Trial Protocol

Fixed versus conventional removable Twinblock for overjet reduction in children – A randomised clinical trial to investigate the burden of care

Trial Acronym	**FTB (F**ixed **T**win**B**lock)
Sponsor	**University of Dundee**
Sponsor Ref Number	**2-020-20**
Funder	**British Orthodontic Society Foundation**
Chief Investigator	**Professor Peter A Mossey**
Principal Investigator	**Gautham Sivamurthy**
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CONTENTS

FTB
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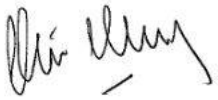
PROTOCOL APPROVAL

Fixed versus conventional removable Twinblock for overjet reduction in children – A randomised clinical trial to investigate the burden of care

Signatures
The undersigned confirm that the following protocol has been agreed and approved by the Sponsor and that the Chief Investigator agrees to conduct the trial in compliance with this approved protocol and will adhere to the principles of GCP, the Sponsor SOPs, and any other applicable regulatory requirements as may be amended from time to time.



Peter A Mossey Chief Investigator	Signature	09-02-2021 Date

Gautham Sivamurthy Principal Investigator	Signature	09-02-2021 Date

Peter Donnan Individual Responsible for Statistical Review	Signature	15-01-2021 Date

LIST OF ABBREVIATIONS
(including Trial abbreviations)

GCP	Good Clinical Practice
TMF	Trial Master File
SOP	Standard Operating Procedure
CRF	Case Report Form
TCTU	Tayside Clinical Trials Unit
GDC	General Dental Council
PI	Principal Investigator
CI	Chief Investigator
AE	Adverse Event
SAE	Serious Adverse Event
AR	Adverse Reaction
UAR	Unexpected Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
CNORIS	Clinical Negligence and Other Risks Scheme
NRES	National Research Ethics Service
REC	Research Ethics Committee
QC	Quality Control
GP	General Practitioner (medical/dental)

SUMMARY

Trial Title	**Fixed versus conventional removable Twinblock for overjet reduction in children – A randomised clinical trial to investigate the burden of care (FTB)**	
Trial Design	**Multicentre Randomised Clinical Trial, two-arm parallel design**	
Trial Population	**Patients will be recruited from NHS primary care orthodontic practices and secondary care orthodontic units in Tayside and Grampian areas**	
Sample Size	**88**	
Planned Trial Period	**3.5 Years**	
Clinical phase duration	**3.5 Years**	
Follow up phase duration	None	
Primary	Objectives **Rate of overjet correction**	Outcome Measures **Overjet measurement in millimetres**
Secondary	Objectives • **Skeletal change** • **Dental change** • **Soft tissue change** • **Patient experience** • **Cost effectiveness**	Outcome Measures • **Lateral cephalometric analysis** • **Tooth movement** • **Facial volumetric analysis** • **Experience questionnaire** • **Number of visits/breakages**
Inclusion Criteria	• **Class II division 1 malocclusion** • **No history of active orthodontic treatment** • **Overjet ≥ 6mm (IOTN 4a/5a)** • **Age 9-14 years** • **Child & parent/carer who are able to assent and consent, respectively**	
Exclusion Criteria	• **Overjet <6mm** • **Mobile/loose deciduous teeth,** • **Profound hypodontia affecting the incisor region (>1 missing tooth per quadrant)** • **Subjects taking growth hormone or endocrine disorders** • **Suspected or identifiable syndromes** • **Subjects with cleft lip and palate** • **Anterior open bite**	

1. INTRODUCTION

Prominent upper front teeth are associated with poor appearance of teeth, inadequate function and psychosocial problems along with an increased risk of trauma to teeth. Most patients with prominent upper front teeth do not like their facial appearance and this has been shown to be an important factor in evoking negative image and self-perception of one's body. It has been noted that the prevalence of bullying in children aged 11-12 years is 15% in the UK. More recently, the prevalence of bullying in children aged between 10 and 14 with malalignment of teeth has been shown to be 12.8% and was primarily noted to be in patients with prominent upper front teeth. Furthermore, teasing and bullying in relation to negative body image are the origin of most of the psychological problems that people are subjected to in later life. This tends to have impact on self-esteem and related quality of life. Children who receive brace treatment report improvements in quality of life and on completing treatment, they report an improved physical, psychological and social impact on their lifestyle. Prominent upper front teeth doubles the risk of trauma to the teeth and this has been calculated at a global level to 100-300 million traumatic injuries to teeth. Dental trauma is of considerable public health concern in the UK and research in Europe has shown the direct health care service costs for management of each traumatised permanent tooth are £240 and total costs (medicine and transport and loss of production) are £371

There are a variety of options for prominent upper front teeth in adolescents. The bite blocks (Twinblocks) invented by William Clark are a two-piece removable brace and these are frequently used in treatment. They work by harnessing the muscular forces to move the teeth and the jaws. Due to the growth potential in younger patients, response of the jaws to treatment can be greater and, in many cases, substantial prominence of upper front teeth can be fully corrected. Patients who wear the removable bite blocks on a full-time basis in the presence of active growth inevitably show an excellent treatment result, whilst those that fail to wear these, fail to produce any positive changes. The issue with compliance has been quantified by Parekh et al (2019) for the Twinblock appliance at mean daily wear of 12.38 hours or 51.6% of that recommended. The solution to the problem of compliance is to develop a fixed bite block appliance that is effective. The compliance, comfort and speed of treatment with fixed bite block brace treatment remains to be tested.

Hence in this clinical trial, we propose to compare the effects of the fixed and removable bite blocks (Twinblocks) in correcting upper prominent front teeth in 120 growing individuals aged between 09 to 14 years old. The speed of correction, changes to the teeth, jaws and face, cost effectiveness and psychosocial aspects of treatment will be studied amongst participants from Tayside and Grampians regions within Orthodontic specialist practices and Hospital services.

2. BACKGROUND AND RATIONALE

Class II division 1 malocclusion is characterised by a combination of skeletal, dental and soft-tissue factors. The most frequent permutation involves an increased overjet and retrognathic mandible combined with a degree of maxillary incisor proclination modulated by the soft tissues.

