The Effect of AcceleDent on Arch Alignment and Pain Level During Orthodontic Treatment with Invisalign

BY

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THESIS

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This thesis is dedicated to my fiancé, Jason, and my parents, Marc and Kathy, for their unwavering support and understanding through this process, as well as my entire academic career. Their love and support has allowed me to realize my true potential to be all that I have become. I would not be the person I am today without the important influence of these three individuals.

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LIST OF ABBREVIATIONS

ClinCheck	Invisalign treatment simulation software
CI	Confidence Interval
II	Irregularity index
IRB	Institutional Review Board
MD	Mandible
MX	Maxilla
PDL	Periodontal Ligament
SD	Standard Deviation
WIRB	Western Institutional Review Board

SUMMARY

Orthodontic treatment is accomplished via a controlled manipulation of bone resorption and deposition due to the forces applied to the teeth in order to create tooth movement (Nishimura, 2008). Orthodontic researchers have suggested a number of methods to help accelerate tooth movement by altering the bone in different manners, for example, corticotomies, mechanical signaling to the bone, low-intensity lasers, photobiomodulation and interseptal bone reduction (Kau, 2011). The evidence that is available for these methods is not very strong and many of these treatments can be very invasive. The medical literature has shown that vibration therapy targeting bone can prevent bone breakdown and increase bone density. Vibrating plates are currently available to treat bone loss (Cerciello, 2016).

OrthoAccel Technologies (Houston, TX) has built on the clinical benefits of vibration to help accelerate the rate of tooth movement in the creation of a device called AcceleDent Aura. This FDA approved Class II medical device provides a light force pulse that transmits through the roots of teeth to the surrounding alveolar bone (OrthoAccel Technologies, 2017). The manufacturer claims that the vibrations help “accelerate the cellular responses and speed the rate which teeth can move.” Patients are asked to use the device for 20 minutes a day. Recent studies and anecdotal evidence have shown that the SoftPulse technology significantly reduces the amount of time required for orthodontic tooth movement (Kau, 2011). There are also current claims made by the company regarding the ability of AcceleDent vibration to decrease pain as a result of

treatment. There is little literature to support this claim, though (Miles, 2012). Additionally, all of the studies that have been completed on AcceleDent usage with orthodontic treatment have been on subjects with traditional brackets. Therefore, the hypothesis that AcceleDent reduces the time for anterior alignment and reduces or eliminates pain associated with treatment using Invisalign® (San Jose, CA) will be investigated.

This study compared a group of subjects using AcceleDent in combination with Invisalign® to a group that is just using Invisalign®. Intraoral scans collected at four times throughout treatment were evaluated using Little's Irregularity Index to determine anterior alignment (Little, 1975). Pain levels were assessed from the data collected through an online survey that patients completed during their orthodontic treatment. This data will help answer whether or not AcceleDent usage can decrease time for anterior alignment and relieve pain associated with tooth movement. The main aim of this study is to investigate the validity of the current data on increased rate of tooth movement with AcceleDent and pain relief or decrease with AcceleDent. Significant results will have a clinical impact, because there will be high quality evidence for practitioners that AcceleDent, an easy to use device that can be used at home, can help their patients by reducing pain and length of treatment. These two key factors, shorter treatment time and less pain, will be highly attractive to new orthodontic patients

I. INTRODUCTION

1.1 Background

Two of the most common concerns of orthodontic patients are the length of time required for treatment and the pain associated with treatment. If the rate of tooth movement can be accelerated, treatment time can be reduced. This would mean less time in braces, hence fewer visits and the inconveniences that come with scheduling appointments around patient's busy schedules. Additionally, reduced treatment time would decrease the likelihood of long-term problems associated with orthodontic treatment, such as decalcifications due to poor oral hygiene, root resorption, periodontal issues and patient burnout.

OrthoAccel Technologies has built on the scientifically proven clinical benefits of vibration to help accelerate the rate of tooth movement in the creation of a device called AcceleDent Aura. This device provides a light force pulse (0.25N at 30 Hz) that transmits through the roots of teeth to the surrounding alveolar bone (OrthoAccel Technologies, 2017). The manufacturer claims that the vibrations help "accelerate the cellular response and speed the rate at which teeth can move" (Lui, 2010). Patients will seek out practices that deliver faster treatment and pay more for this service. If total treatment time is reduced, patients will have higher overall satisfaction with orthodontic therapy.

Another barrier to orthodontic treatment is the anticipated pain associated with tooth movement. Orthodontic treatment will inevitably cause pain, because there is a biological response to mechanical stimulus via fixed appliances that

place forces on teeth. These forces result in inflammation to the PDL which causes a release of histamine, bradykinin, prostaglandins, substance P and serotonin. These chemical mediators stimulate nerve endings and send pain signals to the brain. Acuscope and Myopluse (Acu/Myo) machine treatment can help reduce the initial discomfort caused by tooth movement after a patient gets braces. The downside of Acu/Myo treatment is the initial benefits wear off over time and the patient needs to come in for additional treatments. Due to busy schedules, few patients make the extra trip for the treatment, so the benefits are only short term. There are not many other non-pharmological methods for decreasing pain associated with orthodontic treatment. A device that is easy to use at home to decrease pain associated with braces, such as AcceleDent, may increase patient comfort, and thus patient satisfaction. There are current claims made by the company regarding the ability of SoftPulse Technology to decrease pain associated with orthodontic treatment based on anectodal evidence from practitioners that use the device.

1.2 **Significance**

Significant results will have a clinical impact, because there will be high quality evidence for practitioners that AcceleDent, an easy to use device that can be used at home, can help their patients by reducing pain and length of treatment. These two key factors will be highly attractive to new orthodontic patients.

1.3 Specific Aim

To investigate the relationship between the AcceleDent device, perceived pain and treatment time for anterior tooth alignment in patients utilizing Invisalign® aligners.

1.4 Hypotheses

- Hypothesis 1: There is no mean difference in anterior alignment associated with AcceleDent use in patients treated with Invisalign®.
- Hypothesis 2: There is no mean difference in pain level associated with AcceleDent use in patients treated with Invisalign®.

II. REVIEW OF LITERATURE

2.1 History of Vibration and Bone

Bone stimulation with vibrational forces has been studied since the 1980s to help heal fractures and treat osteoporosis due to the understanding this stimulation can improve bone remodeling (OrthoAccel Technologies, 2017). Studies have shown that vibration can increase rate of fracture healing, increase bone density in long bones (Leung, 2009), increase rate of bone formation (Judex and Rubin, 2010) and facilitate bone healing (Ogawa et al, 2014). For example, Judex and Rubin applied vibration to the tibia of a mouse and compared it to contralateral controls. They found greater bone formation on the side with vibration and concluded that vibrational stimulation has a direct effect on bone formation (Judex and Rubin, 2010).

Physical exercise has also been shown to increase bone mass and bone density due to the mechanical stress that it causes (Honda, 2001). Specifically, Honda and colleagues found that high-impact, low-repetition jump training could increase bone mass in pre and postmenopausal rat models (Honda, 2001). Although these results are promising, patients who are not able to exercise sufficiently to prevent bone loss related to aging have to turn to another method. Additional evidence indicates that the non-pharmacological method of machines that provide high frequency, low-magnitude “whole-body vibration” can have a similar effect. As a result, vibrational therapy is currently recommended to increase bone density in postmenopausal women and children with immobility

associated disabilities to increase the rate of fracture healing and possibly help tone and define muscles in the gym (Cerciello et al, 2016).

2.2 Bone Biology

Bone is composed primarily of osteogenic cells, organic matrix and minerals. The osteogenic cells are osteoblasts, osteoclasts and osteocytes. Osteoblasts are responsible for the formation of new bone, where as osteoclasts are involved in bone breakdown and resorption. Osteocytes maintain mature bone (Florencio-Silva et al, 2015).

Unfortunately, the exact mechanism related to the response of osteogenic cells to vibrational stimuli is still not well understood (Lau et al, 2011). Ota and colleagues studies the effect of vibrational stimuli on osteoblasts, specifically. They concluded that vibrational stimulation may induce immature osteoblast differentiation into mature osteoblasts that can form new bone (Ota et al, 2016). Another study found that children may have a more pronounced effect from this vibrational stimulation possibly due to the increased number of progenitor cells (Thompson et al, 2017). More recent studies involving the application of vibration to bone are attempting to quantify local factors to help understand the mechanism (Leethanakul, 2015).

2.3 Accelerated Sutural Growth with Cyclic Forces

The application of vibration on sutures within bones has also been investigated. The majority of the current literature regarding accelerated bone

remodeling has been completed in the appendicular skeleton (Alihkani et al, 2012). Although these studies have provided the fundamental information relating to the response of bone to stimulation, the appendicular skeleton differs in that these bones are all weight bearing (Alihkani et al, 2012). The craniofacial skeleton, conversely, is non-weight bearing and, although it seems logical to generalize them as having the same properties, they may differ due to their different embryonic origins (Alihkani et al, 2012). Most craniofacial bones elongate by intramembranous apposition at sutures compared to the endochondral growth of appendicular bones (Vij and Mao, 2008). The craniofacial skeleton is unique in that it contains sutures, which are composed of fibroblastic cells in the center and osteogenic cells on the periphery. Normal growth at sutures occurs by the combination of flibroblastic proliferation and osteogenesis at the bony edge (Kopher and Mao, 2003).

Multiple studies have been designed to quantify the vibrational acceleration of sutural growth using the animal model. Researchers have studied the sutures of growing rats and rabbits that were treated with cyclic or static forces. In each of the studies, cyclic forces caused significantly more sutural growth than static forces (Kopher and Mao, 2003; Vij and Mao, 2008; Peptan et al, 2008). Peptan and colleagues were additionally able to distinguish that cyclic forces on sutures under compression or tension induce modeling and growth.

Another differentiating factor of craniofacial bones is that the maxilla and the mandible are indirectly loaded via teeth. Therefore, the effect of vibrational stimulation has also been examined in alveolar bone with force application on a

molar (Alihkani et al, 2012). The force applied to the molar produces strain via the periodontal ligament (PDL). Alikhani (2012) applied vibration on the first molar of rats for 28 days. They found that the vibrations had an osteogenic effect in alveolar bone formation and maintenance near the point of application, as well as a gradient response further away from the site of application (Alihkani et al, 2012).

2.4 **Accelerated Tooth Movement**

Investigation into the effect of vibrational stimulation on tooth movement is of interest due to the relationship between vibrational stimulation and bone remodeling, especially in the bones of the cranium. Sutural sites of the craniofacial bones are similar to the relationship of a tooth to the alveolar bone, because the teeth are surrounded by fibrous PDL which is essentially a suture between the alveolar bone and root cementum (Herring, 2008). Teeth move through the bone by resorption on the compressed side and bone formation on the stretched side of the PDL (Nishimura, 2008). Orthodontic forces induce compression of the PDL which causes vascular changes that lead to activation of cellular signaling pathways and release of proinflammatory molecules (Nishimura, 2008). Ultimately, the speed of tooth movement greatly depends on the speed of alveolar bone remodeling (Nishimura, 2008).

To date, there are many methods to accelerate tooth movement that have been studied. Researchers have concluded that micro-osteoperformations increase the rate of canine retraction in human subjects (Alihkani et al, 2013).

There has also been investigation that suggests that low-level laser therapy could accelerate orthodontic tooth movement in humans (Ghizlane et al, 2013). Corticotomies have been reported to have a transient effect on the rate of tooth movement, as well (Aboul-Ela et al, 2011). In the photobiomodulation technique, subjects are asked to wear a device (OrthoPulse, Biolux Research, Canada) in the mouth that emits near-infrared light for 20 minutes per day. This methodology has reported faster leveling an aligning with use (Kau et al, 2013). Another device that reports increasing tooth movement is an acrylic plate that generates an electromagnetic pulse for eight hours every day (Showkatbakhsh et al, 2013). Lastly, pharmacological approaches with the injection of prostaglandin E_2 (PGE_2) and 1,25-$(OH)_2D_3$ during tooth movement, have been investigated. (Nishimura, 2008*)* Albeit the numerous methods on the market to accelerate tooth movement, the focus of this paper will be on accelerated tooth movement in relation to vibrational stimuli.

Accelerated movement has been observed experimentally in teeth that have orthodontic forces applied to them and are receiving mechanical vibration. Nishimura et al (2008) activated the PDL in rat molars that were undergoing expansion. Vibrational stimulation was applied at 60 Hz, 1 m/s^2 for 8 minutes once a week. Compared to the control group, the group that received vibrational stimulation had an increased rate of molar expansion and no damage to periodontal tissues (Nishimura et al, 2008). Lui presented a study at two AADR annual meetings in an animal model where a vibrating force of 4Hz was applied

for 20 minutes per day to the first molars every three days. He reported that this vibrational effect could decrease treatment time by 30-40% (Lui, 2010).

Another study examined the proinflammatory mediators in humans specifically to determine if levels of interleukin (IL)-1β related to the application of vibratory stimuli. Human subjects that had undergone extractions and were in the process of canine retraction were asked to use an electric toothbrush as their vibrating device. Subjects were instructed to hold the toothbrush on the experimental canine for five minutes three times a day for two months. Gingival crevicular (GCF) fluid was collected from the gingival margin of the experimental and control canines to measure (IL)-Iβ. They concluded that the vibratory stimuli enhanced secretion of (IL)-Iβ and accelerated tooth movement. (IL)-Iβ induces RANKL in osteoblasts which promotes osteoclast differentiation and thus bone resorption (Leethanakul et al, 2015). This information suggests that mechanical stimulation may cause an increase in proinflammatory mediators and may directly affect bone remodeling to cause enhanced tooth movement (Teixeira et al, 2010). Iwasaki and colleagues investigated this further by blocking proinflammatory mediators and they found that this significantly reduced the rate of tooth movement (Iwasaki et al, 2001).

