Protocol Number: MRF-002

CSP-300291-00

Sponsor:	Align Technology, Inc. 2820 Orchard Parkway San Jose, CA 95134 (408)-470-1000
Amendment No.:	[redacted]

INVESTIGATOR SIGNATURE PAGE

Invisalign System [redacted] Mandibular Repositioning Feature

Approved by: [redacted]

[redacted] _____ _____

Director of Clinical Affairs Signature Date

Investigator signature:

I confirm that I have read and will follow this protocol. I understand it, and I will work according to the principles of Good Clinical Practices (GCP) as described in the ICH E6, Good Clinical Practice: Consolidated Guidelines and in the United States Code of Federal Regulations (CFR) – 21 CFR parts 50 (Protection of Human Subjects), 56 (Institutional Review Boards), and 812 (Investigational Device Exemptions). Further, I will conduct the study in keeping with any other federal, state, local, and institutional legal and regulatory requirements.

Investigator

_____ _____ _____

Print name Signature Date

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1. INTRODUCTION AND BACKGROUND

1.1 Background

In 1945, Dr. H.D. Kesling envisioned that one day modern technology would enable the use of a series of tooth positioners to produce the kinds of movements required for comprehensive orthodontic treatment. Technology has made this vision a reality. Using advanced computer technology, Align Technology Inc. generates Invisalign®, a series of customized clear appliances, called "aligners." Each aligner is worn sequentially by the patient to produce extensive tooth movements in both upper and lower arches.

Class II malocclusions are often characterized by mandibular retrognathia and increased overjet. In patients with Class II malocclusions that are undergoing growth, appliances that reposition the mandible in a forward position can be used to correct class relationship. [redacted]
Numerous clinical studies have demonstrated the effectiveness of such appliances in treating Class II malocclusions, as indicated by improved overjet, molar relationship, canine relationship, and/or orthopedic changes [redacted] The aim of these appliances is to maintain the lower jaw in a forward position for as long as the appliances are worn, such that orthopedic and/or postural changes can take place to correct the patient's occlusion to a Class I by the end of the appliance treatment.

Most existing Class II appliances reposition the mandible in one step, such that the patient's jaw is positioned at the desired final position (or an overcorrected position) throughout the course of treatment. An alternative to this method is incremental repositioning, in which the total amount of A-P correction is divided into multiple steps. This method has been shown to be effective with the [redacted] and one advantage to this method is increased patient comfort especially at the start of therapy.

2. DESCRIPTION AND INDICATIONS FOR USE

2.1 Device Description

The Invisalign® System consists of a series of clear plastic aligners that are intended to replace conventional wire and bracket technology for many orthodontic cases. Each custom manufactured aligner exerts gentle, continuous forces to move teeth incrementally from their original state to a final, treated state. Each aligner is worn for about two weeks, then replaced by the next in the series until the final position is achieved. For years, orthodontists and dentists have used removable appliances for orthodontic treatment. Today, with the application of computer technology and custom manufacturing, Invisalign treats a broader range of cases with greater precision.

The Invisalign System with [redacted] Mandibular Repositioning Feature (MRF) are removable devices that consist of an aligner with [redacted] The upper and lower ramps are designed to interlock in such a manner that the mandible is held in a more protrusive position. The repositioning of the mandible can be done sequentially in multiple increments (steps), in order to meet the doctor's treatment goal. The Invisalign System with MRF is made from the [redacted], a clear thermoplastic and utilizes current Invisalign System manufacturing processes.

[redacted]

2.2 Invisalign Intended Use

The Invisalign® System is indicated for the alignment of teeth during orthodontic treatment of malocclusion.