Class II division 1 malocclusion is associated with aesthetic, functional and psychosocial problems along with an increased risk of dental trauma. Most patients with a substantial overjet do not like their facial appearance and some have difficulty in biting certain types of food. As with Class III malocclusions and other dentofacial disproportions, Class II malocclusion has been shown to be an important factor in negative body image and negative self-concept. It has been noted that the prevalence of bullying in children aged 11-12 years is 15% in the UK (Boulton and Underwood, 1992). Boys are known to suffer direct bullying such as physical and verbal abuse, whilst girls endure indirect bullying such as malicious gossip and rumours (Baldry and Farrington, 1999). More recently, the prevalence of bullying in adolescents aged between 10 and 14 with a malocclusion has been shown to be 12.8% and was primarily noted to be in patients with Class II division 1 malocclusion. Moreover, adolescents who are bullied due to a malocclusion report a negative impact on both their self-esteem and oral-health-related quality of life (OHRQoL; Seehra *et al*., 2011a). Furthermore, teasing and bullying in relation to negative body image are the origin of most of the psychological problems that people are subjected to in later life. The financial costs of the adverse effects of mental illness on people’s quality of life

are estimated at £41.8 billion per annum, with 10% of children in the UK having a diagnosable mental health condition (National mental health development unit – factfile 3).

On the positive side, adolescents who receive orthodontic treatment report improvements in most OHQoL domains when assessed using the Child Perception Questionnaire 11- to 14-year olds and on completing orthodontic treatment, adolescents report an improved physical, psychological and social impact on their lifestyle relating to their occlusion (Bernabé *et al.,* 2008). An increased overjet doubles the risk of dental trauma and large overjets treble the risk of a traumatic dental injury. This has been calculated at a global level to 100-300 million traumatic dental injuries (Petti S 2015). Dental trauma is of considerable public health concern in the UK and research in Europe has shown the direct health care service costs for management of each traumatised permanent tooth are £240 and total costs (medicine and transport and loss of production) are £371.

There are a variety of options for managing a Class II malocclusion. These are classified as comprehensive, camouflage, compromise and monitoring/observation. Comprehensive treatment is offered to patients with a severe skeletal Class 2 relationship where a combination of orthodontic treatment and orthognathic surgery are used to produce a Class I occlusion on a Class I skeletal base relationship at the end of treatment. Where the skeletal relationship is less severe, premolar extractions and fixed appliances can camouflage the skeletal pattern and for patients who only want upper arch alignment, compromise treatment using an upper fixed appliance can deliver this on either an extraction or non-extraction basis with any residual overjet being left untreated. This option is the least stable whilst comprehensive treatment is more stable by virtue of correcting the relationships between the skeletal, dental and soft-tissue aetiological factors. Monitoring/observation is an appropriate strategy where there are no patient concerns, no desire for treatment or where the medical/dental health and/or treatment logistics preclude participation in treatment.

Functional appliances are frequently used for the treatment of Class II division 1 malocclusion by harnessing the muscular forces to move the teeth and the jaws. The American Dental Association describes them as “loose, usually removable intra-oral devices which alter the muscle forces against the teeth and craniofacial skeleton. These are dynamic appliances, which depend on altered neuromuscular action to effect bony growth and occlusal development. They are usually used in mixed dentition to treat pediatric malocclusions” (Glossary of American Dental Association, 1992). As such, functional appliances (and other growth modification techniques) straddle the comprehensive and camouflage categories. Due to the growth potential in younger patients, the skeletal response to treatment can be greater than with adolescent patients. In many cases with a substantial overjet (i.e. Index of Orthodontic Treatment Need categories 4 and 5), a Class I skeletal relationship can be produced at the end of treatment, particularly where a retrusive mandible is a key presenting feature. In adolescent patients the skeletal response is reduced with most of the occlusal change resulting from dentoalveolar compensation. Although the age at treatment has not been shown to influence the amount of skeletal change delivered by functional appliances in a single randomised controlled trial (O’Brien et al, 2009), a favourable vector and magnitude of growth underpins cases that are successful with orthodontic growth modification (Tulloch et al, 2004) and it is logical to harness this where possible.

Research has so far failed to identify the precise effects of functional appliances although the evidence points to additional skeletal growth being delivered for growing patients with Class II malocclusions. In randomised controlled trials, this has been quantified at 1-2mm (Keeling et al, 1998; O’Brien et al, 2003 a,b; Kinzinger & Diedrich, 2005; Cozza et al, 2006; Thiruvenkatachari et al, 2013). Furthermore, the enigma of the effects of functional appliances where some cases demonstrate dramatic skeletal changes whilst other cases show only a modest skeletal improvement is thought by the clinical community to result from the paradigm of compliance in addition to the positive contribution from active growth. Thus patients who wear removable functional appliances on a full-time basis in the presence of active growth inevitably show an excellent treatment result, whilst those that fail to wear removable functional appliances also fail to produce any positive dentoskeletal changes.

The Clark Twinblock is one of several functional appliances that have been invented by orthodontists for the treatment of Class II malocclusion. It was developed by William Clark in the 1980's as a two-piece functional appliance and is easier to wear than other single piece functional appliances. It is therefore now the most commonly used functional appliance in the UK for several reasons:

- relatively well tolerated by the patient
- robust and easy to repair
- compensatory expansion is easy using a midline screw
- suitable for mixed or permanent dentition treatment

A national UK survey in 2000 discovered that the following design principles are popular:

- Upper appliance: Adams' cribs for the upper first premolars and the upper first permanent molars, midline screw, blocks with optional labial bow.
- Lower appliance: Adams' cribs on lower first premolars and lower first molars, incisor capping and blocks.
- The division between upper and lower blocks at a steep angle of 70 degrees to the occlusal plane and should be mesial to the lower first molars, permitting removal of the lower molar crib and grinding of the upper block if accelerated eruption of these teeth is required.

However, like all removable functional appliances, compliance with the removable Twinblock appliance can be problematic. The issue with compliance has been quantified by Parekh et al (2019) for the Twinblock appliance at mean daily wear of 12.38 hours or 51.6% of that recommended. Furthermore, age is also a factor in compliance with O'Brien et al. (2003c) finding older patients had unusually high failure rates (34%) compared to younger patients (O'Brien et al. 2003a) at 19%. The solution to the problem of compliance is to use a fixed functional appliance. The oldest known fixed functional appliance is the Herbst appliance which was first described at the start of the 20th century and re-introduced by Hans Pancherz more recently. It is comprised of two maxillary and mandibular sections – either cast or banded. However, problems include breakages, regular re-cementing of the appliance, and patient acceptance. The most recent version of the Herbst appliance was used in the UK MRC-funded multicentre RCT (O'Brien et al. 2003c) comparing the removable Twinblock appliance with the Herbst. The rate of failure during the functional phase was surprisingly high in the Twinblock group at 34%, and much lower in the Herbst group at 13%.