2.5 **AcceleDent and Tooth Movement**

AcceleDent Aura (OrthoAccel Technologies, Houston, TX) (Figure 1) has built upon the clinical benefit of vibration effecting bone remodeling and applies SoftPulse Technology to help speed up the rate of tooth movement. AcceleDent

is a Class II medical device that has been cleared by the FDA for use due to clinical trials that demonstrated that it is harmless. The device emits a 0.25 N force at a frequency of 30 Hz and patients are asked to use it 20 minutes daily. This is less force to the teeth than a power toothbrush or chewing. Additionally, Kau and colleagues demonstrated that this force does not cause root resorption greater than 0.5-1mm and DiBiase confirmed this in the maxillary central incisor specifically (Kau et al, 2013; DiBaise et al, 2016).

Figure 1: AcceleDent Aura Device And Carrying Case

Today, AcceleDent is the most common treatment technique used by orthodontists to accelerate treatment according to the Journal of Clinical Orthodontics. As a result, there is another competitor on the market. Propel Orthodontics LLC (Ossining, NY) recently introduced VPro5, a c-shaped wafer that delivers high frequency vibration to the teeth and is only required to be worn for five minutes per day. VPro5 is marketed as an “aligner seater” as it helps to seat aligners fully on to the dentition. The manufacturer claims that the device can help to decrease treatment time, because of the ability to seat the aligners more efficiently. In addition, there are claims that the vibration can be pain relieving. The literature on the VPro5 device is limited, though.

Numerous studies have investigated the AcceleDent device and the claims regarding its effectiveness. The literature regarding the effectivenss of AcceleDent is conflicting. Pavlin and colleagues measured the rate of maxillary canine retraction with TADs after first premolar extraction in patients with fixed appliances using the AcceleDent device and compared this to subjects that were

using a different device that did not vibrate. The experimental group showed statistically and clinically significant differences in the rate of tooth movement, 1.16mm/month compared to 0.79mm per month (Pavlin et al, 2015). Bowman also studied a group of patients with fixed appliances utilizing the AcceleDent device. He found that there was faster leveling by 48 days in the AcceleDent group as determined by the appointment that a 19x25 SS archwire could be engaged in the brackets (Bowman, 2014). Orton-Gibbs evaluated the patients at her private practice that were using the AcceleDent device. She compared the actual treatment time to her estimated treatment time for her patients based on her 25 years of clinical experience. On average, patients with fixed appliances and Invisalign® had shorter treatment times by 33.5% and 37.2%, respectively (Orton-Gibbs and Kim, 2015).

On the other hand, there has also been data to suggest that AcceleDent does not increase rate of tooth movement. Woodhouse (2015) studied the effect of AcceleDent on the mandibular arch alignment in orthodontic patients with fixed appliances in extraction treatment. They compared the effect of AcceleDent between three groups: an AcceleDEnt group, a sham group and a group that did not use AcceleDent device. There were no significant differences found among the groups for mean irregularity index at initial and final alignment, as well as the mean time to reach the initial and final alignment (Woodhouse et al, 2015). Miles and Fisher completed a similar study in 2016 on patients with fixed appliances undergoing extraction treatment, but they did not use a sham device. This study spanned over 10 weeks and also measured the mandibular arch only, where

there were no teeth extracted. Miles and Fisher also found that there was no statistically or clinically significant effect of AcceleDent on change in the anterior arch perimeter or change in irregularity index.

2.6 **AcceleDent and Pain**

As has been described above, the remodeling process of the alveolar bone causes tooth movement. This process is initiated by forces placed on teeth which results in inflammation or ischemia to the PDL. This phenomenon causes the release of proinflammatory factors which stimulate nerve endings and send pain signals to the brain. Therefore, pain is a common consequence of orthodontic treatment and is usually the most significant immediately after an adjustment or aligner change.

Orthodontists often suggest over the counter medications to relieve pain. Acetaminophen has been shown to be the analgesic of choice, because it does not inhibit prostaglandin synthesis, thus it does not have an anti-inflammatory effect. Inflammation is an important part of the process of orthodontic tooth movement, so lack of inflammation can reduce orthodontic tooth movement. Therefore, NSAIDs that reduce inflammation, i.e. ibuprofen, are not recommended.

OrthoAccel Technologies has made claims that the AcceleDent device is a non-pharmocological method to help reduce orthodontic pain. These claims can be hypothetically explained with the assumption that the vibration increases

blood flow to the area of inflammation, reduces ischemia and activates large-diameter sensory nerve fibers (Woodhouse et al, 2015).

Three authors have studied the AcceleDent device in relation to pain and the conclusions are also contradicting. Lobre used a VAS (visual analog scale) to evaluate pain on the first seven days after a wire adjustment and then weekly afterwards in patients who were using the AcceleDent device (n=35) versus those that were not (n=35) over a four month period. She found that patients that used the AcceleDent device had significantly lower overall pain. This is in accordance with other author that showed that vibration diminishes pain (Lobre et al, 2016).

The other two studies offer a different conclusion. Woodhouse (2015) evaluated pain with the VAS 4 hours, 24 hours, 3 days and 1 week after appointments in orthodontic patients with fixed appliances using the AcceleDent device (n=29) versus those using a sham device (n=25) versus those using no device (n=27). They found no difference in the perceived pain with the device versus those that were using the sham device (Woodhouse et al, 2015). Miles and Fisher also asked two groups of orthodontic patients, one utilizing the AcceleDent device (n=20) and one not using any device (n=20), to fill out a VAS at baseline, 6-8 hours later, 24 hours later, 3 days later and 7 days later. They also found no difference in pain levels between the two groups (Miles and Fisher, 2016).

2.7 **Invisalign**

Invisalign® (Align Technology, San Jose, CA) is a clear aligner system that is custom-made to move teeth in a sequence as determined by the doctor to correct malocclusion. Invisalign® is a popular patient preferred method of orthodontic treatment today, because it is an esthetic, removable and allows for easier oral hygiene. Patients undergoing Invisalign® treatment are instructed to wear the aligners for 22 hours per day and remove for eating and brushing.

When this study was designed, Align Technology recommended changing trays every two weeks, or once a week if the patient was using AcceleDent. In October 2016, Align Technology recommended weekly aligners changes for patients without Acceledent. Align Technology indicated that this suggestion was based on “progress data from 200 cases…that shows that cases with weekly aligner changes exhibit the same level of predictability as two-week wear without increased refinement rates.” This recommendation was made possible with the unique technology of SmartForce® features, SmartTrack® material and SmartStage™ technology. The manufacturer warns that this is not to be used for every case, though, and that doctors must monitor more significant movements and compliance. For the purposes of this study, aligners were changed according to the old recommendations, 14 days without AcceleDent and 7 days with AcceleDent.

The Invisalign® system relies on gentle pressure to move teeth into the proper position. Teeth move at a rate of 0.2mm translation and 3% tip/rotation

per aligner with Invisalign® (Align Technology). This is accomplished with a combination of specifically placed attachments on the teeth and plastic aligners fabricated to apply force against the teeth and the attachments. The current literature indicates that attachments help to create higher forces on teeth (Simon et al, 2014). This force is highest initially and then decreased exponentially throughout the time that the aligner should be worn (Simon et al, 2014). A systematic literature review from of 11 articles from 2000-2014 found that clear aligners have been shown to level the arches predictably. The aligners also are effective at intruding, but ineffective extruding (Rossini et al, 2014). A study completed at the University of Illinois at Chicago, also indicated that the overall accuracy of the Invisalign® system is 41% when comparing the patient's final occlusion to the final ClinCheck (Kravitz et al, 2009). Difficulty finishing and the limitations in treating extraction cases have been reported as disadvantages with the Invisalign® system (Ercoli et al, 2015).

2.7.1 **Invisalign and Pain**

The design of smooth plastic clear aligners is much more comfortable than traditional fixed appliances. The lack of metal brackets, wires and ligatures in the mouth is less of an irritant to the soft tissue. Anecdotal evidence suggests that tooth movement with Invisalign® aligners is also less painful. Fujiyama (2014) proved this with a study comparing pain levels between patients with Invisalign® and fixed appliances. Pain was recorded on the VAS throughout treatment. They

found that there were statistically significant lower pain levels in the Invisalign® subjects (Fujiyama et al, 2014).

2.8 **Pain Evaluation**

Pain is one of the most complex human experiences. There have been sensory, emotional, autonomic, motor and cognitive components of pain identified (Bushnell et al, 2013). As a result, measuring pain is a difficult task. In orthodontics, pain and discomfort during treatment are the most negative concerns. Due to the complex nature of pain, discomfort with orthodontic appliances can affect a patient's quality of life. Therefore, it is in an orthodontist's best interest to find the best way to evaluate this pain level in order to best serve patients.

The most common pain scales currently used today are the visual analog scale (VAS), numeric rating scale (NRS), verbal descriptor scale (VDS), faces pain scale (FPS), thermometer pain scale (TPS), McGill pain questionnaire (MPQ), short-form McGill pain questionnaire (SFMPQ) and Brief Pain Inventory (BPI) (Sayin and Akyolcu, 2014). Sayin and Akyolcu completed a study to determine which of the above pain scales were most preferred and compared whether or not there was agreement among these scales. 621 patients that received surgical treatment were included in this study. The authors concluded that it is important to have a verbal, visual and numerical component to pain evaluation. The most preferred pain scale is the faces pain scale and the least preferred was the visual analog scale. Additionally, the visual analog scale

showed consistently higher values for pain levels. Ultimately, it is important that the patient responds well to the pain scale, as this will have an effect on their compliance with completing a pain evaluation.

III. MATERIALS AND METHODS

This prospective, randomized controlled trial comparing the effect of AcceleDent on rate of anterior tooth alignment and perceived pain in Invisalign® patients was carried out over a 12-month period for each subject involved in the study. All data were collected from a private practice owned by two well-calibrated private practice orthodontists that have been practicing for over 30 years. The practice obtained a WIRB (Western Institutional Review Board) approval to preform the study (APPENDIX A). The current study received local institutional review board (IRB) approval to obtain and analyze the data from the private practice's study (APPENDIX B).

3.1 Subject Recruitment and Eligibility

Direct mailers and emails were sent to current patients before subject recruitment began in January 2015 (APPENDIX C). Staff were given the following script to utilize when interested patients contacted the office regarding a complimentary orthodontic consultation (APPENDIX D):

"Our office is doing a clinical study on a device called AcceleDent. This research study involves an FDA approved appliance called AcceleDent. AcceleDent claims to reduce treatment time and pain levels and we are conducting a study to measure and compare the speed of treatment and level of discomfort between two groups with and without the AcceleDent unit. The decision to participate or not to participate does not change the standard of care

that you will receive. All participants will receive a financial reward of $600 for successfully completing the study. Would you like to schedule a complimentary orthodontic consultation?"

New patients that presented to the private practice were introduced to the study during a complimentary orthodontic consultation by the doctors with the following statement:

"Our office is doing a clinical study on a device called AcceleDent. The manufacturer says that AcceleDent affords the opportunity to finish treatment faster and potential with less pain. Our study is to establish if this is true. If you would like to participate, here is what is in it for you: 1) If you are randomly assigned for the group receiving AcceleDent, you will get the unit for free as long as you use is as instructed or 2) If you are randomly assigned to the group not receiving the device, then you get the cash value as a reduction in your fee."

If they were interested, then the two doctors evaluated whether they met the initial eligibility criteria. Eligibility criteria included:

- 13-50 years old
- Generally healthy patient
- Class I malocclusion
- 6 mm or less of crowding or spacing
- No missing anterior teeth from the maxillary and mandibular arches
- Can be treated with 50 aligner trays or less
- Can be treated in 12 months as determined by the doctors making the selection
- Do not need tooth removal to solve crowding

Once the doctors concluded that a patient was eligible according to the above criteria, the treatment coordinators used a screening form (APPENDIX E) to determine if the patient was still eligible according to these criteria:

- Did not have periodontitis and/or root resorption
- Non-smoking
- No NSAIDs and Vitamin D supplement during the treatment, but they were allowed to take acetaminophen

Patients that qualified for the study were told that their personal information would be kept encrypted and secure until the end of the study and those that did not qualify were told that their screening information would be shredded. Patients that qualified were asked to read and sign a specific consent form for the study (APPENDIX F). After completing the consent form, subjects were asked to draw straws to be randomly assigned for the control or experimental group by the treatment coordinator at the office and supervised by the office manager. All subjects who enrolled in the study were compensated with either a free AcceleDent unit (experimental group) or $600 (control group) at the end of the study to ensure their cooperation in filling out evaluation forms and compliance with AcceleDent.

A power analysis indicated that a sample size of 17 subjects per group would be required to have a power of 80% with type error I at P=0.05 (Pavlin et al, 2015; Miles and Fisher, 2016). The enrollment goal for this study was 40 subjects per group to allow for limited number of Invisalign® patients at the private practice and approximately 10% dropouts and from the study sample. A total of 40 total participants started treatment as part of the study. There were three dropouts in the experimental group and one drop out in the control group which resulted in 18 participants in each group.

3.2 **Study Design**

The doctors treating the case were blinded as to who was part of the experimental and control groups throughout the entire experimental period. All patients were treated by both doctors in the private practice, but the Invisalign® treatment plan and ClinCheck was completed only by one of the doctors. The doctor treating the case did not know whether the subject would or would not be receiving AcceleDent when completing the ClinCheck. The number of total aligners per patient varied based on the malocclusion as determined by the doctor treating the case.

