hyoid bone by stimulating mandibular growth, increasing glossopharyngeal and hypopharyngeal airway. TB-TPPW and V-LPW measurements will be used to assess the widths of the middle and lower segments of the upper airway.

Safety monitoring

The MADs used in both groups in this study have no obvious adverse effects on the participants if they are worn according to the doctor's advice. Possible risks are mainly the adverse effects of poor oral hygiene during orthodontic treatment, such as enamel demineralization, gingivitis and gingival hyperplasia. Mild enamel demineralization and gingivitis can be alleviated by timely measures such as oral cleaning and hygiene promotion. Participants with severe enamel demineralization and caries should stop wearing the appliance and continue with mandibular advancement after filling treatment. Patients suffering from severe gingivitis with gingival hyperplasia should be terminated from the study and undergo periodontal scaling. Gingival trimming will be performed to cure gingival hyperplasia in patients with no obvious relief after periodontal scaling for one month.

Sample size calculation

Based on the data from a pilot study, the primary outcome is the change of SN-MP at 12 months post-treatment relative to that before treatment, with a mean difference of 1.5° and a standard deviation (SD) of 1.87°. Using a conventional α of 5% and β of 20%, 26 participants are required for each group. With a dropout rate of 10%, the number of participants in each group is 30, and the final sample size for this study is 60 participants, randomized in a 1:1 ratio.

Statistical analysis

During the measurement process, statistical analysts will be blinded to the participants' personal information and group assignments. Statistical significance will be set at $p<0.05$, based on a two-sided test. Continuous variables will be described as mean ± SD or median (P25-P75), depending on whether they conform to a normal distribution.

All statistical analyses will be performed using the statistical software SPSS V.26.0.

All analyses will be based on ITT(Intention-to-Treat) principle. The primary analysis strategy for the primary and secondary outcomes will be the mixed-effect model with baseline adjustment. Multiple imputation will be used as sensitivity analysis. Safety endpoints will be compared by $\chi 2$ test or Fisher's exact test. Subgroup analysis stratified by age and gender is pre-planned.

ETHICS AND DISSEMINATION

The study has been approved by the ethics committee of Shanghai Stomatological Hospital (approval no. [2021]023; [2022]005) and will comply with the Declaration of Helsinki. All amendments to the program will be implemented with the approval of the ethics committee. All the participants and their guardians will be fully informed of the study and sign an informed consent form before joining the study. They will be informed that they can withdraw from the study at any time without explanation.

The results will be publicly available in peer-reviewed scientific journals and presented at academic conferences. Any public reporting of study results will not disclose personal information about participants.

DISCUSSION

The influence of breathing patterns on maxillofacial growth and development has been confirmed by the previous studies. Compared with nasal breathing, mouth breathing causes children and adolescents to show vertical growth patterns with increased facial height and a retrognathic mandible with a high mandibular plane angle due to backward and downward rotation[22 23].

Currently, it is difficult to treat children with hyperdivergent mandibular retrognathia. Orthodontists can guide and improve mandibular growth in the adolescent growth spurt by making good use of the growth potential[24]. However, due to the backward rotation of the mandible and infra-anterior inclination of the occlusal plane, the effect of mandibular advancement in children with hyperdivergent mandibular retrognathia is not satisfactory[25]. Increase in vertical dimension is the most obvious change in the children with vertical growth patterns. Traditional MADs such as activator or TB, not

only stimulate mandibular growth in the sagittal direction but also cause an increase in the vertical direction, which makes the long-face pattern more severe[17 18]. Studies have shown that children of long-face type are more susceptible to vertical growth stimuli[26]. It has been reported that the high-pull headgear and chin cup can control the vertical growth of the mandible[27], and present cephalometric outcome stability of treatment even after a long-term follow-up[28]. Lione confirmed that posterior bite-blocks could reduce the vertical dimension in children with a high mandibular angle after treatment with rapid maxillary expansion[29]. However, the study of Jung-Yul Cha revealed that patients with severe hyperdivergent mandibular retrognathia showed very similar vertical maxillofacial results regardless of whether or not they were treated with functional appliances, manifesting a clinical tendency for a higher mandibular plane and excessive eruption of teeth after treatment[30].