Combining the extensive research literature on the Herbst appliance with clinical experience produces the following summary:

- The Herbst appliance reduces almost all overjets in 6 months which compares to an average of nine months with the removable Twinblock appliance
- Patients find the Herbst appliance not excessively intrusive after the first week - like the removable Twinblock appliance
- There is an inconveniently high rate of decementation, mechanical failure and lower incisor proclination with the Herbst appliance
- A functional appliance that can be rapidly and reliably added to a conventional fixed appliance will probably prove very popular.

The Bass Dynamax appliance has been proposed as an alternative and an improvement to the Herbst appliance. It is a two-part appliance, with the interlock lingual to the occlusal surfaces of the teeth. The lower half can be fixed or removable and this design has some of the attributes of other appliances. Whilst it has potential advantages including theoretical incremental advancement resulting in greater co-operation and potentially greater contribution of mandibular growth than dentoalveolar effects, it remains un-resolved whether the Bass Dynamax is more efficient than other functional appliances as a substantial UK RCT involving this appliance and a Twinblock appliances has been abandoned due to excessive breakages of the Dynamax (Thiruvenkatachari et al.2010). This appliance is therefore not used widely.

The fixed design of the Twinblock appliance has three significant advantages when compared to a Herbst and Dynamax appliances:

- The appliance is significantly cheaper as no complex components are required for construction whilst the clinician involvement in treatment is no more complicated when compared to other removable functional appliances

- The appliance is located on the occlusal plane and not in the buccal sulcus, which assists robustness and patient comfort
- Because the two halves of the appliance are not permanently linked together, the problems of leverage on the fixation points does not arise.

However, the simplicity and versatility of the fixed Twinblock appliance in relation to accelerating functional appliance treatment times remains to be tested. Initial data from a scoping study (REC 17/ES/0126) shows significant difference in overjet reduction at 3 months treatment duration with the fixed Twinblock. The patient experience with the Fixed Twinblock did not report any negative experience in relation to soreness from the appliance. Free text comments from patients were positive for the use of the fixed appliance.

2.1 RATIONALE FOR TRIAL

The fixed design of the Twinblock appliance offers an opportunity to reduce treatment time using a simple and versatile device which is fixed, reducing the problems with compliance. Outcomes of this trial are clinically relevant with major dental health and financial benefits for the Scottish population and globally. This patient centred innovative research trial could potentially maximise correction of the malocclusion during growth and negate the challenges of dental trauma and malocclusion associated psychosocial problems in adolescents. The available evidence is presently limited and further high quality, well-designed clinical trials assessing the relative merits of both clinician and patient centred outcomes are needed (Pacha M M 2015). We are presently reviewing the literature further on effects of removable and fixed appliances on overjet correction and conducting a large network meta-analysis on the topic (Overjet correction in preadolescent and adolescent age groups: fixed versus removable appliances. PROSPERO 2018 CRD42018112703)**.**

The aim of our trial is to investigate the speed of correction of the overjet (upper front teeth prominence) as well as the patient's perception of treatment and the associated changes, and experience with the fixed and removable Twinblock appliances.

3. TRIAL OBJECTIVES AND OUTCOMES

3.1 OBJECTIVES

3.1.1 Primary Objective

1. Does the fixed Twinblock appliance accelerate overjet reduction for a Class II division 1 malocclusion in comparison to the conventional removable Clark Twinblock appliance?

3.1.2 Secondary Objectives

2. Does the fixed Twinblock appliance produce more skeletal than dentoalveolar contribution for a Class II division 1 malocclusion in comparison to the conventional removable Clark Twinblock appliance?
3. Does the fixed Twinblock appliance produce more facial volume increase in comparison to the conventional removable Clark Twinblock appliance?
4. Are patient's treatment experience better with the fixed Twinblock appliance as compared to the removable Twinblock appliance.
5. Is the fixed Twinblock appliance more cost effective and safer for correcting increased overjets as compared to the removable Twinblock appliances.

3.2 OUTCOMES

3.2.1 Primary Outcomes

1. Rate of overjet correction by comparing change in millimetre/month from clinical measurements with fixed and removable Twinblock appliances.

3.2.2 Secondary Outcomes

2. Relative skeletal, facial and dentoalveolar contributions to overjet correction by comparing lateral cephalogram changes via cephalometric analyses (Mills 1982), and facial volumetric changes (Camison et al 2018) and tooth movements by superimposing 3D scans, respectively, at the end of orthodontic treatment.
3. Patients' perception and experience with the fixed and removable Twinblock appliance will be assessed using the three questionnaires approach (Pre-Treatment questionnaire, Orthodontic Experience Questionnaire and Post-Treatment questionnaire (Al-Naseri et al 2017)
4. Cost-effectiveness of overjet reduction with fixed and removable Twinblock by comparing direct costs of treatment i.e., number of visits for Twinblock phase of treatment and number of breakages/loss with the fixed and removable Twinblock appliances.
5. Potential adverse effects of the fixed Twinblock and removable Clark Twinblock appliance.

Table 1: Primary Objectives and Outcome Measures

Primary Objective:	**Outcome Measure:**	**Timepoint of outcome measured**
Rate of Overjet correction	change in millimetre/month from clinical measurements	T0, T1, T2, T3, T4, T5

Table 2: Secondary Objectives and Outcome Measures

Secondary Objective:	**Outcome Measure:**	**Timepoint of outcome measured**
Skeletal, facial and dentoalveolar contributions to overjet correction	Lateral cephalometric analyses, Facial volumetric changes, and tooth movements by superimposing 3D scans	T0, T4, T5
Patients' perception and experience	Pre-Treatment questionnaire, Orthodontic Experience Questionnaire and Post-Treatment questionnaire	T0, T1, T4
Cost-effectiveness of treatment	Number of visits for Twinblock phase of treatment and number of breakages/loss	T4

4 TRIAL DESIGN

4.1 INTERVENTION

Participants will be treated either the fixed or removable Twinblock appliances. Following completion of the Twinblock treatment, all participants will continue treatment with fixed orthodontic appliance (train-track braces), which isstandard treatment protocol following completion of twinblock treatment.