3. STUDY PURPOSE AND OBJECTIVES

3.1 Study Objectives

To demonstrate that growing teenagers which present up to full cusp Class II malocclusions can be treated using Invisalign with MRF. The primary objective of the study will be to demonstrate that Invisalign with MRF is not inferior to existing functional appliances to treat up to full cusp Class II malocclusions in growing teenagers. The objective will be met if Invisalign aligners with MRF correct Class II malocclusions at a rate that is not inferior to previously reported repositioning rates. This will be achieved if the median rate of correction using Invisalign with MRF at the end of mandible repositioning is non-inferior to published rates of movement (e.g. 0.42 mm/mo. [redacted] ([redacted] to a confidence level of 80%. [redacted]

[redacted] The secondary endpoints will be measured by comparing length of treatment [redacted]. [redacted] Both subject and doctor perception will be assessed.

All statistical comparisons will be conducted to an 80% confidence level.

3.2 Definitions

Term or Abbreviation	Definition
AE	Adverse event
A-P	Type of anterior-posterior orthodontic malocclusion treatment correction
Buccal	Surfaces of crowns of teeth that face away from the tongue (toward the lips or toward the cheek)
Class II Malocclusion	A type of orthodontic malocclusion
CRF	Case Report Form
FDA	Food and Drug Administration
IRB	Institutional Review Board
Investigator	The person responsible for the conduction of this study at each individual site. This will be the treating orthodontist. The term "Investigator" is used synonymously in this Protocol with "Principle Investigator", "Orthodontist" and "Doctor".

IO	Intraoral scans
IPR	Interproximal Reduction
[redacted]	[redacted]
[redacted]	[redacted]
OPG	Panoramic radiograph
PVS	An orthodontic impression material (polyvinyl siloxane material)
SAE	Serious adverse event
[redacted]	[redacted]
Sponsor	Align Technology, Inc.
Study Monitor or Clinical Research Associate (CRA)	Person from the Sponsor who monitors the study data for completeness, accuracy through on site visits, remote monitoring, etc.
TMD	Temporomandibular joint dysfunction
MRF	Mandibular Repositioning Feature
SOP	Standard Operating Procedure

4. STUDY DESIGN

4.1 Overview of Study Design

This study is a prospective, non-randomized Investigational Device Exemption study. It is designed to measure how safely and effectively Class II malocclusions are corrected in teenagers by repositioning the mandible. It will also examine how efficiently the repositioning will occur. [redacted]

During the course of treatment, Investigators will monitor the use of the MRF in subjects and complete case report forms. Monitoring of the cases and completion of the case report forms will continue throughout the treatment of the Class II to Class I correction as well as through to the subject's end of Invisalign treatment or withdrawal from the study. Data from this correction will be analyzed and may be used for publication or regulatory purposes. After the use of the Invisalign aligners with MRF portion of treatment is completed, the subject will continue with their Invisalign treatment through to the end of treatment for the final study visit.

[redacted] This data collection will coincide with the 3 and 6 month follow-up periods of the IDE clinical study. The data collected will be similar to that obtained at follow up visits.

All study subjects will be treated with Invisalign aligners that have been modified to meet the study requirements. All sites will be monitored by the Sponsor in accordance to the monitoring plan. All data collected will be analyzed by the Sponsor or a designated statistician.

[redacted]

All participating Investigators and designated office coordinators will be trained on the clinical study protocol and good clinical practices (GCP) by representatives of the Sponsor.

4.1.1 Materials

The cases will be submitted and fabricated at Align Technology, Inc. [redacted]

4.1.2 Methods

Clinical and diagnostic methods to be used during this study are those which are routinely used in the diagnosis and treatment of malocclusions [redacted]. Investigators will also complete case report forms at each follow-up period as part of this study.

Inclusion Criteria:

A subject will be considered eligible if all of following inclusion criteria are fulfilled:

- Subject must have fully erupted dentition* excluding second premolars (5s), 2nd and 3rd molars
- Age range 11-19 years old
- Subject that requires bilateral Class II correction and must require at least 3mm of correction as measured by first molar relationship

Exclusion Criteria:

A subject will be considered ineligible if any one of following exclusion criteria are fulfilled:

- Subject who has unerupted, erupting, partially erupted dentition (except unerupted second premolars with less than half root development, for 2nd and 3rd molars)
- Subject who has spaces between adjacent teeth larger than 3mm
- Subject with active caries
- Subject with periodontal disease
- Subject does not have at least 1st molar fully captured in PVS impression or intraoral scan.
- Subject with TMD symptoms
- Subject has undergone pre-treatment with any sagittal orthodontic appliance
- Subject has undergone pre-treatment with any orthodontic appliance 1 year prior to enrollment in the study
- Subject has known allergy to latex and plastic
- Subjects who are pregnant or will become pregnant during treatment

[redacted]

All subjects are free to withdraw from the study at any time without stating a reason or suffering from any disadvantage. In addition [redacted]

[redacted]

Group Assignment

[redacted]

Schedule of Study Visits

Screening

Subjects must be screened before enrollment in the study. Screening procedures by the investigator will include the following:

1. Perform a dental history exam
2. Review inclusion and exclusion criteria (Eligibility criteria)
3. Inform subject and obtain written informed consent

Initial Visit

Initial visit procedures and tasks will include the following:

[redacted]

[redacted]

8. Case Report Form: Enrollment Form

Aligner Delivery Visit

1. Deliver Aligners: Give the prescribed aligners to the subject and instruct them on how to wear the aligners with MRF features
2. Subject (QoL) Form: To be filled out by the subject.

3 Months After Start of Mandibular Advancement

For prospective patients, all records must be collected at time of visit. [redacted], please provide any available [redacted] obtained from the follow up visit, and complete the Mandibular Advancement Treatment Progress Form.

[redacted]

4. Case Report Form: Mandibular Advancement Progress Form (3 month)

6 Months After Start of Mandibular Advancement

For prospective patients, all records must be collected at time of visit. [redacted]

[redacted]

4. Case Report Form: Mandibular Advancement Progress Form (6 month)

End of Mandible Repositioning (Class II to Class I Correction)-MCC/Refinement

End of mandible repositioning is defined as the point at which the Class II malocclusion is corrected to Class I [redacted]

8. Case Report Form: End of Mandible Repositioning Phase Form.

9. Subject (QoL) Form: To be filled out by the subject.

Final Visit/ Withdrawal From Study

Final visit procedures and tasks will include the following:

[redacted]

7. Case Report Form: End of Treatment Form.
[redacted] Subject QoL Form: To be filled out by subject. [redacted]

4.1.3 End Study

The End of Study occurs when a subject has completed all study related visits. When all subjects have completed the study, a report will be written concluding the findings from the study.

4.2 Number of Subjects/ Assignment to Treatment Groups

This study will enroll up to 165 patients. It is recommended that each site enroll a minimum of 10 subjects, to facilitate pooling of the data. It is recommended that each site recruits a minimum of 1 subject to have the occlusal feature set and a minimum of 1 subject [redacted]

4.3 Sites

This study will be conducted at multiple sites in North America.

4.4 Subject Withdrawal

Subjects have the right to withdraw from the study at any time for any reason. The Investigator or Sponsor may withdraw the subject at any time for any reason. If any subject withdraws or is withdrawn from the study, any non-study records that were taken while the subject was enrolled in the study will not be shared with the study Sponsor and there will be no requirement to continue treatment according to this protocol. Withdrawal from the study will not result in any penalties and will not preclude or interfere with the investigator's treatment of the subject outside of the study. Additional subjects may be enrolled to substitute for any withdrawn subject until the study target enrollment is reached.

[redacted]

5. DATA COLLECTION PLAN

The schedule of all study activities and procedures is provided [redacted]

No additional invasive or other burdensome interventions in comparison to the standard care will be performed.

6. DATA ANALYSIS

Data will be analysed by the Sponsor's statisticians or an identified consultant. The data will be analysed using standard univariate and bivariate techniques. [redacted] Significance will be demonstrated to a 80% confidence level.

6.1 Primary endpoint analysis:

The primary objective of the study will be to demonstrate that Invisalign with MRF is not inferior to existing functional appliances to treat up to full cusp Class II malocclusions in growing teenagers. The objective will be met if Invisalign aligners with MRF correct Class II malocclusions at a rate that is not inferior to previously reported repositioning rates. This will be achieved if the median rate of correction using Invisalign with MRF at the end of the mandible repositioning is non-inferior to published rates of movement (0.42 mm/mo. [redacted] to a confidence level of 80%. [redacted]

[redacted] The secondary endpoints measured by comparing the length of treatment [redacted]

[redacted] Both subject and doctor perception will be assessed.