Subjects in the experimental group (with AcceleDent) were instructed to change their aligners every seven days. This recommendation is made by OrthoAccel and is based on users clinical experience with the product. Doctors found that AcceleDent accelerated tooth movement by up to 50%; therefore it became a simple math of taking 14 days to 7 days, a 50% reduction. The recommendation from OrthoAccel Technologies was based on anecdotal evidence from consumers. Subjects that were not compliant with aligner wear, as determined by the doctors in the practice, were instructed to change the aligners every 10 days. Subjects in the control group were instructed to change their aligners every two weeks, per the usual Invisalign® recommendations.

Each patient underwent normal variations of Invisalign® treatment including: IPR, elastics, replacement trays and/or refinements as needed. Patients presented to the private practice at regularly scheduled intervals for Invisalign® checks and to receive more aligners.

3.2.1. **AcceleDent Aura**

Subjects randomly assigned to the experimental group were given the AcceleDent Aura device when they received the Invisalign® aligners. They were instructed to use the AcceleDent device 20 minutes before leaving the office and then 20 minutes that evening before going to bed. On the second day of treatment, the patient was instructed to bite on the biteblock two separate times for 20 minutes each. This alternative schedule was designed to help the subject get into the habit of using the AcceleDent device. After the first two days of treatment, the subjects were asked to bite on the biteblock for 20 minutes every night before going to bed. These instructions were included in their new patient folder (APPENDIX G).

3.2.2 **Pain Survey**

Throughout their treatment, both groups completed a combined Visual Analog Scale and Faces-type pain scale survey to evaluate perceived pain on the day a new aligner was placed, daily for 3 more days and then weekly. This survey was created on and disseminated via Survey Monkey. At the initial appointment, patients were given a folder with their identification number on the front and instructions inside explaining when and how to fill out the Survey Monkey survey (APPENDIX H). Every week, the subjects received an email reminding them to fill out the survey and providing a direct link to the survey on the Survey Monkey

website. The survey required each subject to enter their identification number and then to rank their pain on a scale of 0-10 with the even numbers (0, 2, 4, 6, 8, 10) corresponding to a face and description of varying levels of pain. For example, 0 corresponded to no pain, 2 corresponded to hurts a little bit, 4 corresponded to hurts a little more, etc. (Figure 2). Subjects could also choose an odd number indicating they were between two of the face levels of pain.

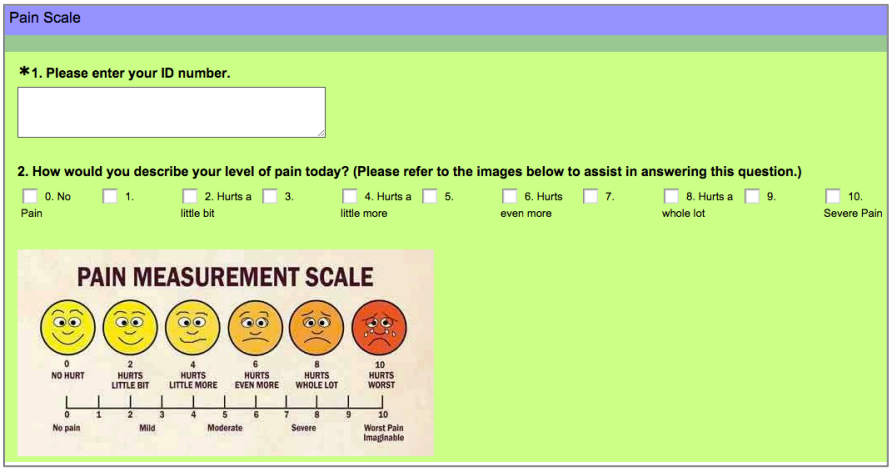

Figure 2: Survey Monkey Pain Scale Screen View

3.2.3 **Time Point Scans**

The orthodontic assistants at the private practice scanned teeth throughout treatment with the iTero HD2.9 intraoral scanner for most of the scans and the iTero Element for a few of the final scans. Scans were sent to myaligntech.com and models were constructed. All assistants were trained on the software and each office was equipped with the same scanner. Scans were taken at four time points: the initial records appointment (T1), approximately 3 months into treatment (T2), approximately 6 months into treatment (T3) and at 12 months or the end

of treatment (T4), whichever came first. Scans were identified with the patient's identification number and the number of the scan taken, i.e. i123456-1, and saved on the office's computer system.

3.2.4 **Compliance**

At adjustment appointments, oral hygiene and tracking of the Invisalign® aligners were evaluated. Oral hygiene was recorded based on the following criteria:

A: excellent OH
B: some plaque and germs, swollen gums
C: lots of plaque and germs, bleeding gums

Patients were also asked about their compliance with the AcceleDent device (when applicable) and completing the surveys. Compliance with AcceleDent was assessed from the AcceleDent FastTrac Usage report. The Usage report provided the percentage that the device was used on a given date. One hundred percent equated to twenty minutes during the day. Any number of minutes that was more or less than twenty was reflected as an increased or decreased percentage, respectively. This report was accessed during appointments at the office by connecting the USB portion of the device (Figure 3) to a computer which allowed the staff to upload and store the report from the subject's device into the computer. If the subject's compliance with the device was less than 50% consistently, the doctors in the office were notified and they made the final decision to drop the patient from the study.

Figure 3: AcceleDent USB

3.3 Data Collection

The principal investigator visited the private practice two times throughout the experimental period to collect subject data from the de-identified charts. The following information was recorded in a master spreadsheet on the principal investigator's computer:

- Identification number
- Gender
- Age
- Dates of the T1, T2, T3, T4 scans
- Number of adjustment between each of the time point scans
- Number of trays between each of the time point scans
- Oral hygiene grades throughout treatment
- Compliance with the aligners

3.3.1 Acceledent Data

The AcceleDent FastTrac usage reports were printed and identified with identification numbers for use in this study. Daily percentages were recorded for the days that the device was used.

3.3.2 Pain Data

The Pain Survey data was collected via Survey Monkey (Palo Alto, California). The date and pain score of each survey submission was inputted into an Excel (Microsoft, Redmond, Washington) spreadsheet. If multiple scores were given in a single day, the higher pain score was recorded one time as the pain value for that particular day. Pain scores were only recorded for the experimental period.

3.3.3 Time Point Scans

De-identified time point scans were uploaded from the main server at the private practice to a Dropbox (San Francisco, California) file or an external hard drive. The principal investigator downloaded the scans to a computer in the UIC Department of Orthodontics with the OrthoCAD software.

3.4 Data Evaluation

3.4.1 AcceleDent Data

AcceleDent daily usage percentages were added together and divided by the total number of percentage recordings in order to get an average daily percentage. The average daily percentages for the experimental group were then averaged to determine the mean compliance for the AcceleDent device.

3.4.2 Pain Data

The pain data was initially evaluated by taking an average pain level for each week based on weeks of the year as defined by Sunday to Saturday. This method made it difficult to evaluate the overall average pain scores for

the different time points. Ultimately, it also did not allow for enough individualization of the pain score. As a result, pain scores were calculated as an average pain level per aligner. The survey responses were affiliated with an aligner number based on the day of adjustment appointments and the number of days a patient was supposed to be wearing the tray. All of the pain values for a given aligner were added and then divided by the number of values provided for that tray.

An average pain score for the first three months of treatment (T1-T2), the second three months of treatment (T2-T3) and the last six months of treatment (T3-T4) was also recorded. This was calculated by adding all of the aligner values for a given time period and dividing them by the total number of pain values recorded during that time period of aligner wear.

3.4.3 **Time Point Scans**

Little's Irregularity Index was used to measure the alignment of the upper and lower anterior teeth for each scan. This involved measuring the horizontal linear distance among adjacent contact points of the six anterior teeth. The sum of these five measurements gave the value of the irregularity index (Little, 1975). Measurements were completed in the OrthoCAD software on a 19-inch monitor under the same magnification. Each arch was individually selected and magnified to three times the original image size by clicking on the zoom-in icon on the software three times. (Figure 4) This was verified measuring the image of the tooth on the computer screen at no

magnification with a plastic ruler and comparing it to the size of the magnified image. The specific magnification ranged from 329%-386%, so the actual magnification was a little more than three times.

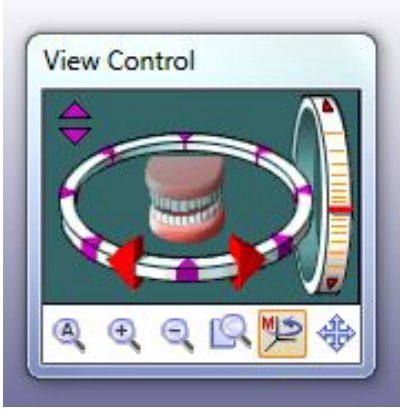

Figure 4: View Control Toolbox Containing the Zoom-In Icon

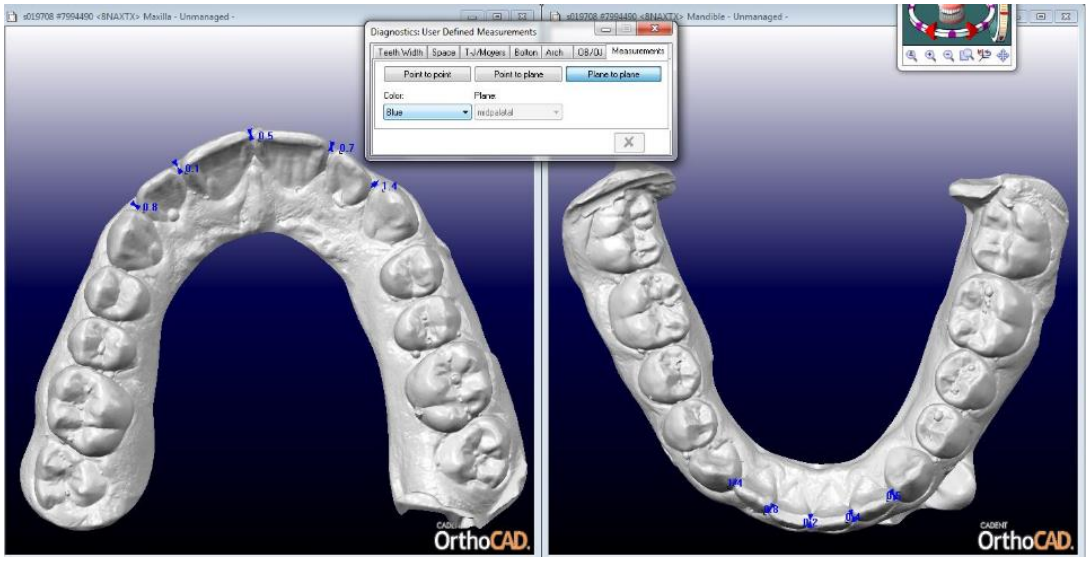

Figure 5: OrthoCAD Viewing Software for Irregularity Measurements

To measure the distance between the contact points of opposing teeth, the “Diagnostics” icon was selected, the “Measurements” tab was chosen and the “Plane to plane” button was clicked. The contact points of two opposing teeth in the anterior region of the upper and lower casts were connected with the “Plane to plane” function. This kept the contact points in the same plane, parallel

to the occlusal plane. (Figures 5 and 6) Once all of the measurements were complete, they were added up for each arch and individually and entered into the principal investigator's master Excel spreadsheet as the irregularity for that particular arch. This was completed for each patient at each of the four time points.

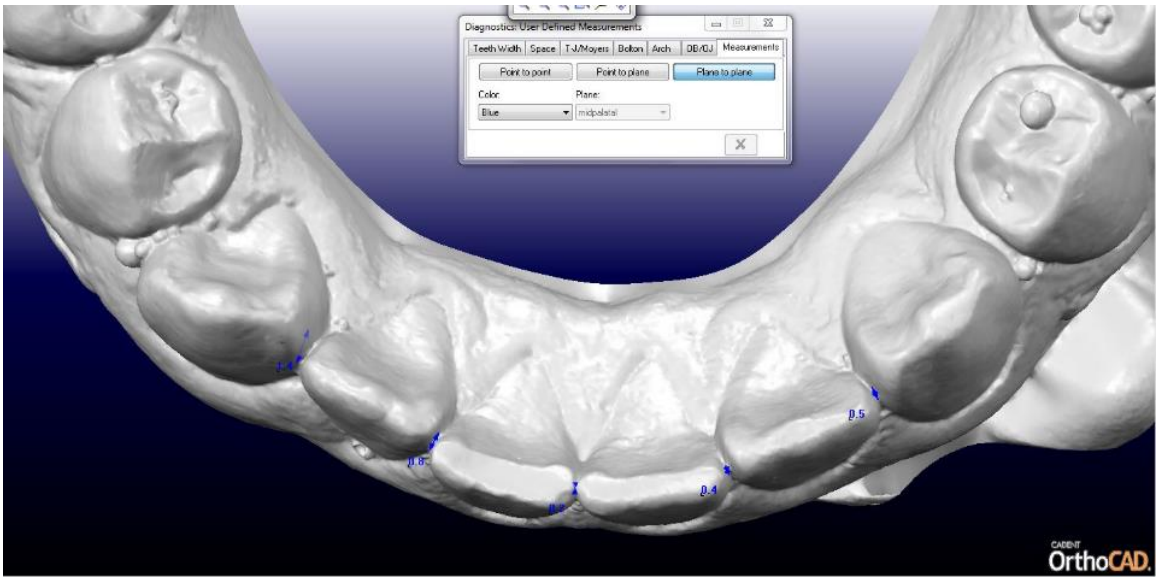

Figure 6: Magnification Level for Measuring Irregularity Index

3.5 Total Treatment Time

Total treatment was evaluated by adding the total number of months between the time points. Weeks were reflected as 0.25 of a month; i.e. three months and one week was recorded as 3.25 months. Unfortunately, due to the limitations of scheduling, patients were not all seen at the exact interval as delineated in the study design (3 months, 6 months and 12 months). Additionally, the methods indicate that the final scan was to be taken at the end of treatment

OR 12 months, if the treatment was not complete. Therefore, the total time between time points was evaluated to determine if there was any significance.