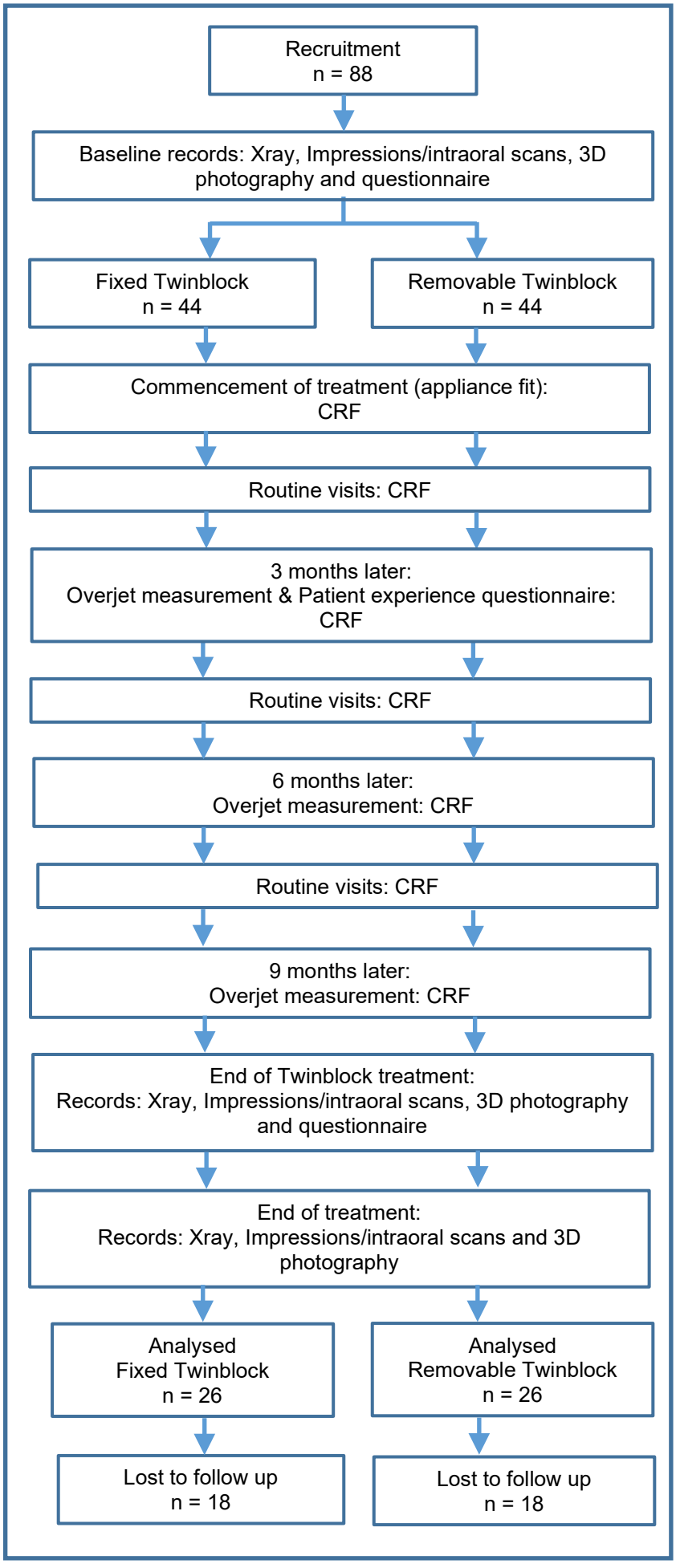
4.2 TRIAL DESCRIPTION

We plan to undertake a multicentre randomised clinical trial in Tayside and Grampian regions as a two-arm parallel design to detect a difference between the fixed and removable Twinblock appliance for overjet reduction.

4.3 TRIAL MATRIX

Data collection	Time points					
	T0 Start	**T1** 3 months	**T2** 6 months	**T3** 9 months	**T4** End of Twinblock treatment	**T5** End of treatment
Clinical Orthodontic assessment	✓				✓	✓
Overjet measurement	✓	✓	✓	✓	✓	✓
Lateral cephalogram	✓				✓	✓ (near end)
Impressions / intraoral scan	✓				✓	✓
3D Facial Stereo – photogrammetry Image	✓				✓	✓
Patient Experience Questionnaire	✓	✓			✓	

4.4 TRIAL FLOWCHART



4.5 TRIAL ASSESSMENTS

Trial assessments will be as described in the trial matrix at 4.3 at all the recruiting sites (primary and secondary care sites). Standard NHS clinical treatment protocol with Twinblock appliance includes a phase of further fixed orthodontic treatment (train track braces) and will be part of the treatment for all participants in this trial. Whilst the primary objective of the trial is to compare the fixed and removable Twinblocks, it is appreciated that skeletal, dental and soft tissue effects could change by the end of fixed orthodontic treatment (T5). Therefore, all data (excluding patient experience questionnaire) will be collected up until T5. To collect experience of participants with Twinblock phase of treatment alone, the patient experience questionnaires will be collected up until T4.

4.6 TRIAL SAFETY ASSESSMENTS

This is a low risk trial, and no serious adverse events are anticipated. However, it is possible that there may be allergic reactions to the Twinblocks and this will be recorded as an expected adverse event in the CRF. The Twinblock appliance treatment will be discontinued in case of allergic reaction and discontinued from the trial and other options for management of the increased overjet will be provided. The site PI will report any SAE that is both related to the research procedures and is unexpected to the CI and the CI will send an NRES Safety Report to the appropriate REC within 15 days of becoming aware of the event. A copy of the Report will be sent in parallel to the Sponsor. An annual progress report will be submitted to the appropriate REC and a copy of the Report will be sent in parallel to the Sponsor.

Consideration and potential impact of the trial following the peak of the COVID-19 pandemic have been mitigated to ensure safety of participants and staff. The visits for treatment during the trial will be part of routine non aerosol generating dental care, with physical access to the dental hospital/orthodontic practice complying with Scottish government restrictions on social distancing. This information will be provided to participant and parent/carer prior to attendance and suitably prepared ahead of their appointment so that total contact time spent in the dental hospital/ orthodontic practice is reduced. Covid-19 screening will be undertaken ahead of the visit where possible and a high level of hand hygiene will be adopted with the provision of antiseptic hand gel on entrance and exit. To reduce contamination, minimised wait times in common areas will be adopted and safe entry/exit will be ensured with appropriate signage. Face coverings will be required to be worn where indicated by Scottish government guidance.