6.2 Sample Size Calculation

The sample needed to demonstrate non-inferiority of the Invisalign with MRF to literature is found using a single sided proportion value, with the hypothesis that Ho P=Po and a 80% power is [redacted] patients.
[redacted]

7. SAFETY INSTRUCTIONS AND GUIDANCE

7.1 Clinical Adverse Events

An adverse event (AE) is any unwanted dental occurence which a subject experiences during a clinical investigation, whether or not the AE is suspected of having a causal relationship with study treatment. Pre-existing dental events, which increase in frequency or severity or change in nature during or as a consequence of use of an appliance clinical trials, will also be considered as adverse events.

An adverse event will not include non-compliance, lost or abuse of aligners which includes soaking of aligners in any substance or cutting of aligners without the permission of the treating orthodontist. This also includes a subject eating or drinking while wearing their aligners.

[redacted]

7.1.1 Assessment of Adverse Events

All AEs assessed by the investigator shall contact Align Clinical Research group and provide to Align information about the AE. This includes the date of onset and resolution, severity, causality (relationship to aligners), outcome and action taken with respect to study appliance. In addition, the events will be assessed by Align Clincial Research to see if it meets the definition of a serious adverse event (SAE). A serious adverse event will be defined as:

- Led to a death
- Led to a serious deterioration in the health of the subject that:
    - Resulted in a life-threatening illness or injury
    - Resulted in a permanent impairment of a body structure or a body function ○ Required in-subject hospitalization or prolongation of existing hospitalization ○ Resulted in medical or surgical intervention to prevent permanent impartment to body structure or a body function

7.1.2 Treatment and Follow-up of AEs

Any AE will be followed until a satisfactory result is reached or until it becomes stable or until it is proven that it resulted from another cause (concurrent condition) and clinical judgment concludes that further evaluation is not indicated.

7.2 Handling of Safety Parameters

7.2.1 Reporting of Adverse Events

Each investigator will report any AE (whether or not a relationship to aligners is suspected) with an onset date, after signing the informed consent form and follow this subject until the last aligners are worn, to the Align Clinical Research group at the following e-mail: [redacted] Investigators should report an incident using the AE CRF within 24 to 48 hours, 7 days a week.

The Investigator will need to report observations and findings potentially relevant to the final outcome of an AE in the subject's medical record.

The Sponsor may request return of the involved device or any potential device-related event, for investigation. A procedure for cleaning and returning of the device will be provided by the Sponsor.

The Sponsor will discuss all AEs and initiate and coordinate the appropriate actions. This includes in particular the notification of the competent authority in case of a device-related AE and - in accordance with the Declaration of Helsinki – the notification of the responsible ethics committee for all SAEs.

7.3 Study Risks and Benefits

The Invisalign System is indicated for the alignment of teeth during orthodontic treatment of malocclusion. The product labeling that describes the use and any warnings and precautions in the use of this device will be provided to Investigators. There is no additional risk involved with participating in this study beyond that associated with current orthodontic treatment practices. Procedures and treatments described in this protocol are in accordance with current orthodontic practices.

8. POTENTIAL SUBJECT RISKS AND BENEFITS

8.1.1 Potential Subject Risks

The Invisalign System is a dental device for the alignment of teeth during orthodontic treatment of malocclusions. A risk analysis of the Invisalign System has been performed for the 510(k) clearance. All identified risks have been minimized or eliminated through appropriate risk control measures, which are largely based on the compliance with harmonized standards. Hazards associated with use errors are reduced to an acceptable risk level by descriptions in the instructions for use. The product labeling that describes the use and any warnings and precautions in the use of the device will be provided to Investigators. There is no risk or foreseeable discomfort involved with being in this study beyond that associated with current orthodontic treatment practices. Procedures and treatments described in this protocol are in accordance with current orthodontic practices and identical to the ones a subject would undergo during clinical care of alignment of malocclusion. As such, subjects will not be subject to additional clinical burden while participating in the study.