3.6 **Statistical Analysis**

Intra-class correlation coefficient (ICC) was used to assess the intra-reliability by the investigator on the study methods used. The distribution of the raw data was analyzed by the Shapiro-Wilks test of normality.

Descriptive statistics and Student sample t-tests were performed. The statistical significance level was set at 0.05. Data analysis were done using SPSS for Windows version 22.0 (IBM Corp. Armonk, NY).

4. RESULTS

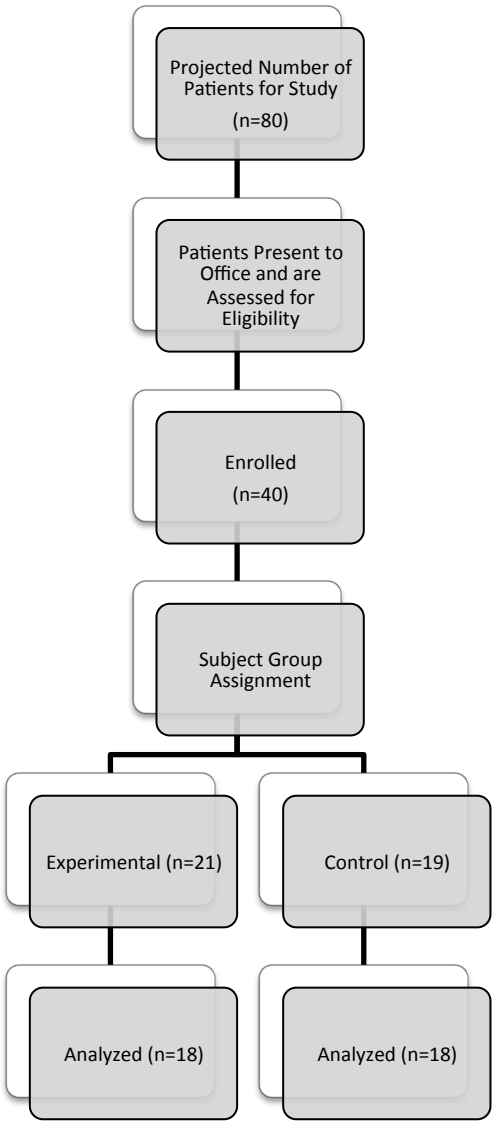

Figure 7: Subject Recruitment and Assignment

Intrareliability of the irregularity index measurements was determined by measuring the 10 maxillary and 10 mandibular scans in each group 10 weeks after the scans were initially measured. The intra- class correlation coefficient (ICC) indicated that the intra-reliability (>0.90) with 95% CI (confidence interval)

ranging from [0. 652 to 0.998] for the Irregularity Index measurements for both the maxillary and mandibular arches is good for the methods used in this study. The Shapiro-Wilks test showed that the majority of the variables in this study had a normal distribution. Mean differences in this study were investigated using the parametric Student t-test. For the variables that did not show normal distribution, non-parametric analyses were also performed and similar results were found with the parametric analysis.

Thirty-six subjects completed the study, half in the experimental group (n=18) and half in the control group (n=18). Recruitment began January 2015 and ended March 2016. Figure 7 demonstrates subjects' progression in the study. One patient in the control group and three patients in the experimental group dropped out due to poor compliance with the AcceleDent device and/or the Invisalign® aligners. This was determined by the doctors in the practice. All of the groups were similar in regard to baseline age, gender and initial irregularity index of the maxillary and mandibular anterior teeth (Table I).

TABLE I

CHARACTERISTICS OF PATIENTS IN EACH GROUP AT T1

Characteristic	Total (N=36)	Control (N=18)	AcceleDent (N=18)
Age (y)	22.35	19.17	25.54
Sex			
Female	22	10	12
Male	14	8	6

4.1 **Irregularity Index**

This study evaluated the irregularity index of the maxillary and mandibular anterior teeth at four separate time points for each group. None of the scans were missing from any of the subjects, besides the T4 scans that were not completed in subjects that have not been in treatment for 12 months to date. One subject in the control group was missing a tooth in the mandibular anterior arch, so the mandibular scans for this subject were eliminated from the analysis, but the maxillary arch was still included.

Student Independent t-tests with the Levene's test for equality of variances and paired t-tests were used for the data analysis. The independent t-tests indicates that there were no statistically significant mean differences in the irregularity index values at each time point in both arches between the experimental and control groups, p-values<0.05 (Figure 8). These mean values are reported in Table II.

The mean values show that there was about a 0.5mm difference in the T4 irregularity index in the maxillary and mandibular arches, the AcceleDent group having the lower value. The differences between the mean values indicate that there are some minor discrepancies in the two groups. Additionally, in the maxillary arch, there is about 0.5mm more overall alignment in the experimental group compared to the control group. In the mandibular arch, there was about 0.6mm more overall alignment in the experimental group compared to the control group during the treatment period.

TABLE II
DESCRIPTIVE STATISTICS AND INDEPENDENT *t*-TEST RESULTS AT EACH TIME POINT

					95% CI of the Difference		
	Groups (Mean; SD)	N	Mean Difference	Standard Error Difference	Lower	Upper	Sig. (2-tailed)
T1 II (MX)	Control (4.7; 2.31)	18	.5778	.6659	-.7754	1.9310	.392
	AcceleDent (4.12, 1.62)	18					
T1 II (MD)	Control (3.52; 1.99)	17	-.4435	.7865	-2.0436	1.1567	.577
	AcceleDent (3.96, 2.60)	18					
T2 II (MX)	Control (3.42; 1.73)	18	.7056	.5627	-.4381	1.8492	.218
	AcceleDent (2.71, 1.65)	18					
T2 II (MD)	Control (2.68; 1.73)	17	-.0788	.7134	-1.5301	1.3726	.913
	AcceleDent (2.76, 2.41)	18					
T3 II (MX)	Control (2.32; 1.21)	18	.5000	.4865	-.4887	1.4887	.311
	AcceleDent (1.82, 1.67)	18					
T3 II (MD)	Control (1.66; 1.72)	17	.1977	.5222	-.8646	1.2601	.707
	AcceleDent (1.46, 1.36)	18					
T4 II (MX)	Control (1.41; 1.24)	12	.4833	.5244	-.5945	1.5612	.365
	AcceleDent (0.93, 1.46)	16					
T4 II (MD)	Control (1.07; 1.26)	11	.6165	.4522	-.3148	1.5478	.185
	AcceleDent (0.46, 1.08)	16					

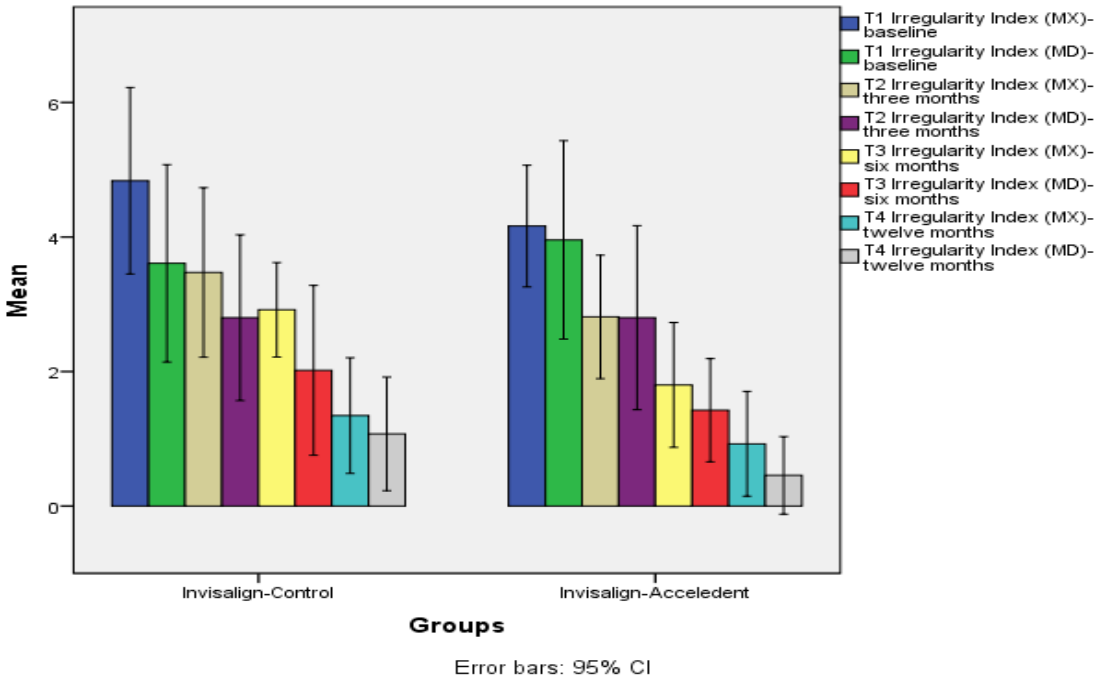

Figure 8: Time Point Irregularity Index Mean Values

A sample paired t-test on each of the control and AcceleDent groups at each time point separately showed that all of the means of the follow-up time

points were statistically significant lower mean values for all of the variables (p-values ranging from 0.000-0.049) (Tables III and IV).

TABLE III
CONTROL GROUP: RESULTS OF IRREGULARITY INDEX PAIRED *t*-TEST

					95% CI of the Difference		
	Groups (Mean, SD)	**N**	**Mean Difference**	**SD**	**Lower**	**Upper**	**Sig. (2-tailed)**
Pair 1	T2 II MX (3.42; 1.73)	18	-1.2833	1.2876	-1.9236	-.6430	.001
	T1 II MX (4.70; 2.31)	18					
Pair 2	T3 II MX (2.32; 1.21)	18	-2.3778	1.9783	-3.3616	-1.3940	.000
	T1 II MX (4.70; 2.31)	18					
Pair 3	T4 II MX (1.41; 1.24)	12	-3.3500	2.2758	-4.7959	-1.9041	.000
	T1 II MX (4.76; 1.98)	12					
Pair 4	T3 II MX (2.32' 1.21)	18	-1.0944	1.5008	-1.8408	-.3481	.007
	T2 II MX (3.42; 1.73)	18					
Pair 5	T4 II MX (1.41; 1.24)	12	-2.0417	2.4055	-3.5700	-.5133	.013
	T2 II MX (3.45; 1. 79)	12					
Pair 6	T4 II MX (1.41; 1.24)	12	-1.4583	1.4126	-2.3558	-.5608	.004
	T3 II MX (2.87, 1.01)	12					
Pair 7	T2 II MD (2.68; 1.73)	17	-.8353	.8580	-1.2764	-.3941	.001
	T1 II MD (3.52; 1.99)	17					
Pair 8	T3 II MD (1.66; 1.72)	17	-1.8588	1.5104	-2.6354	-1.0822	.000
	T1 II MD (3.52; 1.99)	17					
Pair 9	T4 II MD (1.07; 1.26)	11	-2.5364	2.1607	-3.9879	-1.0848	.003
	T1 II MD (3.61; 2.18)	11					
Pair 10	T3 II MD (1.66; 1.72)	17	-1.0235	.9284	-1.5009	-.5462	.000
	T2 II MD (2.68; 1.73)	17					
Pair 11	T4 II MD (1.07; 1.26)	11	-1.7273	1.4860	-2.7256	-.7290	.003
	T2 II MD (2.80; 1.83)	11					
Pair 12	T4 II MD (1.07; 1.26)	11	-.9455	1.2786	-1.8044	-.0865	.034
	T3 II MD (2.02; 1.88)	11					

TABLE IV
ACCELEDENT GROUP: RESULTS OF IRREGULARITY INDEX PAIRED *t*-TEST

					95% CI of the Difference		
	Groups (Mean, SD)	**N**	**Mean Difference**	**SD**	**Lower**	**Upper**	**Sig. (2-tailed)**
Pair 1	T2 II MX (2.71; 1.65)	18	-1.4111	.7738	-1.7959	-1.0263	.000
	T1 II MX (4.12; 1.62)	18					
Pair 2	T3 II MX (1.82; 1.67)	18	-2.3000	1.3155	-2.9542	-1.6458	.000
	T1 II MX (4.12; 1.62)	18					
Pair 3	T4 II MX (.925; 1.46)	16	-3.2375	1.5466	-4.0616	-2.4134	.000
	T1 II MX (4.16; 1.70)	16					
Pair 4	T3 II MX (1.82; 1.67)	18	-.8889	1.2611	-1.5160	-.2617	.008
	T2 II MX (2.71; 1.65)	18					
Pair 5	T4 II MX (.93; 1.46)	16	-1.8875	1.3431	-2.6032	-1.1718	.000
	T2 II MX (2.81; 1.72)	16					
Pair 6	T4 II MX (.93; 1.46)	16	-.8750	.7844	-1.2930	-.4570	.000
	T3 II MX (1.80; 1.74)	16					
Pair 7	T2 II MD (2.76; 2.41)	18	-1.2000	.6843	-1.5403	-.8597	.000
	T1 II MD (3.96; 2.60)	18					
Pair 8	T3 II MD (1.46; 1.36)	18	-2.5000	1.5726	-3.2820	-1.7180	.000
	T1 II MD (3.96; 2.06)	18					
Pair 9	T4 II MD (.46; 1.08)	16	-3.5000	2.2512	-4.6996	-2.3004	.000
	T1 II MD (3.96; 2.77)	16					
Pair 10	T3 II MD (1.46; 1.36)	18	-1.3000	1.4451	-2.0186	-.5814	.001
	T2 II MD (2.76; 2.41)	18					
Pair 11	T4 II MD (.46; 1.08)	16	-2.3438	2.1049	-1.2221	-4.454	.000
	T2 MD (2.80; 2.57)	16					
Pair 12	T4 II (MD (.46; 1.08)	16	-.9687	.9769	-1.4893	-.4482	.001
	T3 II MD (1.43;1.44)	16					

The irregularity index for both arches in each group was calculated for the differences of the follow up time points. Independent t-tests with Levene's tests for equality of variances and paired sample t-tests were performed to evaluate the differences between time points. The tests showed no statistically significant mean difference between the control and the AcceleDent groups, p-values>0.05 (Figure 9). These mean values are reported in Table V.