Radiographs are part of routine clinical investigations. Effective Dose per lateral cephalogram - 0.004mSv (from HPA-CRCE-012 'Frequency and Collective Dose for Medical and Dental X-Ray Examinations in the UK, 2008'). As the patients in this study are 9-14 years old, the risk is age corrected to 11% per Sv. The combined risk of cancer mortality from both exposures in this study is of the order of 1 in 1.1 million

4.6.1 Potential Risks

If there is a problem with the fixed or removable Twinblock, the patient may need to make an additional appointment for advice/assistance/repair. The participant will be compensated for any additional visits due to breakage of blocks with a £10 voucher.

4.7 INCIDENTAL FINDINGS

Any incidental findings previously undiagnosed condition) considered to be clinically significant will be reported to the participant’s GP by the Site PI, with the consent of the participant.

4.8 TRIAL POPULATION

Patients will be recruited from NHS primary care orthodontic practices and secondary care orthodontic units in Tayside (Dundee) and Grampian (Aberdeen) region.

4.9 NUMBER OF PARTICIPANTS

We plan to undertake a multicentre randomised clinical trial in Tayside (primary and secondary care) and Grampian (primary care) regions as a two-arm parallel design of fixed and removable Twinblock appliance for overjet reduction. To detect a clinical important difference, 26 participants per arm, giving a total of 52 are required to complete the trial. With the long nature of treatment and high levels of drop out, combined with missing data from non-treatment visits, it was decided to allow for 40% drop out or incomplete data collection and therefore 88 patients will be recruited, 44 to each arm of the trial. The recruitment is anticipated to take around 18-months to complete.

4.10 INCLUSION CRITERIA

- Class II division 1 malocclusion
- No history of active orthodontic treatment
- Overjet $\geq$ 6mm (IOTN 4a/5a)
- Age 9-14 years
- Child & parent/carer who are able to assent and consent, respectively

4.11 EXCLUSION CRITERIA

- Overjet <6mm
- Mobile/loose deciduous teeth,
- Profound hypodontia affecting the incisor region (>1 missing tooth per quadrant)
- Subjects taking growth hormone or endocrine disorders
- Suspected or identifiable syndromes
- Subjects with cleft lip and palate
- Anterior open bite

5 PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

All patients referred to the recruiting centres (Dundee Dental Hospital, Beam Orthodontics (Dundee), Perla Orthodontics (Dundee) and The Orthodontic Clinic (Aberdeen)) for orthodontic treatment, attend for initial assessment. At this initial assessment, the treating orthodontist (local PI) and/or a delegated member of the clinical team will identify those patients who appear to meet inclusion criteria. A suitably trained member of the local clinical team will then explain to them the trial, provide written information, and invite them to participate.

5.2 CONSENTING PARTICIPANTS

Identified patients will be invited to participate in the trial by the site PI or one of the delegated member of the clinical team trained in taking informed consent, who will be a registered practitioner with the General Dental Council (GDC). The study will be discussed with parents/guardians and potentially eligible children. Participants and parent / carers will be given the opportunity to ask questions and appropriate consent/assent forms will be completed. This would be at the next appointment (4-6 weeks) to allow for time for patients'/parents' to process the information. Where a parent/carer/ or participant requests to speak with a member from the trial team the consent process will not be completed until the parent/carer or participant has spoken to the team member and had all their questions answered to their satisfaction.

As age of legal capacity says patients can consent from 12yrs for dental care if they have capacity, therefore for patients aged 09-11 years, child assent and parental consent forms will

be completed. For children aged 12-14 years old, participant consent and parental assent forms will be completed.

5.3 SCREENING FOR ELIGIBILITY

Screening will be done by the PI from the initial records (impressions or intra-oral scan) collected. Confirmation of eligibility will be given by the chief investigator on viewing clinical records.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

Patients who are screened and found to be ineligible will have normal care provided as per normal clinical protocols. Similarly, patients identified who decline to participate will enter treatment as per normal clinical protocols.

5.5 RANDOMISATION

5.5.1 Randomisation

Randomisation will be stratified by gender, overjet measurement (IOTN 4a or 5a) and site, using the on-line TCTU (TRuST – Tayside Randomisation System) randomisation system. TCTU's Randomisation System (TRuST) provides GCP compliant web-based randomisation to produce balanced randomisation allocation based on a minimisation with stratification algorithm.

The system has been built to deal with each combination of variables by making up a block, which is how the participants are stratified across at point of randomisation. However, to make it more difficult to predict the allocation it uses random block sizes. Therefore, over time it will keep the variable balanced, with an automatic notification from the system to stop recruiting to a particular group.

5.5.2 Intervention Allocation

The TCTU TRuST system will allocate patients randomised to the two groups and generate both an on-screen message at time of randomisation and an e-mail to the PI and CI.

5.5.3 Withdrawal procedures

Although a participant is not obliged to give reason(s) for withdrawing prematurely, if the participant appears lost to follow up, the Chief Investigator (CI) will make a reasonable effort to ascertain the reason(s), while fully respecting the individual's rights, and will demonstrate that everything possible was done in an attempt to find any participant lost to follow-up. Those lost to follow-up or withdrawn will be identified and a descriptive analysis of them provided, including the reasons for their loss and its relationship to treatment and outcome.

If participants withdraw/dropout within 3 months of treatment, no further records would be collected, as any change would not be clinically meaningful. Any data collected thus far will be imputed and intention to treat analysis will be used.

If participants withdraw/dropout after 3-month period, attempt to clinically measure overjet will be made and any previously collected questionnaire data, 3D facial scans, scans of teeth and questionnaire data will be imputed and intention to treat analysis will be used.

6 DATA COLLECTION& MANAGEMENT

6.1 DATA COLLECTION

Overjet measurement
Overjet will be measured (in millimetres) between the upper incisal edge and the labial surface of the lower incisors using a metal ruler at all appointments to assess rate of reduction. This will be measured at start of treatment (T0), 3 months (T1), 6 months (T2), 9 months (T3), end of Twinblock appliance phase, i.e., when overjet has reduced to 0-3mm and remains unchanged at two consecutive appointments (T4), for a maximum of 12 months from start of treatment and end of fixed appliance treatment (T5). If overjet has reduced earlier than anticipated, follow-up time points will be skipped to T4 and T5.