Therefore, the treatment for children with long-face growth patterns should incorporate vertical control methods that may help prevent the continued increase in the mandibular plane and improve the facial profile in both sagittal and vertical dimensions. Most studies on vertical control have focused on orthognathic surgery and compensatory orthodontic treatment in adult patients with high mandibular plane angles[31 32]. But few studies have investigated the improvement in mandibular advancement in children with hyperdivergent mandibular retrognathia. Zervas found that the cervical headgear showed more control over the vertical dimension and produced more favorable changes in mandibular position by normalizing the occlusal plane in children with Class II Division 1 malocclusion[33]. However, this study did not involve a significant sagittal discrepancy between the maxilla and the mandible. A review of the literature found that studies on modified functional appliances were limited to patients with normal growth patterns[34 35], and there was a lack of systematic high-quality studies on children of long-face growth patterns.

For children with hyperdivergent mandibular retrognathia, a modified LLTB appliance was designed to take vertical control measures to intrude incisors and inhibit the elongation of posterior teeth during mandibular advancement, which can avoid the side effects of the traditional appliance and effectively guide the growth of the mandible in a normal direction. The comparison of treatment mechanisms between LLTB and TB is shown in figure 3. The effect of LLTB on growth improvement and vertical control

needs to be systematically analyzed and evaluated in a large number of cases. In this study, a single-center, randomized, single-blind, parallel controlled trial is conducted to verify the efficacy of the new appliance in improving dentomaxillofacial growth guidance in children with hyperdivergent retrusive mandibles. This study focuses on comparing the efficacy of modified and traditional appliances. The randomized controlled trial in this study is expected to clarify the potential benefits of the modified appliance over conventional appliances. The evaluation will include sagittal and vertical analysis of the teeth, jaws, facial soft tissues, and upper airway width measurement.

Since the primary differences between the two groups are the appliance and procedure, it is not possible to blind the orthodontists who will perform the treatment. To minimize trial bias, we will blind the patients and data surveyors, and the data will be averaged from repeated measurements by a third-party reader.

Authors' contributions:

YLu was responsible for the trial design and protocol writing, YLiu supervised the study protocol, and read and reviewed the manuscript. AL participated in the study design and helped draft the manuscript; WeiZ contributed in randomization and group assignment design, statistical consultation and manuscript revision; WeihuaZ obtained ethical approval; SS participated in the study and coordination; and ZC is responsible for the table and schematic diagrams. All authors have read and approved the final manuscript.

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Competing interests: None declared.

Patient consent for publication: Not required.