8.1.2 Potential Subject Benefits

There are no known additional benefits to the subject as a result of participating in this study other than the benefits of the orthodontic treatment. [redacted]

9[redacted]

[redacted]

11. ETHICAL ASPECTS

11.1 Local Regulations/Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. [redacted] Consolidated Guideline or with local law if it affords greater protection to the subject. All investigators will additionally ensure that the basic principles of "Good Clinical Practice" as outlined in the current version of United States 21 CFR, Part 812 "Investigational Device Exemptions", Part 50, "Protection of Human Subjects", and Part 56, "Institutional Review Boards", are adhered to.

11.2 Informed Consent

It is the responsibility of the Investigator, or a person designated by the Investigator (if acceptable by local regulations), to obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives and potential risks of the study. It must also be explained to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time for any reason without any penalty. The Informed Consent will be reviewed and approved by the reviewing IRB.

11.3 Institutional Review Board

It is the understanding of the Sponsor that this protocol and any modifications as well as appropriate consent forms/procedures, will be reviewed and approved by an Institutional Review Board. This board must operate in accordance with the current Federal, State, Local and institutional regulations and requirements. A letter or certificate of approval will be sent by the Investigator to the Sponsor prior to initiation of the study and also whenever any subsequent modifications to the protocol are made.

12. CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications to ongoing studies must be made only after consultation between an appropriate representative of the Sponsor and the Investigators in this multi-center trial. Protocol modifications must be prepared by a representative of the sponsor and initially reviewed and approved by the Sponsor.

All protocol modifications must be submitted to the appropriate Institutional Review Board for information and approval in accordance with local requirements, and to Regulatory Agencies, if required. Approval must be awaited before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial subjects, or when the change[s] involve[s] only logistical or administrative aspects of the trial (e.g. change in monitor[s], change of telephone number[s]).

[redacted]

14. STUDY DOCUMENTATION, CRFS AND RECORD KEEPING

14.1 Investigator's Files / Retention of Documents

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two separate categories [1] Investigator's Study File, and [2] subject clinical source documents.

[redacted]

Should the Investigator wish to assign the study records to another party or move them to another location, the Sponsor or its designee must be notified in advance.

[redacted]

14.2 Source Documents and Background Data

The Investigator shall supply the Sponsor, on request, with any required background data from the study documentation or clinic records. This is particularly important when CRFs are illegible or when errors in

data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

14.3 Audits and Inspections

The Investigator should understand that source documents for this trial must be made available to appropriately qualified personnel from the Sponsor or its designees, or to health authority inspectors after appropriate notification. The verification of the CRF data must be by direct inspection of source documents.

14.4 Case Report Forms

[redacted]

15. MONITORING THE STUDY

It is understood that the responsible monitor or designee will contact and visit the Investigator and will be allowed, on request, to inspect the various records of the trial including CRFs and other pertinent data, provided that subject confidentiality is maintained, and in accord with local requirements.

It will be the study monitor's responsibility to inspect the CRFs at regular intervals throughout the study to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The study monitor should have access to laboratory test reports and other subject records needed to verify the entries on the CRF. The Investigator or his/her deputy agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

[redacted]

16. [redacted]

[redacted]

[redacted]

17 [redacted]

[redacted]

18. [redacted]

[redacted]

http://dx.doi.org/10.1016/j.ajodo.2007.10.042

[redacted]

[redacted]
http://dx.doi.org/10.2319/111010-656.1
[redacted]

19. TABLE 1: SCHEDULE OF ASSESSMENTS

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]					
[redacted]	[redacted]					
[redacted]	[redacted]					
[redacted]	[redacted]				[redacted]	
[redacted]			[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]					
[redacted]	[redacted]				[redacted]	[redacted]
[redacted]	[redacted]				[redacted]	[redacted]
[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	
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