TABLE V
DESCRIPTIVE STATISTICS AND INDEPENDENT t-TEST RESULTS FOR THE IRREGULARITY INDEX TIME POINT DIFFERENCES

					95% CI of the Difference		
	Groups (Mean; SD)	N	Mean Difference	Standard Error Difference	Lower	Upper	Sig. (2-tailed)
Difference from T1-T2 (MX)	Control (-1.28; 1.29)	18	.12778	.35407	-.59767	.85323	.721
	Acceledent (-1.41; .77)	18					
Difference from T1-T2 (MD)	Control (-.85; .86)	17	.36471	.26156	-.16745	.89686	.173
	Acceledent (-1.2; .68)	18					
Difference from T1-T3 (MX)	Control (-2.38; 1.98)	18	-.07778	.55997	-1.21577	1.06022	.890
	Acceledent (-2.30; 1.32)	18					
Difference from T1-T3 (MD)	Control (-1.86; 1.51)	17	.64118	.52175	-.42034	1.70269	.228
	Acceledent (-2.50, 1.57)	18					
Difference from T1-T4 (MX)	Control (-3.35; 2.28)	12	-.11250	.72165	-1.59587	1.37087	.877
	Acceledent (-3.24; 1.55)	16					
Difference from T1-T4 (MD)	Control (-2.54; 2.16)	11	.96364	.86774	-.82350	2.75077	.277
	Acceledent (-3.50; 2.25)	16					
Difference from T2-T3 (MX)	Control (-1.09; 1.50)	18	-.20556	.46205	-1.14455	.73344	.659
	Acceledent (-.89; 1.26)	18					
Difference from T2-T3 (MD)	Control (-1.02; .93)	17	.27647	.40831	-.55838	1.11132	.504
	Acceledent (-1.30; 1.45)	18					
Difference from T2-T4 (MX)	Control (-2.04; 2.41)	12	-.15417	.71328	-1.62034	1.31201	.831
	Acceledent (-1.89; 1.34)	16					
Difference from T2-T4 (MD)	Control (-1.73; 1.49)	11	.61648	.73710	-.90161	2.13457	.411
	Acceledent (-2.35; 2.10)	16					
Difference from T3-T4 (MX)	Control (-1.46; 1.41)	12	-.58333	.41819	-1.44294	.27627	.175
	Acceledent (-.88; .78)	16					
Difference from T3-T4 (MD)	Control (-.95; 1.28)	11	.02330	.43376	-.87006	.91665	.958
	Acceledent (-.97; .98)	16					

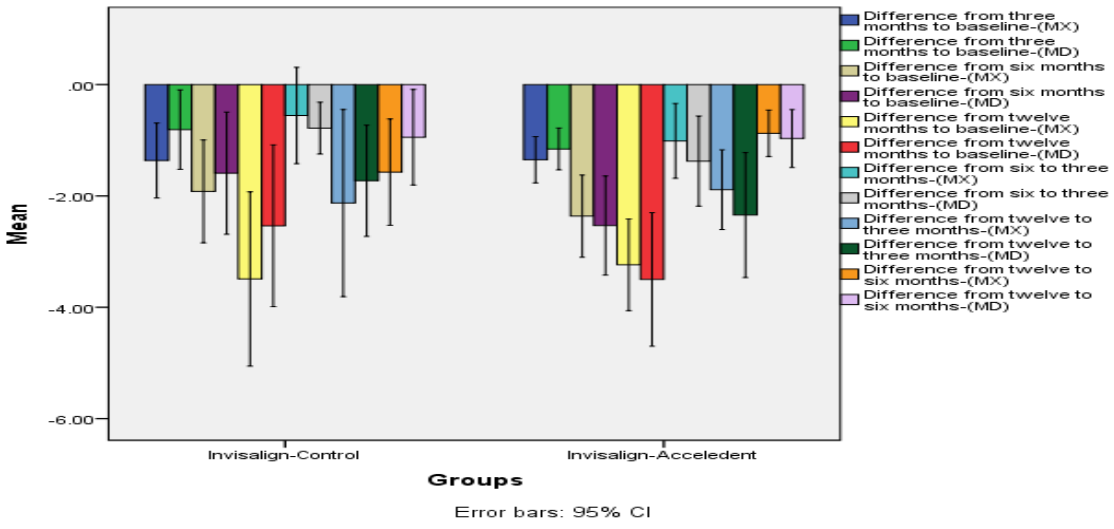

Figure 9: Differences Between Time Point Irregularity Index Mean Values

4.2 **Pain Data**

Subjects were instructed to complete a pain survey the day that they changed to a new aligner, for the first three days of the new aligner and then once weekly until they changed to another aligner, when the pain scores started over. Therefore, each aligner should have had four pain scores. None of the of the subjects in either group completed the pain survey accurately. The range of number of pain scores per subject was large.

An independent t-test determined that there were statistically significant differences (p-value=0.047) between the control and the experimental groups in the pain levels during 6-12 months (T3-T4) of Invisalign® treatment with the AcceleDent group significantly lower than the control, 0.51 and 1.49, respectively. No statistically significant differences were found in the mean pain levels from 0-3 months (T1-T2) or 3-6 months (T2-T3) between the groups. All values can be found in Table VI.

TABLE VI
PAIN LEVEL DESCRIPTIVE STATISTICS AND RESULTS OF THE INIDEPENDENT *t*-TEST

					95% CI of the Difference		
	Groups (Mean; SD)	**N**	**Mean Difference**	**Standard Error Difference**	**Lower**	**Upper**	**Sig. (2-tailed)**
Average Pain 0-3 mon	Control (1.02; 0.86)	18	.10641	.28730	-.47811	.69092	.713
	AcceleDent (.91; .84)	17					
Average Pain 3-6 mon	Control (.99; 1.27)	17	.39441	.33347	-.29841	1.08723	.250
	AcceleDent (.61; .54)	18					
Average Pain 6-12 mon	Control (1.49; 1.49)	12	.97971	.44615	.01308	1.94633	.047
	AcceleDent (.51; .48)	17					

There are statistically significant mean differences within each group for all variables except pain level between 0-3 months in the control group and between

6-12 months in the AcceleDent group, p-value> 0.05. In the control group, there was a statistically significant difference in the mean pain score between 3-6 months (p-value=0.016) and 6-12 months (p-value=0.052) (Table VII). In the experimental group, there were statistically significant differences in the mean pain score between 0-3 months (p-value=0.030) and 3-6 months (p-value=0.023) (Table VIII). Overall, the pain scores for the AcceleDent group reduced as time in treatment continued. On the contrary, in the control group, the pain values initially decreased and then increased from 6-12 months. (Figure 9)

TABLE VII
CONTROL GROUP: RESULTS OF PAIN LEVEL TIME PERIOD PAIRED *t*-TEST

					95% CI of the Difference		
	Groups (Mean; SD)	**N**	**Mean Difference**	**SD**	**Upper**	**Lower**	**Sig (2-tailed)**
Pair 1	Mean Pain Level 3-6 months (0.99; 1.27)	17	-.081	.86101	-.52446	.36093	.701
	Mean Pain Level 0-3 months (1.08; .85)	17					
Pair 2	Mean Pain Level 6-12 months (1.49; 1.49)	12	.741	1.17591	-.00631	1.48797	.052
	Mean Pain Level 0-3 months (0.74; 0.64)	12					
Pair 3	Mean Pain Level 6-12 months (1.62; 1.49)	11	.927	1.06660	.21072	1.64383	.016
	Mean Pain Level 3-6 months (0.69; 1.04)	11					

TABLE VIII
ACCELEDENT GROUP: RESULTS OF PAIN LEVEL TIME PERIOD PAIRED *t*-TEST

					95% CI of the Difference		
	Groups (Mean; SD)	**N**	**Mean Difference**	**SD**	**Upper**	**Lower**	**Sig (2-tailed)**
Pair 1	Mean Pain Level 3-6 months (0.64; 0.53)	17	-.274	.47362	-.51763	-.03061	.030
	Mean Pain Level 0-3 months (0.91; 0.84)	17					
Pair 2	Mean Pain Level 6-12 months (0.54; 0.48)	16	-.426	.67120	-.78391	-.06859	.023
	Mean Pain Level 0-3 months (0.96; 0.84)	16					
Pair 3	Mean Pain Level 6-12 months (0.51; 0.48)	17	-.134	.34936	-.31315	.04609	.135
	Mean Pain Level 3-6 months (0.64; 0.54)	17					

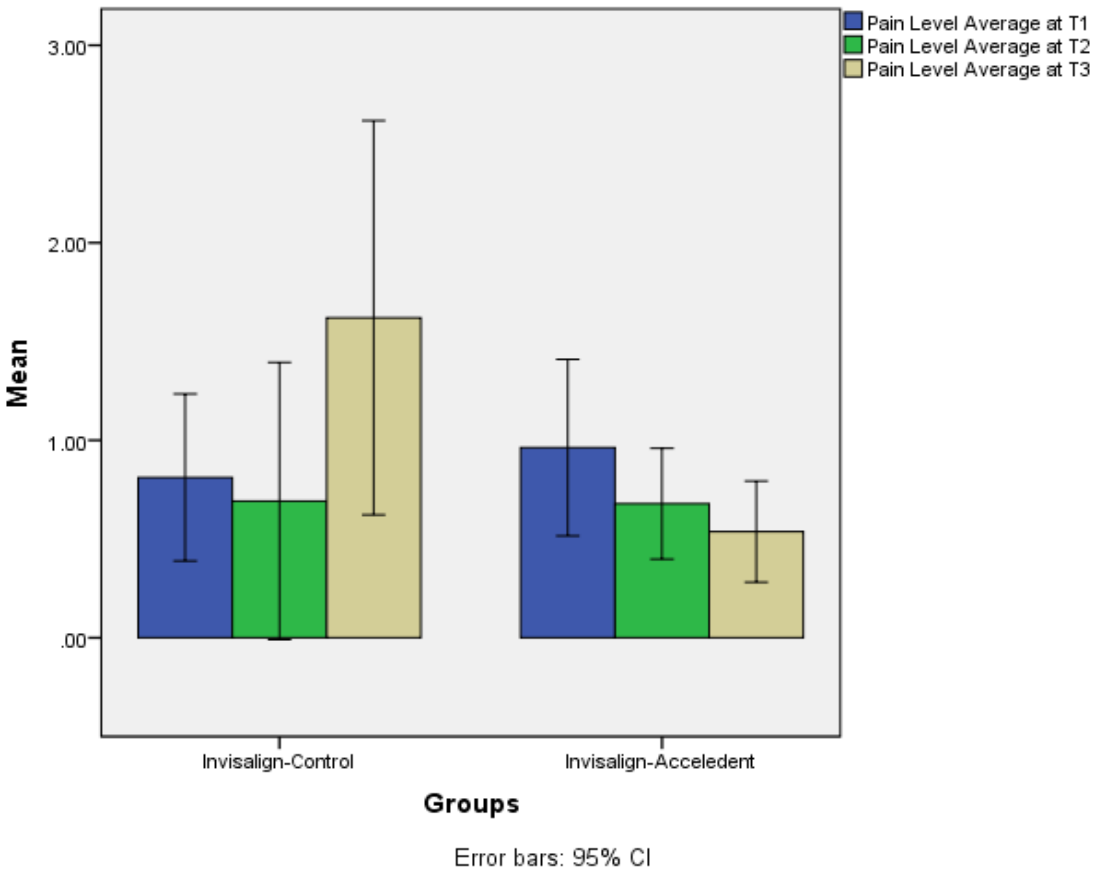

Figure 10: Mean Pain Scores In Each Group For Each Time Period

4.3 Total Treatment Time

There was a statistically significant difference in the total treatment time at each of the time points, the AcceleDent group having shorter intervals compared to the controls (Table IX). Figure 10 is a graphic representation of the increase in total time throughout treatment for both groups. Quantifying this data, about a two-week difference at T2, a three-week difference at T3 and a six-week difference at T4 is noted.