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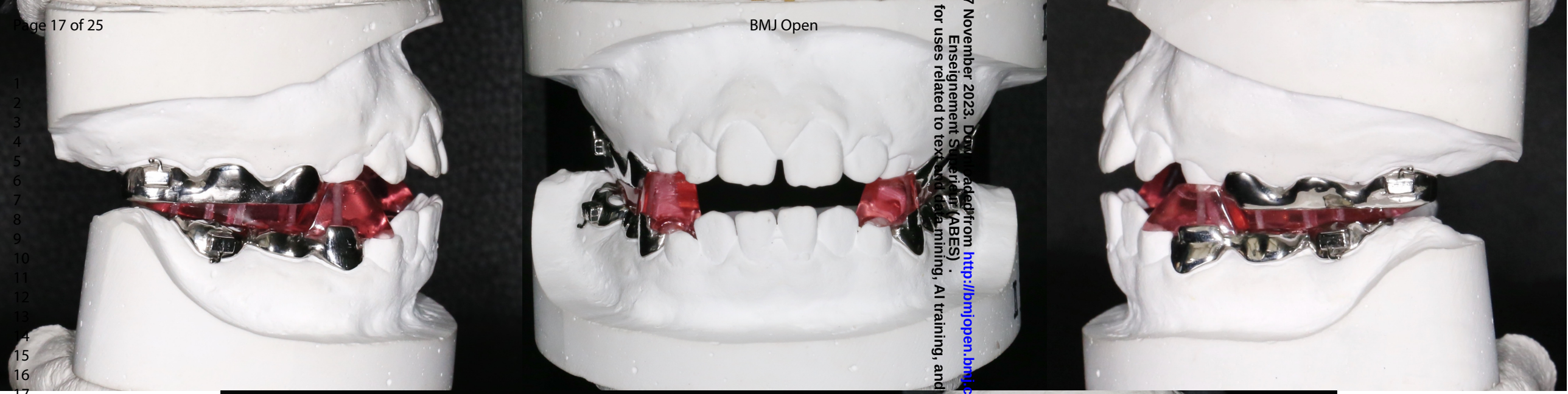
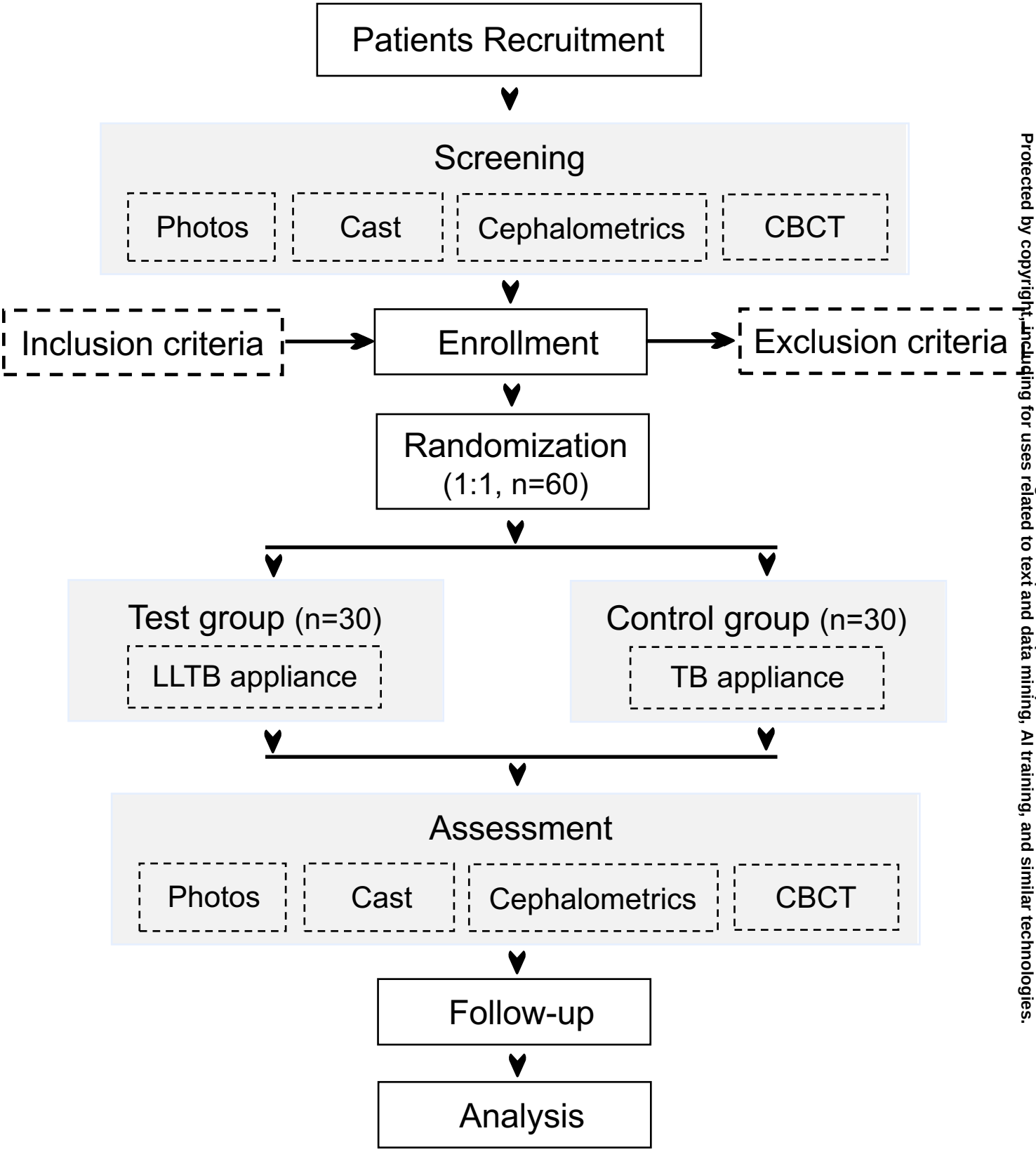
Figure 1: Modified Twin Block (LLTB) appliance