Impressions
A negative imprint of teeth and soft tissues will be made using alginate impression material to produce plaster models (positive reproduction), allowing fabrication of the fixed and removable Twinblocks at the Orthodontics laboratory within Dundee Dental Hospital. A typical impression takes 10 minutes and is routine procedure for all patients undergoing Orthodontic treatment.

Intra oral scans
3Shape Trios® or iTero Element ® will be used to record intra- Oral scans for digital study models. These use a non-contact laser scanning technology to record a three-dimensional record of the tooth position and occlusion. A scan takes 10 minutes to collect depending on operator experience and patient compliance. There is no discomfort or sensation associated with the scanning procedure. The pre- and post-treatment study models are essential records in orthodontics and the digital version will allow precise tracking and quantifying (mapping) of tooth movements during treatment. The mapping of teeth movements will provide details of the extent of dental contributions in overjet reduction. If an intraoral scanner is not available at a site, the impression or plaster models will be scanned using the 3Shape dental lab 3D scanner. The superimposition function on 3Shape Ortho Analyzer software will be used to calculate distance between pre- and post-treatment scan landmarks in millimetres.

Stereophotogrammetry

Vectra® H1 handheld 3D camera will be used to record the patient's three-dimensional (3D) facial characteristics, allowing quantification of 3D soft tissue volume changes. The camera works like any other and would require three facial captures which are automatically stitched into one 3D image with the provided software. The whole process will take 10 minutes. The need for 3D quantification of the soft-tissue effects of functional appliances has been highlighted (Flores-Mir 2006). The immediate soft tissue effects, especially of the soft tissue chin (Sharma 2005) have been shown to be only 40% of the predicted outcome (Salloum 2018). Landmarking of the pre- and post-treatment 3D images will be done using the VAM (Vectra Analysis Module) software and superimposed to measure the difference in linear distance in millimetres.

Lateral Cephalogram
Cephalometric radiographs are routinely taken as part of assessment and planning for orthodontic treatment. Modern digital lateral cephalometric radiographs are very low dose. It is used to assess whether the aetiology of malocclusion is due to skeletal relationship, dental relationship or both and quantify treatment changes. The radiographs will be taken at baseline, end of twinblock treatment and towards end (near end) of fixed appliance treatment in accordance with normal clinical practice. Eastman cephalometric analysis (Mills, 1982) will be done on the radiographs to assess the skeletal and dental changes associated with both the groups. The analysis will include angles SNA (sells-nasion-point A), SNB (sella-nasion-point B), ANB (difference between SNA and SNB), upper incisor long axis to maxillary plane (anterior nasal spine -posterior nasal spine), lower incisor to mandibular plane (gonion-menton), MMPA (maxillary-mandibular plane) and linear measurements - facial proportion (ratio of lower face height to total anterior face height) and APog (tip of lower incisor form line connecting point A-Pogonion)

Patient Experience questionnaire
This validated questionnaire, based on the three-questionnaire approach, will evaluate patients perception of their malocclusion pretreatment (T0) and patients' experience with wearing the fixed and removable Twinblock appliances 3 months into treatment (T1) and at the end of Twinblock phase of treatment (T4).

6.2 DATA MANAGEMENT SYSTEM

Data management will be conducted in compliance with TASC SOPs on Data Management, TASC SOP53 Data Management Systems in Clinical Research and TASC SOP48 Data Management in CTIMPs using Excel.

The data management system (DMS) will be Excel, as approved by Sponsor.

The DMS will be based on the protocol and CRF for the trial and individual requirements of the investigators. The CRF will collect only information that is required to meet the aims of the trial and to ensure the eligibility and safety of the participant. The trial database will be compliant with TASC SOP53 Data Management Systems in Clinical Research.

The database is managed in line with all applicable principles of medical confidentiality and UK law on data protection, namely, the General Data Protection Regulation. The Data Controller will be the University of Dundee and the Data Custodian will be Chief Investigator.

The CI may delegate CRF completion but is responsible for completeness, plausibility and consistency of the CRF. Any queries will be resolved by the CI or delegated member of the trial team.

Database lock will be conducted in compliance with TASC SOP32 Locking Clinical Study Databases.

7 CLINICAL PROTOCOL AND TRIAL PLAN

7.1 FIXED TWINBLOCK APPLIANCE DESIGN

The fixed Twinblock (*Figure 1*) comes as preformed occlusal blocks and wires. The occlusal blocks will be custom adapted to the individual participant's models with the upper block fitted to cover the second premolar and extend distally over the molars. The lower block will cover the premolars, avoiding the cusp of the canine.

In occlusion, the occlusal blocks will be inclined at 70° to allow forward positioning of the lower jaw. The fixed Twinblocks will be cemented onto the occlusal surfaces simply with conventional glass ionomer cement. The upper palatal arm can be expanded (prior to cementation) to allow for upper arch expansion.

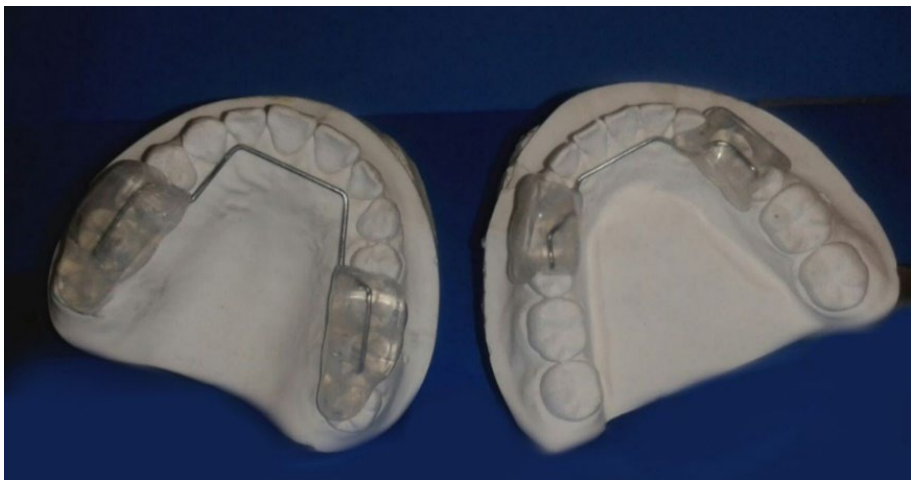


Figure 1: Fixed Twinblocks with occlusal blocks adapted to the teeth and supporting wire components.