TABLE IX
DESCRIPTIVE STATISTICS AND INDEPENDENT t-TEST RESULTS REGARDING THE TOTAL TREATMENT TIME

					95% CI of the Difference		
	Groups (Mean; SD)	N	Mean Difference	Std. Error Difference	Upper	Lower	Sig (2-tailed)
Treatment Time 0-3 mon	Control (3.22; 0.44)	18	.40278	.12893	.14076	.66480	.004
	AcceleDent (2.82; .32)	18					
Treatment Time 0-6 mon	Control (6.61; 0.99)	18	.70833	.30809	.08222	1.33445	.028
	AcceleDent (5.90; 0.85)	18					
Treatment Time 0-12 mon	Control (12.25; 1.07)	12	1.56250	.56574	.39960	2.72540	.010
	AcceleDent (10.69; 1.72)	16					

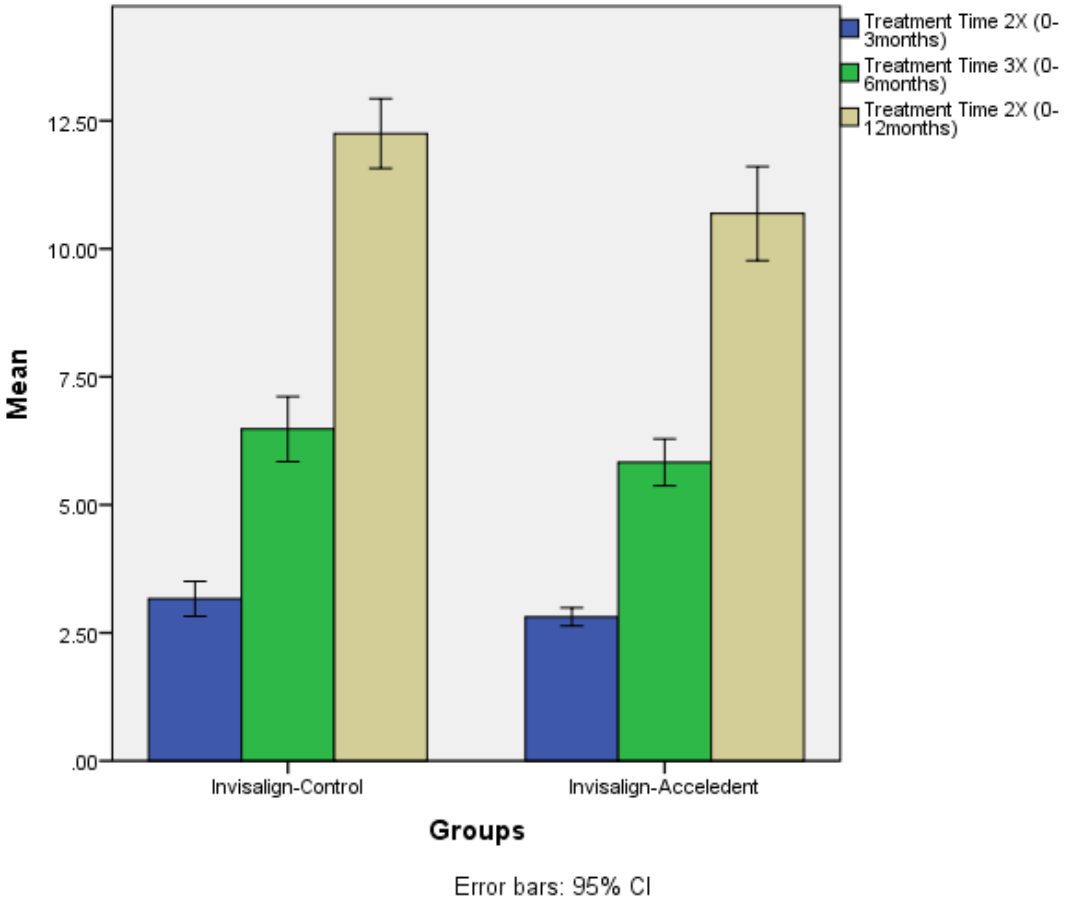

Figure 11: Treatment Time For AcceleDent and Control Groups

4.4 **AcceleDent Compliance**

The mean of the AcceleDent compliance values for the experimental group was approximately 77%, with a range of 12-121%. These data are approximate, because they cannot be correlated to the time points due to an internal error in the AcceleDent devices that were used in this study. According to the data that was collected, most subjects did not use the device 20 minutes per day, as recommended.

4.5 **Harms**

No harms were reported by any of the subjects to the private practice staff and doctors throughout the study duration.

5. DISCUSSION

5.1 Discussion

This is the first study that compared the tooth movement and pain levels in an Invisalign® population using the AcceleDent device. There have been a few studies that have studied these two parameters in patients with fixed appliances (Pavlin et al, 2015; Bowman, 2014; Woodhouse et al, 2015; Miles and Fisher, 2016), but the Invisalign® intervention is unique to this study.

5.1.1 Anterior Tooth Alignment

Anterior tooth alignment was measured by using Little's Irregularity Index. This is the first study evaluating anterior tooth alignment with the AcceleDent device that measured the irregularity index at different time points in the mandibular and maxillary arches. Other studies have measured canine retraction (Pavlin et al, 2015; Leethanakul et al, 2015), alignment described as the ability to seat a 17x25 stainless steel archwire and leveling described as the ability to seat a 19x25 stainless steel archwire (Bowman, 2014) and irregularity index of just the mandibular arch (Woodhouse et al, 2015; Miles and Fisher, 2016). Utilizing both arches gave this study more data to analyze in order to enhance the body of evidence on the topic.

This study found no statistically significant difference between the mean irregularity indexes at any of the time points, as well as no difference in the differences of the mean irregularity index values between the time points for either of the groups. The only significant finding

regarding alignment was that the mean irregularity index values in the control and the experimental groups decreased significantly throughout treatment. This makes sense considering that they were in orthodontic treatment with Invisalign® in order to align their teeth. Therefore, the null hypothesis can be accepted and it is assumed that the experimental group did not progress through alignment any faster than the control group.

These findings are in agreement with the findings of Woodhouse et al and Miles and Fisher who also found no statistically significant difference between their experimental and control groups. Both of these studies also measured tooth alignment using the irregularity index, but only in the mandibular arch. This study was carried out over a longer time period, about 12 months, compared to about 2 months in the other studies, and this discrepancy is reflected in the final irregularity index measurements for each study. The major difference in the methods between those studies and this one is the use of Invisalign®. Thus, based on the above mentioned results, whether undergoing treatment with Invisalign® or fixed appliances, there is no difference in alignment with the use of AcceleDent compared to a group that does not use AcceleDent.

There are four current studies that contradict the findings on anterior tooth alignment, but neither is a direct comparison to the methods used in this study. Pavlin (2015) found that canine retraction with fixed appliances occurred faster in an AcceleDent group in a study that was funded by OrthoAccel Technologies (Pavlin et al, 2015). Leethanakul

(2015) came to the same conclusion with the use of vibrations from an electric toothbrush to help accelerate canine retraction. The movement of canine retraction is very different than incisor alignment, though. In canine retraction, there is the added benefit of a fresh extraction socket which can aid in tooth movement due to the regional acceleratory phenomenon. The regional acceleratory phenomenon is an increase in rate of healing following an original injury thought to be cause by an increased inflammatory response (Verna, 2016). Additionally, the translational movement of canine retraction is much different than correcting rotations in alignment. Pavlin's study, although reported as statistically significant, also included zero in the confidence interval of the difference between the means, which suggests no significant difference (Adlrees, 2016).

Bowman reported that leveling was 27 days faster and alignment was 48 days sooner in the AcceleDent subjects. This study is evaluating alignment, but it is difficult to compare directly to the subjects in this study who were not using archwires. The Bowman study design was also retrospective and subject to bias. Orton-Gibbs deduced that treatment occurred 37% faster in an Invisalign® AcceleDent group than what she would have predicted. This anecdotal evidence has a high risk of bias considering that the investigator was not blinded when she was making the treatment time predictions.

The mean values reported from the current study show that there was about a 0.5mm difference in the T4 irregularity index in the maxillary

and mandibular arches, the AcceleDent group having the lower value. It is up to the practitioner's discretion as to whether or not this is clinically significant. Additionally, the differences between the mean values indicate that there are some minor discrepancies in the two groups. In the maxillary arch, there was about 0.5mm more overall alignment in the experimental group. In the mandibular arch, there was about 1mm more overall alignment in the experimental group. Regardless, there still was no statistically significant difference in any of the mean values.

Despite limited number of controlled studies, OrthoAccel Technologies has provided recommendations regarding Invisalign® aligner wear to doctors and patients that are using the AcceleDent device. They suggest changing aligners once a week based on users clinical experience with the product. The Vice President of Clinical Education for OrthoAccel explained this as such, "Doctors found that AcceleDent accelerated tooth movement by up to 50% therefore it became a simple math of taking 14 days to 7 days, a 50% reduction." The methods of this study utilized their suggestions and the experimental subjects were instructed to change their aligners every 7 days. On the contrary, until October 2016, Invisalign® recommended 14 days per aligner, so this was the protocol for the control group. Ultimately, this could have had an effect on anterior tooth alignment, but because there was no statistically significant difference between the two groups, the effect would have been minimal. As of October 2016, Invisalign® recommended 7 days per

aligner for most cases based on progress data from over 200 cases. In turn, clinicians that offer AcceleDent, are now reporting that aligners can be changed every 3-5 days with the device.

5.1.2. **AcceleDent and Pain**

The current study demonstrated that there was a statistically significant difference between the control and the experimental groups in the pain levels during 6-12 months only. Therefore, the null hypothesis that there is no mean difference in pain level associated with AcceleDent use in patients treated with Invisalign® can be rejected.

A combined FACES and VAS type pain score was employed to evaluate pain levels. According to the literature, this is the most patient preferred and specific. Huskisson determined in 1974 that the VAS was the most sensitive method for measuring pain based on a study that found a correlation between descriptive terms and the visual analog scale. More recently, Sayin et al determined that a visual type of pain scale is what most surgical patients prefer when asked about their pain (Sayin, 2104).

The results of the current study are in agreement with those of Lobre. They evaluated pain over a longer period of time, as the current study did. The number of subjects was larger than the current study, but they also used the VAS to evaluate pain a few times right after adjustment and then weekly until the following adjustment. They found that patients with the AcceleDent device had lower overall pain compared to the control

each month of treatment for the first four months. Their findings are more significant than this current study, but the similarity is noteworthy. Lobre's was well designed, but the primary outcome was to evaluate pain, versus this study that looked at pain as a secondary outcome. Therefore, a placebo effect could have effected the results.

The findings of the current study do contradict those of Woodhouse and Miles and Fisher. Both of these studies also employed a VAS. The major difference in their methods were that they used the device in patients with fixed appliance extraction-based treatment and they only recorded pain values for the first week after adjustments. These two variables are significant in orthodontic treatment. Canine retraction is a large translational movement very different from anterior alignment with Invisalign® treatment. Additionally, they measured pain levels on a much smaller scale by just measuring the first week after adjustments, when most orthodontic pain is reported in general. Therefore, both of these studies may indicate that AcceleDent does not have an effect during the time of most intense orthodontic pain, but the current study was looking at pain over the entire duration of treatment. Due to the different study parameters, it is difficult to directly compare the findings.

The current study found that pain decreased throughout treatment in the AcceleDent group. This decrease in pain level was a statistically significant between 1-3 months and 3-6 months, as well as 1-3 months and 6-12 months. It seems that patients using the AcceleDent device

adapt to orthodontic tooth pain as treatment progresses, even though forces continue to be applied. This is reflected in the study by Lobre, as well.

In the control group, pain initially decreased from 0-3 months to 3-6 months, but then increased in the 6-12 month period. The differences in pain levels between 0-3 months to 6-12 months and 3-6 months to 6-12 months are statistically significant, as a result. This result was unexpected, but perhaps speaks to the highly subjective nature of pain.

It is up to the individual practitioner to decide if there is clinical significance to the findings regarding AcceleDent and pain. The mean values only varied by one point at most on the ten-point scale used in this study. Regardless, the current study has provided evidence to support the idea that AcceleDent can help alleviate perceived pain over the duration of orthodontic treatment.

5.1.3 **Total Treatment Time**

The current study found statistically significant lower time values for the AcceleDent group at the three month, six month and 12 month time points compared to the control. Considering that the irregularity index values at each of these time points are not statistically significant between the two groups, it can be assumed that the AcceleDent group took less time to reach each irregularity index. Quantifying this assumption, there is a two-week difference at T2, three-week difference at T3 and a six-week

difference at T4. The differences are T2 and T3 are not clinically significant, but a six week difference in treatment time overall would be considered clinically significant.

The only confounding factor to this finding is that the AcceleDent group did change their aligners more frequently than the control group, seven days compared to 14 days, respectively. A conclusion regarding AcceleDent decreasing the amount of time in treatment cannot be made until is it clear that more frequent aligner changes alone does not have an effect on the amount of time in treatment.

5.1.4 **AcceleDent Sham**

There is controversy over whether or not a sham device should be used when comparing the effects of the AcceleDent vibrations on tooth movement and pain level. Studies that have used a sham argue that it is important to distinguish if the effects of the AcceleDent device are from the vibrations or the biting force on the device. Those that have not used a sham argue that the sham could cause unwanted effects to treatment. These unwanted effects include the device acting like an aligner chewie, helping to seat the aligner and, thus, moving teeth more efficiently. In addition, the sham could act as a bite wafer, which has been shown to decrease, as well as increase, pain in different studies (Lobre, 2016).

Woodhouse compared three groups in his study, a control with no device, an AcceleDent sham device and an AcceleDent group, and found

no difference in alignment or pain among any of the groups. Pavlin also used a sham, but found a difference in the rate of treatment between the groups. As reported before, Pavlin's was retrospective and very subjective. Lobre did not use a sham device in the study, but their primary outcome was to evaluate pain, thus, there could have been a placebo effect involved. In the current study, a sham was not used because of feasibility. Future studies should include the comparison of sham and non-sham controls in order to control for the unwanted effects that the device could cause.