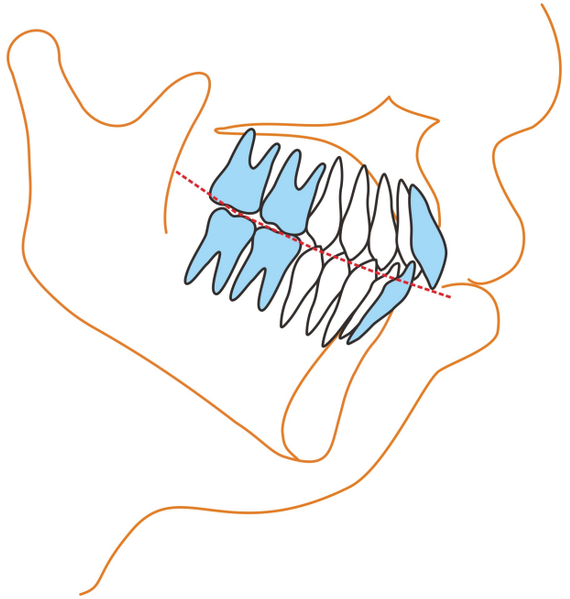
Figure 2: Flowchart of the study. CBCT, cone beam CT; TB, Twin-Block

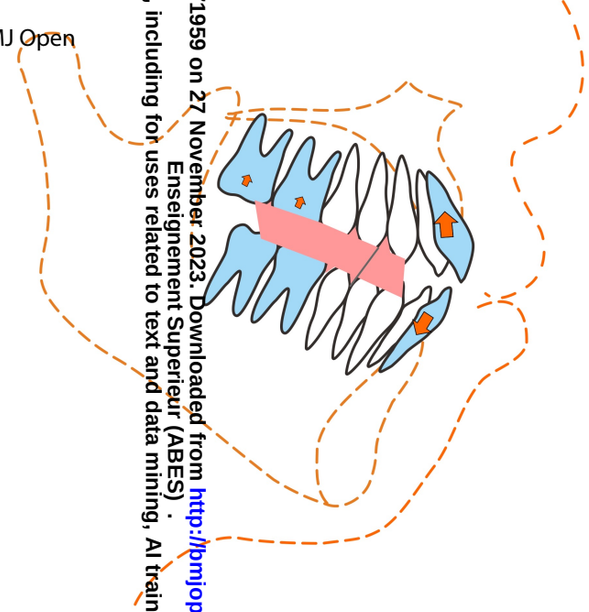
Figure 3: The comparison of treatment mechanisms between LLTB and TB