7.2 REMOVABLE TWINBLOCK APPLIANCE DESIGN

The removable Twinblock (*Figure 2 & 3*) design used in this trial will be upper and lower appliances with clasps on upper 1st premolars and 1st molars, lower 1st premolars and lower incisors for retention. Where additional retention is deemed to be required clinically, clasps will be included on lower molars, in addition to above. The upper appliance will include a jack screw for expansion and no labial bow will be used.

In occlusion, the occlusal blocks will be inclined at 70° to allow forward positioning of the lower jaw.

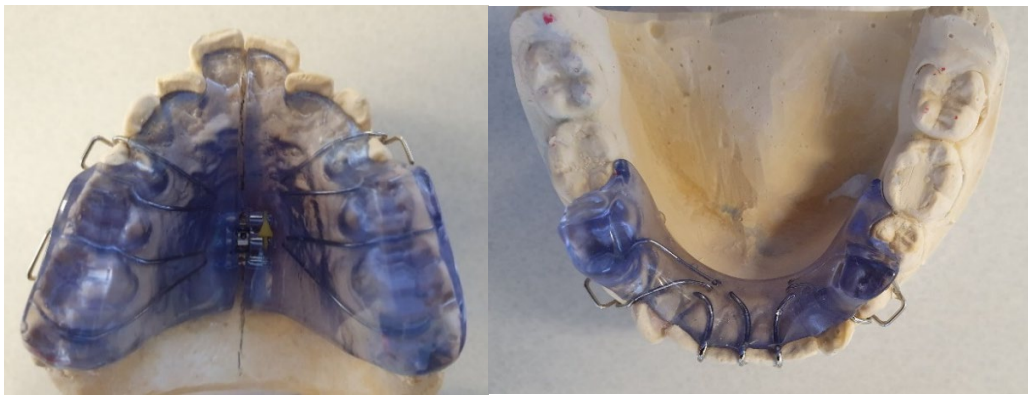


Figure 2 & 3: Removable Twinblocks with jack screw in the upper arch and clasps for retention

7.3 TRIAL PLAN

Gantt Chart (*Table 3*) with details of the clinical trial

Tasks	Jul-Dec'20	Jan-June'21	Jul-Dec'21	Jan-June'22	Jul-Dec'22	Jan-June'23	Jul-Dec'23	Jan-June'24
Ethical approval								
Setting up RCT								
Recruitment								
Data Collection								
Data analysis								

8 STATISTICS AND DATA ANALYSIS

8.1 SAMPLE SIZE CALCULATION

The feasibility study conducted by us in Dundee Dental Hospital (REC 17/ES/0126) has produced a clear route of progression (NIHR criteria) to the substantive multicentre RCT by estimating all the important parameters. Using initial data obtained from our feasibility study, for an effect size of 0.80 (difference of 81 days and SD 101 days), an alpha value of .05 and a power of 80% the required sample size was computed as 26 participants per group giving a total of 52. This is a assuming a simple independent t-test analysis and utilising sample size software PASS20. Recruitment will be across 4 sites and so randomisation will be stratified by site. With the long nature of treatment and high levels of drop out, combined with missing data from non-treatment visits we decided to allow for 40% drop out or incomplete data collection and therefore 88 patients will be recruited, 44 to each arm of the trial.

8.2 PROPOSED ANALYSES

Descriptive statistics will be prepared to show the mean, standard deviation and range for the outcome variables in the fixed and removable Twinblock groups.

The primary outcome measure will be millimetre change in overjet per month. This will be compared between the fixed Twinblock group and the removable Twinblock control group using a Multilevel Linear Model (MLM). This will allow us to assess the difference between treatment groups while controlling for any differences in effect between treatment centres. In the event that the collected data violates the assumptions for a parametric test, heterogeneity between centres will be assessed using the MLM and checked with a Friedman's ANOVA within treatment groups. If no heterogeneity between returning centres is observed, data from all centres will be collapsed and a bootstrapped independent t-test will be run. If both non-parametric data and heterogeneity between centres is encountered, separate analyses will be conducted for each of the different returning centres and a Bonferroni correction will be applied for running multiple analyses. Estimates of effect size will be calculated from the data to better inform the sample size calculations of future studies.

The effect of the Twinblock appliance upon secondary measures will be explored using descriptive statistics. Data on the patients' perceptions and experience of their appliances will be analysed with descriptive statistics to produce graphs and tables

8.3 MISSING DATA

Incomplete data will be imputed and intention to treat analysis will be used to include subjects who terminate the trial early (see 5.5.3 above)

8.4 TRANSFER OF DATA

The data will be confined to the clinical team who will transfer data only using strong password encrypted USB sticks from all participating centres in Tayside and Grampian. This will be collected by the PI during the regular site visits to all participants centres and anonymised records will be held securely at the study centre (University of Dundee) for secure storage and analysis.

9 TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

9.1 TRIAL MANAGEMENT GROUP

The trial will be co-ordinated by a Trial Management Group, consisting of the Chief Investigator, Principal Investigator, clinical trial investigators and trial Statistician

9.2 TRIAL MANAGEMENT

The PI will oversee the trial and will be accountable to the CI. The clinical trial investigators will be responsible for checking the CRFs for completeness, plausibility, and consistency. However, this will remain the overall responsibility of the CI. Any queries will be resolved by the CI or one of the clinical trial investigators.

As this is a low risk trial where standard treatment protocols are being used, the Trial Management Committee will monitor safety as data is accumulated.

9.3 INSPECTION OF RECORDS

The CI, clinical trial investigators and all sites involved in the trial will permit trial related monitoring, audits, REC review, and regulatory inspection(s). In the event of an audit, the CI will allow the Sponsor, representatives of the Sponsor or regulatory authorities direct access to all trial records and source documentation.

10 GOOD CLINICAL PRACTICE

10.1 ETHICAL CONDUCT OF THE TRIAL

The trial will be conducted in accordance with the principles of good clinical practice (GCP).
In addition to Sponsorship approval, a favorable ethical opinion will be obtained from an appropriate REC and NHS R&D permissions will be obtained prior to commencement of the trial.