5.1.5 **Advantages of AcceleDent**

Even though there was no statistically significant difference found in tooth alignment, the differences in pain levels may lead the practitioner to decide that because the pain level is decreasing throughout treatment, aligners can be changed more frequently. Therefore, theoretically, the total treatment time can also be reduced, because more frequent aligner changes would lead to less total treatment time. In addition, most patients will be charged for the device and pay a larger overall fee for treatment. If treatment can occur quicker at a higher price, this may influence a practice's business decision.

5.1.6 **Disadvantages of AcceleDent**

The lack of efficacy demonstrated by this study is a clear disadvantage of the AcceleDent device. In addition, there were additional complaints regarding the device made by the private practice where the data were collected. First, they did not hold the charge which affected daily use as well as patient satisfaction if the device needed to be replaced. There were also patient complaints regarding the amount of time required for daily use of the device (20 minutes). The devices cost $900 each, which is also a large amount to add on to treatment that already is about $5000 dollars. Finally, the devices were designed to be single use and had a chip in them that would deactivate them after certain number of months. This made it impossible for a family of orthodontic patients to derive the benefits from a single device.

5.2 Limitations of the Study

There were a few limitations to this study design, but as in any real world study, variation is to be expected. The sample size could have been larger which would increase the clinical significance. Because this was a prospective study, patients were recruited as they presented to the office during the enrollment period. Therefore, the study sample was limited to how many people presented to the office interested in Invisalign® treatment. During the enrollment period, we extended the ending enrollment date three months in order to increase the numbers. Although, the office that the data was collected from treats a lot of patients, the majority are not treated with Invisalign®.

Additionally, the subjects were not blinded to the use of the device. During recruitment, patients were made aware of the current claims that AcceleDent can decrease treatment time and pain. This should not have any significant effect on the irregularity index measurement, but it may have had a placebo effect influencing reported discomfort due to the highly subjective nature of pain. Pain is a combination of behavioral and emotional sensations and different people feel the same pain differently. Therefore, there is also a chance that those that were interested in the study had a lower pain threshold in general which could have had an effect on the results of this study.

A sham device was not used in this study due to the possible side effects disrupting the results. Biting on the AcceleDent mouthpiece without vibrations could have had a pain relieving and aligner-seating effect. A better designed sham control would have been ideal.

Another aspect of the study that was difficult to control was the number of days that subjects were changing their aligners. The experimental group was mostly changing once a week, but some increased to changing every 10 days due to issues with compliance. The control group changed every 10 to 14 days, based on the recommendations of the doctor treating the case. This variety in aligner wear is based on the current protocol of the office where the data was collected from. The subjective assessment is ideal for the private practice setting, because no two patients are the same. In a controlled study, though, changing the aligners with the same interval and recording the days that aligners were changed would be best. The decision on when to change the aligners was based on the recommendations from OrthoAccel Technologies and Aligntech. OrthoAccel recommends seven-day aligner wear with the AcceleDent device and Aligntech recommended 14 days without the device.

More frequent aligner changing alone could have had an effect on the anterior tooth alignment. Interestingly, during this study, Aligntech changed their recommendations to seven-day aligner wear for all patients due to data from their clinical studies. Therefore, the discrepancy in aligner change for the protocol of the current study may not have been that significant, because the aligners could have been passive for the second seven days of the wear period.

Patient compliance was another limitation to this study. Patients were required to comply with specified aligner wear time, using the device 20 minutes per day and filling out the pain survey. This was a lot to ask of patients and very few followed instructions exactly for the full 12 month study period. Exact

compliance with the aligners is difficult to measure exactly, because it is all patient reported. The subjects knew that compliance with the study would allow them the reward, which may have influenced their reporting. Also, the AcceleDent devices did not have accurate dates on the FastTrac Usage report. This was an internal flaw with the devices that, at the time, could not be solved by OrthAccel Technologies. The pain data reporting was the most varied due to variations in frequency and timing of subject input, but due to the large number of scores that were collected over the 12-month period, an overall pain was still analyzed. A final limitation was the lack of reporting of pain medication, which clearly would have affected the results.

5.3 **Future Research**

Despite the limitations, this study is the first of its kind and provides a framework for further research. Firstly, future studies could include a sham control. Ideally, there would be sham and non-sham control in order to control for any chance that the mouthpiece has an effect on pain or alignment. Also, days of aligner wear should be controlled. Ideally, subjects should switch to the next aligner when the previous one is completely passive. This subject design would require more patient education or dental monitoring.

Since the reporting of the pain data was very difficult to complete per this study design, it would be best to change the method of pain data collection. Other studies have provided subjects with booklets to fill out pain levels between

adjustments and return at the next appointment. This provides the subject with a record of completion of the pain score. The online method of pain data collection was determined to be the best platform for the patients, but this may have been hard for patients to keep track of. With more resources, designing an app with push notifications that alerts subjects to provide a pain score on the days that they are required to would be best.

This study did not measure rate of tooth movement, because irregularity indexes were only collected on the dates of the specified time points, which were approximately three to six months apart. In a future study, scans could be taken at more frequent intervals. This would provide more data to collect rate.

It would also be interesting to compare the movement of canine retraction to that of alignment. Past studies with AcceleDent that measured canine retraction found that the device had an effect on the rate of tooth movement, but the studies that measured alignment did not find any difference. Therefore, it would be interesting to measure both of these movements in the same subjects.

6. CONCLUSIONS

The following conclusions were obtained from the present study:

- There was no statistically significant mean difference in the Irregularity Index values between the groups.
- There was a statistically significant mean difference of the pain scores between the groups during 6-12 months, the AcceleDent group having the lower value.
- The AcceleDent group had significantly shorter intervals between time points compared to the control.

Increasing anterior tooth alignment and decreasing pain caused by orthodontic forces will have a positive effect on patient well being and recruitment. Based on the extent of the present study, it cannot be concluded that AcceleDent had an effect on alignment of anterior teeth. This study does demonstrate that there is lower perceived pain level by six month into treatment between patients that are using the AcceleDent device versus those that are not. Pain levels decrease throughout treatment in patients using AcceleDent. It is possible that if pain levels decrease throughout Invisalign® treatment with AcceleDent, then the aligners can be changed sooner without additional discomfort to the patient, thus decreasing treatment time.

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APPENDIX A

Western Institutional Review Board®
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Certificate of Approval

THE FOLLOWING WERE APPROVED

INVESTIGATOR: Terry Sellke DDS, MS
30 North Slusser Street
Grayslake, Illinois 60030

BOARD ACTION DATE: 01/18/2015
PANEL: 5
STUDY APPROVAL EXPIRES: 01/18/2016
STUDY NUM: 1150956
WIRB PRO NUM: 20142261
ONLINE TRACKING:
INVEST NUM: 115356
WO NUM: 1-860670-1
CONTINUING REVIEW: Annually
SITE STATUS REPORTING: Annually
INST. NUM:

SPONSOR: Sellke and Reily LTD
PROTOCOL NUM: AD-ALIGN11012014
AMD. PRO. NUM:
TITLE:
The effect of AcceleDent application on discomfort level and rate of tooth movement in orthodontic treatment with Invisalign.

APPROVAL INCLUDES:
Investigator
Pain Scale #12734428.0 - As Submitted
Protocol (10-30-2014)
Screening Script #12555811.0 - As Submitted
Consent Form [S0]
Financial Disclosure Form (10-27-2014) Terry Sellke

WIRB APPROVAL IS GRANTED SUBJECT TO:
The Board requires that all adult subjects must be able to consent for themselves to be enrolled in this study. This means that you cannot enroll incapable subjects who require enrollment by consent of a legally authorized representative.

WIRB HAS APPROVED THE FOLLOWING LOCATIONS TO BE USED IN THE RESEARCH:
Drs. Sellke and Reily, LTD, 30 North Slusser, Grayslake, Illinois 60030
Drs. Sellke and Reily, LTD, 1138 South Main Street, Route 83 and 173, Antioch, Illinois 60002
Gurnee Orthodontics, 101 S Greenleaf Ave, Gurnee, Illinois 60031

If the PI has an obligation to use another IRB for any site listed above and has not submitted a written statement from the other IRB acknowledging WIRB's review of this research, please contact WIRB's Client Services department.

ALL WIRB APPROVED INVESTIGATORS MUST COMPLY WITH THE FOLLOWING:

1. Conduct the research in accordance with the protocol, applicable laws and regulations, and the principles of research ethics as set forth in the Belmont Report.

2. Although a participant is not obliged to give his or her reasons for withdrawing prematurely from the clinical trial, the investigator should make a reasonable effort to ascertain the reason, while fully respecting the participant's rights.

3. Unless consent has been waived, conduct the informed consent process without coercion or undue influence, and provide the potential subject sufficient opportunity to consider whether or not to participate. (Due to the unique circumstances of

APPENDIX B

2007-0220 Page 1 of 1 3/29/2007

Notice of Determination of Human Subject Research

June 26, 2015

20150698-90990-1

Claire Pescheret
Orthodontics
801 S, Paulina Street, Rm 131
M/C 841
Chicago, IL 60612
Phone: (847) 271-7720 / Fax: (312) 996-0873

RE: Protocol # 2015-0698
"The Effect of AcceleDent Application on Discomfort Level and Rate of Tooth Movement in Orthodontic Treatment with Invisalign"

Sponsor: None

Dear Ms. Pescheret:

The UIC Office for the Protection of Research Subjects received your "Determination of Whether an Activity Represents Human Subjects Research" application, and has determined that this activity **DOES NOT meet the definition of human subject research** as defined by 45 CFR 46.102(f).

You may conduct your activity without further submission to the IRB.

If this activity is used in conjunction with any other research involving human subjects or if it is modified in any way, it must be re-reviewed by OPRS staff.

APPENDIX C

Terry A. Sellke, DDS, MS
Donald J. Reily, DDS, MS
Simply Spectacular Smiles

1138 South Main Street
Antioch, IL 60002
TEL (847) 838-0105

30 North Slusser Street
Grayslake, IL 60030
TEL (847) 223-2876

101 S. Greenleaf Ave.
Gurnee, IL 60031
(847) 249-1000

three locations for your convenience

Maybe it's time to invest in a beautiful new smile....

Drs. Sellke & Reily have been involved in clinical research to advance the profession of orthodontics for many years. (Please read to the right to learn more about us.)

This is YOUR invitation to participate in our latest study on a wonderful new tool that allows us to treat you or your child faster and with virtually no discomfort, Acceledent®. This FDA approved accessory when used just 20 minutes a day speeds treatment with either of two technologies we have offered since 2008, Invisalign® and Suresmile®.

All participants will receive a no charge Orthodontic Evaluation ($400 value) and:

- *A free Acceledent® Appliance ($1100 value),* **or**
- *A $600 Reward for participation in the research project.*

Come in and learn more about how our advanced treatment systems benefit YOU!

Call one of our convenient offices to schedule your free orthodontic evaluation.

Treatment must be started by December 31, 2014 to participate in the research project.

Drs. Sellke and Reily are both licensed specialists in orthodontics serving the Antioch, Grayslake and Gurnee communities.

Dr. Sellke has been a Professor and Master Clinician at the University of Illinois Dental School, Department of Orthodontics. His text on Bioprogressive Orthodontics has been translated into 4 languages.

Drs. Sellke and Reily have published numerous articles on orthodontics in professional journals worldwide and are well known for their research and continuing education programs.

Visit Us at
SR-Orthodontics.com

SRO 1014

APPENDIX D

Phone Etiquette for Study

11/13/2014

When patients call and are interested in participating in the study because they have heard about it from the direct mailer or some other venue. We are to follow the following scripting. We are not permitted to share with them if they are or are not eligible for the study, since they have called our office they are interested in orthodontic treatment and the doctor will see them and acknowledge at that consultation appointment if they are an eligible candidate at that time. However if they have not had a dental cleaning and checkup in a very long time, it's always a good idea to encourage them to schedule that appointment because starting treatment would be on hold until after that appointment is taken care of.

This research study involves an FDA approved appliance called AcceleDent. AcceleDent claims to reduce treatment time and pain levels and we are conducting a study to measure and compare the speed of treatment and level of discomfort between two groups with and without the AcceleDent unit. The decision to participate or not to participate does not change the standard of care that you will receive. All participants will receive a financial reward of $600 for successfully completing the study. Would you like to schedule a complimentary orthodontic consultation?

At the consultation, the same standard of care is followed and the doctor will share with the TC if the patient meets the study criteria and can move forward to the next step. Once the doctor's portion is complete then the TC will follow the screening requirement process for the study (see that document).

APPENDIX E

Screening Requirements for Study:

To see if you might qualify for this study, I need to ask you some questions about your health history and present condition. Some of these questions may be sensitive. You do not have to answer any questions you do not want to answer. You may stop this interview at any time. If you do not qualify for this study, the information you give me will be immediately shredded.

Do I have your permission to proceed?

1. Are you in good health?
2. Do you have periodontitis?
3. Do you smoke?
4. Do you take Advil or other NSAIDs, like ibuprofen?
5. Do you take a Vitamin D supplement?
6. Do you take bisphosphonates?

Thank you for answering these questions.
If they qualify: Based on this information you qualify to participate in the study and your files will be kept encrypted and secure till the end of the study which we anticipate the date of June 2017. Is it ok with you if we use your information that we collect from this study for possible future studies?

If they do NOT qualify: I'm sorry you do not qualify for participation in this study and the information you gave me will be immediately shredded.