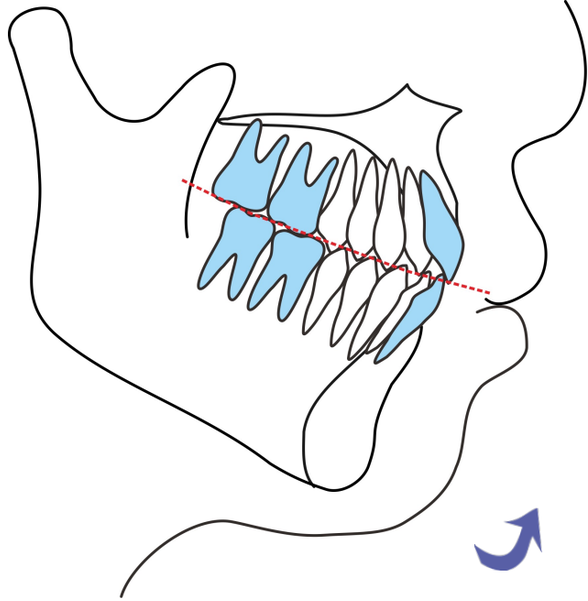




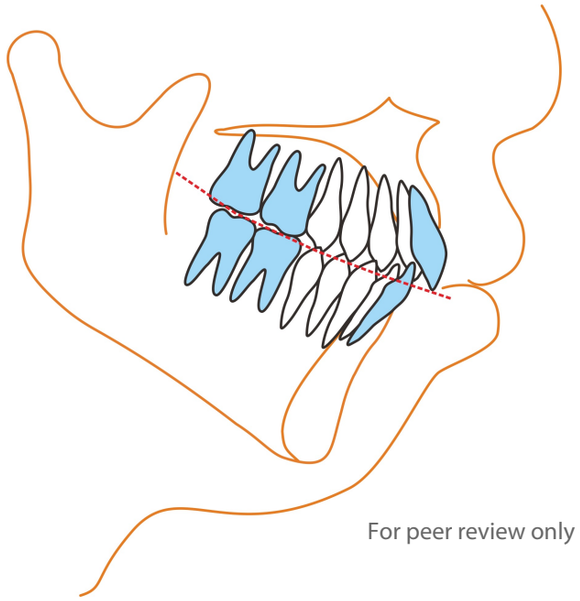
LLTB

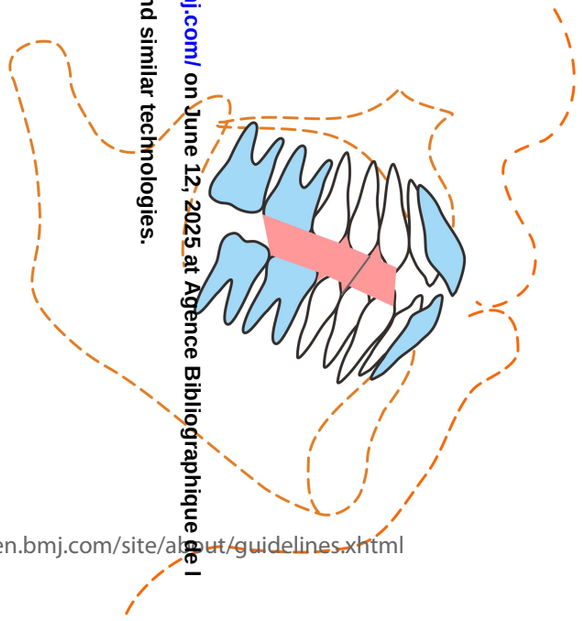


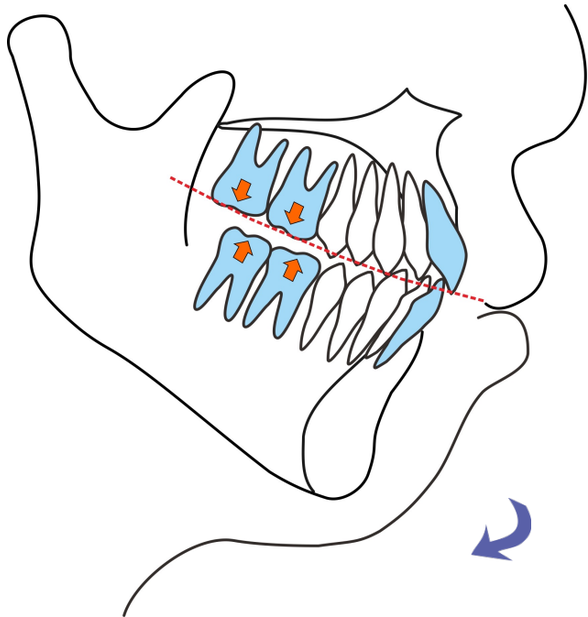




TB







Supplementary Table 1： Trial schedule chart

	Screening	Enrollment	Randomization	Treatment			Follow-up		
				0 month	6 months	12 months	2 months	4 months	6 months
Informed consent	O								
Demographic characteristic	O								
Medical history	O								
Oral/facial examination	O					O	O	O	O
Photograph	O					O			O
Dental cast	O					O			
Cephalometrics	O					O			
CBCT	O					O			
Inclusion criteria		O							
Exclusion criteria		O							
Allocation			O						
Orthodontic treatment				O	O	O			
Questionnaire						O			
Safety assessment					O	O			
Compliance of participants					O	O			

CBCT, cone beam CT

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	5
Protocol version	3	Date and version identifier	2
Funding	4	Sources and types of financial, material, and other support	12
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	12
	5b	Name and contact information for the trial sponsor	12
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14 c
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	10, 11
	6b	Explanation for choice of comparators	8, 9
Objectives	7	Specific objectives or hypotheses	2, 5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	2, 5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6, 7
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7, 8
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7, 8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8, 9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9,10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5, 6
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	7
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	9

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	10
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	10
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not applicable
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	10
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	5

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Not applicable
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	12
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	8
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2, 10
	31b	Authorship eligibility guidelines and any intended use of professional writers	14
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	12
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	10
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	Not applicable

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.