10.2 CONFIDENTIALITY AND DATA PROTECTION

The CI and clinical trial investigators involved with this trial will comply with all applicable medical confidentiality and data protection principles and laws with regard to the collection, storage, processing and disclosure of personal information and will uphold the Act's core principles. The CI and trial staff will also adhere to the NHS Scotland Code of Practice on Protecting Participant Confidentiality. Access to collated participant data will be restricted to the CI and clinical trial investigators.

All trial records and personal data will be managed in a manner designed to maintain participant confidentiality. All records, electronic or paper, will be kept in a secure storage area with limited access to trial staff only. Computers used to collate personal data will have limited access measures via user names and passwords. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor or its designee. The CI and clinical trial investigators involved with this trial will not disclose or use for any purpose other than performance of the trial, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the trial. Prior written agreement from the Sponsor or its designee will be obtained for the disclosure of any said confidential information to other parties.

Personal data concerning health will not be released except as necessary for research purposes including monitoring and auditing by the Sponsor, its designee or regulatory authorities providing that suitable and specific measures to safeguard the rights and interests of participants are in place.

10.3 INSURANCE AND INDEMNITY

The University of Dundee sponsoring the trial.

Insurance – The University of Dundee will obtain and hold a policy of Public Liability Insurance for legal liabilities arising from the trial.

Where the trial involves University of Dundee staff undertaking clinical research on NHS patients, such staff will hold honorary contracts with Tayside Health Board which means they will have cover under Tayside's membership of the CNORIS scheme.

Indemnity - The Sponsor does not provide trial participants with indemnity in relation to participation in the trial but has insurance for legal liability as described above

11 ADVERSE EVENTS

11.1 DEFINITIONS

Adverse Event (AE)	Any untoward medical occurrence in a clinical research participant which does not necessarily have a causal relationship with study participation
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life threatening • requires hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • Or is otherwise considered serious

11.2 RECORDING AND REPORTING AES AND SAES

All AEs and SAEs will be recorded from the time a participant consents to join the trial until the last visit and will be assessed for severity by the CI or delegate. Participants with unresolved AEs at the last visit will be followed up until resolution or 30 days after last patient, last visit (LPLV), whichever is sooner. The CI or clinical trial investigator will ask about the occurrence of AEs and hospitalisations at every visit during the trial.

The Investigator will make a clinical judgment as to whether an AE is of sufficient severity to require the participant's removal from the study. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant should, if required, be offered an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable. AEs/SAEs will be followed up until 30 days after participant's last visit.

The CI or delegate will ask about the occurrence of AEs/SAEs and hospitalisations at every visit during the study. SAEs which are both unexpected and related to study participation will be submitted on an HRA NCTIMP Safety Report form to the REC by the CI, within 15 days of becoming aware of the SAE, and copied to the Sponsor Research Governance Office.

Worsening of the condition under study will not be classed as an AE but will be defined as an outcome. Elective admissions and hospitalisations for treatment planned prior to randomisation, where appropriate, will not be considered as an AE. However, AEs/SAEs occurring during such hospitalisations will be recorded.

12 ANNUAL REPORTING REQUIREMENTS

Annual reporting will be conducted in compliance with TASC SOP 15: Preparing and Submitting Progress and Safety Reports in CTIMPs and Non-CTIMPs, as a condition of sponsorship and as a condition of a favourable opinion from a REC. An HRA Annual Progress Report for NCTIMPs will be prepared and submitted by the CI to REC, and copied to the Sponsor, on the anniversary date of the REC favourable opinion.

Any safety reports additional to SAE reports, for example, reports of a DMC, will be sent by the CI to REC, with a Safety Report Form, and to the Sponsor.

13 TRIAL CONDUCT RESPONSIBILITIES

13.1 PROTOCOL AMENDMENTS, DEVIATIONS, BREACHES

The CI will seek approval for any amendments to the Protocol or other study documents from the Sponsor, REC and NHS R&D Office(s). Amendments to the protocol or other study docs will not be implemented without these approvals.

The CI will not implement any deviation from the protocol without agreement from the Sponsor, except where necessary to eliminate an immediate hazard to trial participants.

In the event that CI needs to deviate from the protocol, the nature of and reasons for the deviation will be recorded in the CRF, documented and submitted to the Sponsor as a potential breach report. If this necessitates a subsequent protocol amendment, this will be submitted to the Sponsor for approval and then to the appropriate REC and lead NHS R&D Office for review and approval.

If a serious breach of GCP or protocol is suspected, this will be reported to the Sponsor Governance Office immediately

13.2 TRIAL RECORD RETENTION

Archiving of trial documents will be carried out for five years after trial end.

13.3 END OF TRIAL

The end of trial is defined as last patient last visit (LPLV) The Sponsor and CI have the right at any time to terminate the trial for clinical or administrative reasons.

The end of the trial will be reported to the Sponsor and REC within 90 days, or 15 days if the trial is terminated prematurely. The CI will ensure that any appropriate follow up is arranged for all participants.

A summary report of the trial will be provided to the Sponsor and REC within 1 year of the end of the trial.

The Trial Steering Committee would consider stopping the trial should data indicate that in one group there was significant adverse effect on patient outcomes, including in terms of lack of effectiveness of one treatment, excessive pain related to one treatment or excessive breakages related to one treatment.

14 REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

14.1 AUTHORSHIP POLICY

Ownership of the data arising from this trial resides with the trial team and their respective employers. On completion of the trial, the trial data will be analysed and tabulated, and a clinical trial report will be prepared. All members of the research team (CI and clinical trial investigators) will be recognised on any outputs, reports, or publications.

14.2 PUBLICATION

Peer reviewed journal publication and presentation at scientific meetings will be prepared to disseminate the data analysed at the end of Twinblock appliance treatment, in addition to using the final clinical trial report for publication in peer reviewed open access journals and presentation at scientific meetings. The CI and clinical trial investigators have the right to publish orally or in writing the results of the trial.

Summaries of results will also be made available to Investigators for dissemination within their clinical areas (where appropriate and according to their discretion).

13.3 PEER REVIEW

This protocol has undergone peer review by Philip Benson, Professor of Orthodontics, University of Sheffield and comments incorporated as appropriate. The trial team acknowledge his advice and support.

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