APPENDIX F

APPROVED
Jan 18, 2015
WIRB®

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE:	The effect of AcceleDent application on discomfort level and rate of tooth movement in orthodontic treatment with Invisalign.
PROTOCOL NO.:	AD-ALIGN11012014 WIRB® Protocol #20142261
SPONSOR:	Sellke and Reily LTD
INVESTIGATOR:	Terry Sellke, DDS, MS 30 North Slusser Grayslake, Illinois 60030 United States
STUDY-RELATED PHONE NUMBER(S):	Terry Sellke, D.D.S., M.S. 847-223-2894 847-204-8127 (24 Hours)
SUB-INVESTIGATOR:	Donald Reily, D.D.S., M.S.
STUDY COORDINATOR(S):	Julie Myrdal

This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

In this consent form, "you" always refers to the subject. If you are a parent or guardian, please remember that "you" refers to the study subject.

You are being asked to be a subject in a research study involving an FDA approved appliance called Acceledent. Acceledent will be used in selected subjects as an add on to Invisalign, a treatment system involving clear plastic "aligners" to straighten teeth approved by the U.S. Food and Drug Administration (FDA). The procedures used are standard of care, although the use of these devices together is investigational in this study. The study doctor, Dr. Terry Sellke, D.D.S., M.S., and his partner, Dr. Donald Reily D.D.S., M.S., will be responsible for carrying out the research procedures for all subjects in the study. You will be in this study for about 1 year. There will be 80 subjects in the study. You will have an equal chance of being in either group.

We ask that you read this consent form and ask any questions you may have before agreeing to be a research subject. Your participation in this research is voluntary. Your decision whether or not to participate will not affect your current or future relations with Dr. Sellke and Reily, LTD or Gurnee Orthodontics or individuals involved in this study. If you decide to participate, you are free to withdraw at any time without affecting that relationship.

What is the purpose of this research?

The goal of this study is to compare the effectiveness of an Acceledent appliance as an add on to standard Invisalign treatment. We will be measuring the speed of treatment, the level of discomfort, and the treatment results in a sample of patients using versus not using an Acceledent appliance.

What procedures are involved?

The treatment procedures that will be used incorporating Invisalign therapy will be identical between the two groups. The doctor developing the treatment plan (clincheck), Dr Donald Reily, will not know whether a patient is using or not using Acceledent as he develops each patient's treatment plan in the study. This allows the only variable that will be studied the efficacy of Acceledent 1) in moderating discomfort when using Invisalign and 2) in reducing the time required to successfully treat the subject with Invisalign.

Patients who agree to participate in the study will be asked to respond to a short email questionnaire assessing their discomfort level one day, two days, three days, and weekly after each appointment.

Subjects in the group using Acceledent will be required to use the device for a 20 minute period after each adjustment, that evening, morning and night on the second and third day, and daily thereafter until the next appointment. This process will be repeated after each appointment until treatment is completed.

iTero scans of the teeth will be taken during the study at the following times:

- Before treatment begins
- Approximately 8 – 10 weeks after appliances are placed
- Approximately 5 – 6 months into treatment
- At the end of treatment or at 12 months into treatment, whichever comes first

iTero scans involve an FDA approved digital scanning device to create 3D digital models of the teeth. This painless non-invasive process involves no injections or harmful actions.

What are the potential risks and discomforts?

The possible risks and discomforts you might experience during this study include:

- The standard risk that patients may incur receiving Invisalign treatment outside of this study, which may include pain.
- The inconvenience in the Acceledent group of using the device at the prescribed times
- That the Acceledent device does not provide a reduction in discomfort nor faster treatment

If at any time you wish to withdraw from the study, you may do so.

There may be risks or side effects which are unknown at this time.

Are there benefits to taking part in the research?

The potential benefits of your participation in this study include:

- the possibility of reduced treatment time and treatment discomfort with the Acceledent group.
- Information learned from this study may help patients in the future.

What are the costs for participating in this research?

There are no additional costs involved for participating in this research. You or your insurance company will be billed for your Invisalign treatment.

Is there payment for participation?

Subjects who complete the study will receive a free Acceledent unit (study group) or $600 off of the total treatment cost (control group) at the end of treatment. Subjects will be reimbursed with a check. Subjects in the control group who do not complete the study will receive a reduced amount. Please talk to your study doctor about payment reduction.

Financial Disclosure
The investigator has received consulting fees from the Sponsor in the past twelve months. Please feel free to ask any further questions you may have about this matter.

Are there alternative treatments?

Absolutely! If you do not desire to participate in the study treatment you will proceed as usual with your Invisalign care.

What about privacy and confidentiality?

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

Federal regulations give you certain rights related to your health information. These include the right to know who will be able to get the information and why they may be able to get it. The investigators, Dr Terry A Sellke and Dr Donald J Reily must get your authorization (permission) to use or give out any health information that might identify you. However, it is the intent of this study to de-identify your records to prevent access to private information that could identify your records as yours.

What information may be used and given to others?

If you choose to be in this study, the co-investigators will get personal information about you. This may include information that might identify you. They may also get information about your health including:

- Past and present medical and dental history
- Research records and photographs
- Records relating to phone calls made as part of this research
- Records about your study visits
- Records about the study devices

Who may use and give out information about you?
De-identified information about your health may be used and given to others by the co-investigators and staff. They might see the research information during and after the study.

Who might get this information?

Your information may be given to the sponsor of this research, Sellke and Reily LTD.

Information about you and your health which might also be given to:

- The U.S. Food and Drug Administration (FDA)
- Department of Health and Human Services (DHHS) agencies
- The Western Institutional Review Board® (WIRB®)

Why will this information be used and/or given to others?

De-identified information will be used to assess study outcomes. To ensure the privacy of your information consultants will analyze and evaluate the results of the study as well as visit the research site. They will follow how the study is done, and they will be reviewing your information for this purpose.

The results of this research may be published in scientific journals or presented at medical meetings, but your identity will not be disclosed.

The information may be reviewed by WIRB®. WIRB is a group of people who perform independent review of research as required by regulations.

What if I decide not to give permission to use and give out my health information?

By signing this consent form, you are giving permission to use and give out the health information listed above for the purposes described above. If you refuse to give permission, you will not be able to be in this research.

May I review or copy the information obtained from me or created about me?

You have the right to review and copy your mental health information. However, if you decide to be in this study and sign this permission form, you will not be allowed to look at or copy your information until after the research is completed.

May I withdraw or revoke (cancel) my permission?

This permission will be good until December 31, 2060.

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to Dr Terry A Sellke, D.D.S., M.S. If you withdraw your permission, you will not be able to continue being in this study.

When you withdraw your permission, no new health information which might identify you will be gathered after that date. Information that has already been gathered may still be used and given to others. This would be done if it were necessary for the research to be reliable.

Is my health information protected after it has been given to others?

Your information will be de-identified to the best of our ability before dissemination to any other party. There is little risk that your private health information can be identified as yours. Once your private health information is disclosed to other parties, it may no longer be protected from disclosure.

What if I am injured as a result of my participation?

There is no more risk of injury participating in this study than receiving standard care as a non-participant. In the unlikely event of injury related to this research study, treatment will be made available through Dr. Sellke and Reily, LTD. However, you or your third party payer, if any, will be billed for this treatment.

Who will provide the source of funding?

Funding for this research study will be provided by Dr. Terry A Sellke, D.D.S., M.S.

Will I receive new information about this study?

During the course of the study, you will be informed of any new findings such as changes in the risks or benefits resulting from participation in this research study or new alternatives to participation that might change your decision to be in the study. If new information is provided to you, your consent to continue participating in this study will be re-obtained.

What will happen if I decide not to participate?

Your participation in this study is voluntary. You may decide not to participate or you may leave the study at any time. Your decision will not result in any penalty or loss of benefits as related to your treatment.

Your participation in this study may be stopped at any time by the co-investigators without your consent.

Who should I contact if I have questions?

If you have any questions concerning your participation in this study, or if at any time you feel you have experienced a research-related injury or a reaction to the study device, contact:

Dr. Terry A Sellke at 847-223-2894 or 847-204-8127 (24 Hours).

If you have any questions about your rights as a research subject, you may contact:

Western Institutional Review Board® (WIRB®)
1019 39th Avenue SE Suite 120
Puyallup, Washington 98374-2115
Telephone: 1-800-562-4789 or 360-252-2500
E-mail: Help@wirb.com.

WIRB is a group of people who perform independent review of research.

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

If you agree to be in this study, you will be given a signed and dated copy of this consent form.

Signature of Subject or Parent/Guardian

APPROVED
Jan 18, 2015
WIRB®

I have read the information in this consent form (or it has been read to me). I have been given an opportunity to ask questions and my questions about the study and my (my child's) participation in it have been answered to my satisfaction. I agree to (allow my child to) participate in this research.

I authorize the use and disclosure of my health information to the parties listed in the authorization section of this consent for the purposes described above.

By signing this consent form, I have not given up any of my/my child's legal rights.

Consent and Assent Instructions:
Consent: Subjects 18 years and older must sign on the subject line below
For subjects under 18, consent is provided by the Parent or Guardian
Assent: Is required for subjects ages 13 through 17 years using the Assent Section below

Printed Name of Subject

CONSENT SIGNATURE:

Signature of Subject (18 years and older) — Date: 7.7.15

Signature of Parent /Guardian (when applicable) — Date

Printed Name of Parent/Guardian — Date

Parent/Guardian's Relationship to Subject

Signature of Person Conducting Informed Consent Discussion — Date: 7/7/15

Printed Name of Person Conducting Informed Consent Discussion: Julie Myrdal — Date: 7/7/15

Signature of Witness — Date: 7/7/15

Printed Name of Witness: Amanda Staines

ASSENT SIGNATURES, For Subjects Ages 13 through 17 years:

Assent:
This research study has been explained to me and I agree to be in this study.

_____	_____	_____
Subject's Signature for Assent	Date	Age (years)

I confirm that I have explained the study to the extent compatible with the subject's understanding, and that the subject has agreed to be in the study.

_____	_____
Signature of Person Conducting Assent Discussion	Date

---------- Use the following only if applicable ----------

If this consent form is read to the subject because the subject (or legally authorized representative) is unable to read the form, an impartial witness not affiliated with the research or investigator must be present for the consent and sign the following statement:

I confirm that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject (or the subject's legally authorized representative). The subject (or the subject's legally authorized representative) freely consented to be in the research study.

_____	_____
Signature of Impartial Witness	Date

_____
Printed Name of Impartial Witness

Note: This signature block cannot be used for translations into another language. A translated consent form is necessary for enrolling subjects who do not speak English.

APPENDIX G

Acceledent usage

Each appointment:

-Bite on the biteblock 20 minutes before leaving the office

-Bite on the biteblock for 20 minutes that evening before going to bed

2nd day:

-Bite on the biteblock twice for 20 minutes each: in the morning and before going to bed

After that:

-Bite on the biteblock for 20 minutes every night before going to bed

Remember:

Bring your AcceleDent unit including the biteblock to every appointment!

APPENDIX H

Pain survey compliance for Invisalign Patients

Each appointment:

-Pain survey needs to be completed in the office before seeing the doctor

Day 1 after appointment:

-Take the pain survey, ranking your tooth pain. You will receive a reminder email to do this with a link.

Day 2 after appointment:

-Take the pain survey, ranking your tooth pain. You will receive a reminder email.

Day 3 after appointment:

-Take the pain survey, ranking your tooth pain. You will receive a reminder email.

After each new set of aligners:

-Take the pain survey three consecutive days after each new aligner set is started. You will NOT receive a reminder email to do this since everyone is on their own schedules to change aligners. Please save the link you receive in the beginning to complete the surveys these days. The survey link: https://www.surveymonkey.com/s/G2R58MW

It is crucial that you fill out these surveys to remain in the study. If you miss a day, be sure to fill it out as soon as you realize it.

Pain relievers are permitted except those containing NSAIDs, no Vitamin D, and no smoking.

VITA

NAME:	Claire N. Pescheret
EDUCATION:	B.S., Molecular and Cellular Biology, University of Illinois at Champaign-Urbana, Champaign-Urbana, IL, 2010
	D.D.S., University of Illinois at Chicago College of Dentistry, Chicago, IL, 2014
	M.S., Oral Sciences, University of Illinois at Chicago College of Dentistry, Chicago, IL, 2017
TEACHING EXPERIENCE:	Department of Orthodontics, University of Illinois at Chicago, Chicago, IL: Orthodontic Pre-Clinical Course Teaching Assistant, 2014-2017
	Department of Periodontics, University of Illinois at Chicago, Chicago, IL: Periodontic Pre-Clinical Course Teaching Assistant, 2013-2014
HONORS:	Omicron Kappa Upsilon, University of Illinois at Chicago College of Dentistry, Chicago, IL, 2014
	American Institute of Orthodontics Research Award, University of Illinois at Chicago College of Dentistry, Chicago, IL, 2014
	American Association of Orthodontists Award, University of Illinois at Chicago College of Dentistry, Chicago, IL, 2014
	Dr. Gerald L. Wine Scholarship, University of Illinois at Chicago College of Dentistry, Chicago, IL, 2014
	ASDA Horace Wells Award, University of Illinois at Chicago College of Dentistry, Chicago, IL, 2014
	Quintessence Award for Clinical Achievement in Periodontics, University of Illinois at Chicago College of Dentistry, Chicago, IL, 2014
	OKU Lina K. Tharp Award, University of Illinois at Chicago College of Dentistry, Chicago, IL, 2014

PROFESSIONAL MEMBERSHIP:	Illinois State Dental Society (ISDS) Chicago Dental Society (CDS) American Dental Political Action Committee (ADPAC) American Dental Association (ADA) American Association of Orthodontists (AAO)